ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IntronA 3 million IU/0.5 mL solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of solution for injection or infusion contains 3 million IU of recombinant interferon alfa-2b produced in *E. coli* by recombinant DNA technology, in 0.5 mL of solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B
Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of DNA of hepatitis B virus (HBV-DNA) and hepatitis B antigen (HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic hepatitis C
Before initiating treatment with IntronA, consideration should be given to the results from clinical trials comparing IntronA with pegylated interferon (see section 5.1).

Adult patients
IntronA is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for hepatitis C virus RNA (HCV-RNA) (see section 4.4).

The best way to use IntronA in this indication is in combination with ribavirin.

Children 3 years of age and older and adolescents
IntronA is indicated, in a combination regimen with ribavirin, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients. The decision to treat should be made on a case by case basis (see section 4.4).

Hairy cell leukaemia
Treatment of patients with hairy cell leukaemia.

Chronic myelogenous leukaemia
Monotherapy
Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia.

Clinical experience indicates that a haematological and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is ≥ 34 %, but < 90 % Ph+ cells in the marrow.

Combination therapy
The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.

Multiple myeloma
As maintenance therapy in patients who have achieved objective remission (more than 50 % reduction in myeloma protein) following initial induction chemotherapy.
Current clinical experience indicates that maintenance therapy with interferon alfa-2b prolongs the plateau phase; however, effects on overall survival have not been conclusively demonstrated.

Follicular lymphoma
Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.

Carcinoid tumour
Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome".

Malignant melanoma
As adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement.

4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dose forms and strengths are appropriate for some indications. Appropriate dose form and strength must be selected.

If adverse events develop during the course of treatment with IntronA for any indication, modify the dose or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dose adjustment, or disease progresses, discontinue treatment with IntronA. At the discretion of the physician, the patient may self-administer the dose for maintenance dose regimens administered subcutaneously.

Chronic hepatitis B
The recommended dose is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/mm^3, granulocytes < 1,000/mm^3, thrombocytes < 100,000/mm^3). Treatment should be discontinued in case of severe leukopaenia (< 1,200/mm^3), severe neutropaenia (< 750/mm^3) or severe thrombocytopaenia (< 70,000/mm^3).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue IntronA therapy.

Chronic hepatitis C

Adults

IntronA is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

Children 3 years of age or older and adolescents

IntronA 3 MIU/m^2 is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsules SPC for dose of ribavirin capsules and dose modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC.)

Relapse patients (adults)

IntronA is given in combination with ribavirin. Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for 6 months.

Naïve patients (adults)

The efficacy of IntronA is enhanced when given in combination with ribavirin. IntronA should be given alone mainly in case of intolerance or contraindication to ribavirin.

- IntronA in combination with ribavirin

Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

- IntronA alone

The optimal duration of therapy with IntronA alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with IntronA alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

Naïve patients (children and adolescents)

The efficacy and safety of IntronA in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Duration of treatment for children and adolescents

- Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Therefore, it is recommended that children and adolescent

patients receiving IntronA/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 log_{10} compared to pretreatment, or if they have detectable HCV-RNA at treatment week 24.

- Genotype 2/3: The recommended duration of treatment is 24 weeks.

Hairy cell leukaemia
The recommended dose is 2 million IU/m^2 administered subcutaneously three times a week (every other day) for both splenectomised and non-splenectomised patients. For most patients with Hairy Cell Leukaemia, normalisation of one or more haematological variables occurs within one to two months of IntronA treatment. Improvement in all three haematological variables (granulocyte count, platelet count and haemoglobin level) may require six months or more. This regimen must be maintained unless the disease progresses rapidly or severe intolerance is manifested.

Chronic myelogenous leukaemia
The recommended dose of IntronA is 4 to 5 million IU/m^2 administered daily subcutaneously. Some patients have been shown to benefit from IntronA 5 million IU/m^2 administered daily subcutaneously in association with cytarabine (Ara-C) 20 mg/m^2 administered daily subcutaneously for 10 days per month (up to a maximum daily dose of 40 mg). When the white blood cell count is controlled, administer the maximum tolerated dose of IntronA (4 to 5 million IU/m^2 daily) to maintain haematological remission.

IntronA treatment must be discontinued after 8 to 12 weeks of treatment if at least a partial haematological remission or a clinically meaningful cytoreduction has not been achieved.

Multiple myeloma
Maintenance therapy
In patients who are in the plateau phase (more than 50 % reduction of myeloma protein) following initial induction chemotherapy, interferon alfa-2b may be administered as monotherapy, subcutaneously, at a dose of 3 million IU/m^2 three times a week (every other day).

Follicular lymphoma
Adjunctively with chemotherapy, interferon alfa-2b may be administered subcutaneously, at a dose of 5 million IU three times a week (every other day) for a duration of 18 months. CHOP-like regimens are advised, but clinical experience is available only with CHVP (combination of cyclophosphamide, doxorubicin, teniposide and prednisolone).

Carcinoid tumour
The usual dose is 5 million IU (3 to 9 million IU) administered subcutaneously three times a week (every other day). Patients with advanced disease may require a daily dose of 5 million IU. The treatment is to be temporarily discontinued during and after surgery. Therapy may continue for as long as the patient responds to interferon alfa-2b treatment.

Malignant melanoma
As induction therapy, interferon alfa-2b is administered intravenously at a dose of 20 million IU/m^2 daily for five days a week for a four-week period; the calculated interferon alfa-2b dose is added to sodium chloride 9 mg/mL (0.9 %) solution for injection and administered as a 20-minute infusion (see section 6.6). As maintenance treatment, the recommended dose is 10 million IU/m^2 administered subcutaneously three days a week (every other day) for 48 weeks.

If severe adverse events develop during interferon alfa-2b treatment, particularly if granulocytes decrease to < 500/mm^3 or alanine aminotransferase/aspartate aminotransferase (ALT/AST) rises to > 5 x upper limit of normal, discontinue treatment temporarily until the adverse event abates. Interferon alfa-2b treatment is to be restarted at 50 % of the previous dose. If intolerance persists after dose adjustment or if granulocytes decrease to < 250/mm^3 or ALT/AST rises to > 10 x upper limit of normal, discontinue interferon alfa-2b therapy.

Although the optimal (minimum) dose for full clinical benefit is unknown, patients must be treated at the recommended dose, with dose reduction for toxicity as described.

IntronA may be administered using either glass or plastic disposable injection syringes.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.
- Combination of IntronA with telbivudine.

Children and adolescents
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

4.4 Special warnings and precautions for use

Psychiatric and central nervous system (CNS)
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during IntronA therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents treated with IntronA in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation is identified, it is recommended that treatment with IntronA be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions:
If treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

Patients with substance use/abuse:
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Children and adolescent population: Growth and development (chronic hepatitis C)
During the course of interferon (standard and pegylated)/ribavirin combination therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children (n=20) despite being off treatment for more than 5 years. Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment.

Case by case benefit/risk assessment in children
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response, (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

Hypersensitivity reactions
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during IntronA therapy. If such a reaction develops, discontinue the medicine and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Adverse experiences including prolongation of coagulation markers and liver abnormalities
Moderate to severe adverse experiences may require modification of the patient's dose regimen, or in some cases, termination of IntronA therapy. IntronA increases the risk of liver decompensation and death in patients with cirrhosis.
Discontinue treatment with IntronA in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decomposition.
Any patient developing liver function abnormalities during treatment with IntronA must be monitored closely and treatment discontinued if signs and symptoms progress.
Liver enzymes and hepatic function should be closely monitored in cirrhotic patients.

Hypotension
Hypotension may occur during IntronA therapy or up to two days post-therapy and may require supportive treatment.

Need for adequate hydration
Adequate hydration must be maintained in patients undergoing IntronA therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Pyrexia
While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Patients with debilitating medical conditions
IntronA must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary conditions
Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events
Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, serous retinal detachment, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with IntronA, must have a prompt and complete eye examination. Periodic visual examinations during IntronA therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of IntronA should be considered in patients who develop new or worsening ophthalmological disorders.

Obtundation, coma and encephalopathy
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of IntronA.

Patients with pre-existing cardiac abnormalities
Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require IntronA therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of IntronA therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia
Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Patients with psoriasis and sarcoidosis
Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of IntronA in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Kidney and liver graft rejection
Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Auto-antibodies and autoimmune disorders
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Concomitant chemotherapy
Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered medicinal product. The most commonly reported potentially life-threatening or fatal adverse events include mucositis, diarrhoea, neutropaenia, renal impairment, and electrolyte disturbance. Because of the risk of increased toxicity, careful adjustments of doses are required for IntronA and for the concomitant chemotherapeutic agents (see section 4.5). When IntronA is used with hydroxyurea, the frequency and severity of cutaneous vasculitis may be increased.

Chronic hepatitis C
Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy
Infrequently, adult patients treated for chronic hepatitis C with IntronA developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using IntronA therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which IntronA may alter thyroid status is unknown. Prior to initiation of IntronA therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of IntronA therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, IntronA treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of IntronA therapy has not reversed thyroid dysfunction occurring during treatment (also see Thyroid supplemental monitoring specific for children and adolescents).

Thyroid supplemental monitoring specific for children and adolescents
Approximately 12 % of children treated with interferon alfa-2b and ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of IntronA therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding IntronA and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with IntronA and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of IntronA and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with IntronA.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during IntronA therapy to greater than or equal to 2 times baseline, IntronA therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, the following liver function tests must be monitored at two-week intervals: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin.

In patients treated for malignant melanoma, liver function and white blood cell (WBC) count and differential must be monitored weekly during the induction phase of therapy and monthly during the maintenance phase of therapy.

Effect on fertility
Interferon may impair fertility (see section 4.6 and section 5.3).

Important information about some of the ingredients of IntronA
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5 mL, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with IntronA.

Interactions between IntronA and other medicinal products have not been fully evaluated. Caution must be exercised when administering IntronA in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dose adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration) (see section 4.4).

Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see sections 4.3, 4.4 and 4.5 of the telbivudine SPC). Moreover, the safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated. Therefore, the combination of IntronA with telbivudine is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Women of childbearing potential have to use effective contraception during treatment. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

IntronA must be used with caution in fertile men.

Combination therapy with ribavirin
Ribavirin causes serious birth defects when administered during pregnancy. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking IntronA in combination with ribavirin. Females of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. IntronA is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Combination therapy with ribavirin
Ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with IntronA, and therefore it is recommended that they avoid driving or operating machinery.

4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/m^2/week in hairy cell leukaemia up to 100 MIU/m^2/week in melanoma), the most commonly reported undesirable effects were pyrexia, fatigue, headache and myalgia. Pyrexia and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

Adults
In clinical trials conducted in the hepatitis C population, patients were treated with IntronA alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of IntronA three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rarely (≥1/10,000 to <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported during clinical trials or following the marketing use of IntronA alone or in combination with ribavirin

System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Pharyngitis*, infection viral*
Common:	Bronchitis, sinusitis, herpes simplex (resistance), rhinitis
Uncommon:	Bacterial infection
Rarely:	Pneumonia§, sepsis
Blood and lymphatic system disorders	
Very common:	Leukopaenia
Common:	Thrombocytopaenia, lymphadenopathy, lymphopenia
Very rarely:	Aplastic anaemia
Not known**:**	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Immune system disorders§	
Very rarely:	Sarcoidosis, exacerbation of sarcoidosis
Not known:	Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis§

Endocrine disorders	
Common:	Hypothyroidism[§], hyperthyroidism[§]
Very rarely:	Diabetes, aggravated diabetes
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hypocalcaemia, dehydration, hyperuricemia, thirst
Very rarely:	Hyperglycaemia, hypertriglyceridaemia[§], increased appetite
Psychiatric disorders[§]	
Very common:	Depression, insomnia, anxiety, emotional lability*, agitation, nervousness
Common:	Confusion, sleep disorder, libido decreased
Rarely:	Suicide ideation
Very rarely:	Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations
Not known:	Homicidal ideation, mental status change[§], mania, bipolar disorders
Nervous system disorders[§]	
Very common:	Dizziness, headache, concentration impaired, mouth dry
Common:	Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion
Uncommon:	Peripheral neuropathy
Very rarely:	Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy
Not known:	Mononeuropathies, coma[§]
Eye disorders	
Very common:	Vision blurred
Common:	Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain
Rarely:	Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§]
Not known:	Serous retinal detachment
Ear and labyrinth	
Common:	Vertigo, tinnitus
Very rarely:	Hearing loss, hearing disorder
Cardiac disorders	
Common:	Palpitation, tachycardia
Rarely:	Cardiomyopathy
Very rarely:	Myocardial infarction, cardiac ischaemia
Not known:	Congestive heart failure, pericardial effusion, arrhythmia
Vascular disorders	
Common:	Hypertension
Very rarely:	Peripheral ischaemia, hypotension[§]
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea*, coughing*
Common:	Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive
Very rarely:	Pulmonary infiltrates[§], pneumonitis[§]
Not known:	Pulmonary fibrosis, pulmonary arterial hypertension[#]

Gastrointestinal disorders	
Very common:	Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia
Common:	Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools
Very rarely:	Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding
Not known:	Periodontal disorder NOS, dental disorder NOS[§]
Hepatobiliary disorders	
Common:	Hepatomegaly
Very rarely:	Hepatotoxicity, (including fatality)
Skin and subcutaneous tissue disorders	Alopecia, pruritus*, skin dry*, rash*, sweating increased
Very common:	Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder
Common:	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Very rarely:	
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, musculoskeletal pain
Common:	Arthritis
Very rarely:	Rhabdomyolysis, myositis, leg cramps, back pain
Renal and urinary disorders	
Common:	Micturition frequency
Very rarely:	Renal failure, renal insufficiency, nephrotic syndrome
Reproductive system and breast disorders	
Common:	Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction*, fatigue, rigors, pyrexia[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise
Common:	Injection site pain
Very rarely:	Injection site necrosis, face oedema
Investigations	
Very common:	Weight decrease

*These events were only common with IntronA alone
[§]See section 4.4
[#]Class label for interferon products, see below Pulmonary arterial hypertension

These undesirable effects have also been reported with IntronA alone.

The undesirable effects seen with hepatitis C are representative of those reported when IntronA is administered in other indications, with some anticipated dose-related increases in incidence. For example, in a trial of high-dose adjuvant IntronA treatment in patients with melanoma, incidences of fatigue, pyrexia, myalgia, neutropaenia/anaemia, anorexia, nausea and vomiting, diarrhoea, chills, flu-like symptoms, depression, alopecia, altered taste, and dizziness were greater than in the hepatitis C trials. Severity also increased with high dose therapy (WHO Grade 3 and 4, in 66 % and 14 % of patients, respectively), in comparison with the mild to moderate severity usually associated with lower doses. Undesirable effects were usually managed by dose adjustment.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4).

Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV-infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Moderate and usually reversible pancytopenia has been reported. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

Children and adolescent population

Chronic Hepatitis C - Combination therapy with ribavirin

In clinical trials of 118 children and adolescents (3 to 16 years of age), 6 % discontinued therapy due to adverse reactions. In general, the adverse reaction profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric- specific concern regarding growth inhibition as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile) were observed during treatment. Within the 5 years follow-up post-treatment period, the children had a mean height of 44th percentile, which was below the median of the normative population and less than their mean baseline height (48th percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years). Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment. During combination therapy for up to 48 weeks with IntronA and ribavirin, growth inhibition was observed that resulted in reduced final adult height in some patients. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from the two multicentre children and adolescent clinical trials. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Adverse reactions very commonly and commonly reported during clinical trials inchildren and adolescent patients treated with IntronA in combination with ribavirin	
System Organ Class	**Adverse Reactions**
Infection and infestations Very common: Common:	 Viral infection, pharyngitis Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Neoplasms benign, malignant and unspecified (including cysts and polyps) Common:	 Neoplasm (unspecified)
Blood and lymphatic system disorders Very common: Common:	 Anaemia, neutropaenia Thrombocytopaenia, lymphadenopathy
Endocrine disorders Very common: Common:	 Hypothyroidism[§], Hyperthyroidism[§], virilism
Metabolism and nutrition disorders Very common: Common:	 Anorexia Hypertriglyceridemia[§], hyperuricemia, increased appetite
Psychiatric disorders[§] Very common: Common:	 Depression, emotional lability, insomnia Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy
Nervous system disorders[§] Very common: Common:	 Headache, dizziness Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence
Eye disorders Common:	 Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Vascular disorders Common:	 Flushing, pallor
Respiratory, thoracic and mediastinal disorders Common:	 Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing
Gastrointestinal disorders Very common: Common:	 Diarrhoea, vomiting, nausea, abdominal pain Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder
Hepatobiliary disorders Common:	 Hepatic function abnormal
Skin and subcutaneous tissue disorders Very common: Common:	 Alopecia, rash Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased

Musculoskeletal and connective tissue disorders Very common:	Arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders Common:	Enuresis, micturition disorder, urinary incontinence
Reproductive system and breast disorders Common:	Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder Male: testicular pain
General disorders and administration site conditions Very common: Common:	Injection site inflammation, injection site reaction, fatigue, rigors, pyrexia[§], influenza-like symptoms[§], malaise, irritability Chest pain, asthenia, oedema, injection site pain
Investigations Very common:	Growth rate decrease (height and/or weight decrease for age)[§]
Injury and poisoning Common:	Skin laceration

[§]See section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: interferon alfa-2b, ATC code: L03A B05

IntronA is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of IntronA is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x 10^8 IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain

several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. IntronA has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/m^2 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C in adult patients
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

IntronA alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of IntronA used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/mL), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

IntronA was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained

virologic response. Sustained virologic response rates for treatment groups treated for one year with IntronA alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of IntronA with ribavirin increased the efficacy of IntronA by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of IntronA + ribavirin, compared with IntronA alone, is maintained across all subgroups. The relative benefit of combination therapy with IntronA + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received IntronA in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

Table 3 Sustained virologic response rates with IntronA + ribavirin (one year of treatment) by genotype and viral load

HCV Genotype	**I** **N=503** **C95-132/I95-143**	**I/R** **N=505** **C95-132/I95-143**	**I/R** **N=505** **C/I98-580**
All Genotypes	**16 %**	**41 %**	**47 %**
Genotype 1	9 %	29 %	33 %
Genotype 1 ≤ 2 million copies/mL	25 %	33 %	45 %
Genotype 1 > 2 million copies/mL	3 %	27 %	29 %
Genotype 2/3	31 %	65 %	79 %

I IntronA (3 MIU 3 times a week)
I/R IntronA (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

HCV/HIV Co-infected patients
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received IntronA plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or IntronA (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or IntronA (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/mL (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

Table 4	Sustained virological response based on genotype after IntronA in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients					
	Study 1[1]			**Study 2**[2]		
	pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg)	IntronA (3 MIU TIW) + ribavirin (800 mg)	p value[a]	pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d]	IntronA (3 MIU TIW) + ribavirin (800-1,200 mg)[d]	p value[b]
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients
A total of 345 interferon alpha relapse patients were treated in two clinical trials with IntronA monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to IntronA increased by as much as 10-fold the efficacy of IntronA used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/mL by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non-pegylated interferon alfa-2b or non-pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

<u>Chronic hepatitis C in children and adolescent population</u>
Three clinical trials have been conducted in children and adolescents; two with standard interferon and ribavirin and one with pegylated interferon and ribavirin. Patients who received IntronA plus ribavirin were less likely to respond than patients who received pegylated interferon alfa-2b and ribavirin.

Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received IntronA 3 MIU/m^2 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. In the two multicentre trials sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in these two multicentre trials for children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

Table 5 Sustained virological response in previously untreated children and adolescents

	IntronA 3 MIU/m^2 3 times a week + **ribavirin 15 mg/kg/day**
Overall Response[a] (n=118)	54 (46 %)*
Genotype 1 (n=92)	33 (36 %)*
Genotype 2/3/4 (n=26)	21 (81 %)*

*Number (%) of patients
[a]Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

Long-term efficacy data
A five-year long-term, observational, follow-up study enrolled 97 paediatric chronic hepatitis C patients after treatment in the standard interferon multicentre trials. Seventy percent (68/97) of all enrolled subjects completed this study of which 75 % (42/56) were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment of the 48-week interferon alfa-2b and ribavirin treatment. All but one of the paediatric subjects remained sustained virologic responders during long-term follow-up after completion of treatment with interferon alfa-2b plus ribavirin. The Kaplan-Meier estimate for continued sustained response over 5 years is 98 % [95 % CI: 95 %, 100 %] for paediatric patients treated with interferon alfa-2b and ribavirin. Additionally, 98 % (51/52) with normal ALT levels at follow-up week 24 maintained normal ALT levels at their last visit.
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b with ribavirin results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Results from the clinical trial conducted with pegylated interferon alfa-2b and ribavirin
In a multicentre trial children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with peginterferon alfa-2b 60 μg/m^2 plus ribavirin 15 mg/kg per day once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of peginterferon alfa-2b with ribavirin needs to be carefully considered in this population (see peginterferon alfa-2b and ribavirin SPCs section 4.4). The study results are summarized in **Table 6.**

Table 6 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects n = 107		
	24 weeks	**48 weeks**
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment, lower limit of detection=125 IU/mL.

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/mL) were to receive 48 weeks of treatment.

5.2 Pharmacokinetic properties

The pharmacokinetics of IntronA were studied in healthy volunteers following single 5 million IU/m^2 and 10 million IU doses administered subcutaneously, at 5 million IU/m^2 administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. C_{max} occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/mL) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

Interferon neutralising factor assays were performed on serum samples of patients who received IntronA in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

Children and adolescent population
Multiple-dose pharmacokinetic properties for IntronA injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 7**. The pharmacokinetics of IntronA and ribavirin (dose-normalized) are similar in adults and children or adolescents.

Table 7 Mean (% CV) multiple-dose pharmacokinetic parameters for IntronA and ribavirin capsules when administered to children or adolescents with chronic hepatitis C		
Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**IntronA** 3 MIU/m^2 3 times a week (n = 54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3,275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	Not done

*AUC_{12} (ng.hr/mL) for ribavirin; AUC_{0-24} (IU.hr/mL) for IntronA

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20×10^6 IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100×10^6 IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

<u>IntronA plus ribavirin</u>
No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if IntronA is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate anhydrous
Sodium dihydrogen phosphate monohydrate
Edetate disodium
Sodium chloride

M-cresol
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

18 months.
Within its shelf-life, for the purpose of transport, the solution can be kept at or below 25ºC for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

0.5 mL of solution (corresponding to 3 MIU) is contained in a single dose vial (type I glass) with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene).

IntronA is supplied as:
- Pack of 1 vial
- Pack of 1 vial, 1 injection syringe of 1 mL, 1 injection needle and 1 cleansing swab
- Pack of 6 vials, 6 injection syringes of 1 mL, 6 injection needles and 6 cleansing swabs
- Pack of 12 vials, 12 injection syringes of 1 mL, 12 injection needles and 12 cleansing swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not all dose forms and strengths are appropriate for some indications. Please make sure to select an appropriate dose form and strength.

IntronA solution for injection or infusion may be injected directly after withdrawal of the appropriate doses from the vial with a sterile injection syringe.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to “How to self inject IntronA”).

Preparation of IntronA for intravenous infusion: The infusion is to be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

No other medicinal product can be infused concomitantly with IntronA.

As with all parenteral medicinal products, prior to administration inspect IntronA, solution for injection or infusion, visually for particulate matter and discolouration. The solution should be clear and colourless.

Any unused medicinal product must be discarded after withdrawal of the dose and in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/127/011
EU/1/99/127/012
EU/1/99/127/013
EU/1/99/127/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 March 2000
Date of latest renewal: 9 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

IntronA 5 million IU/0.5 mL solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of solution for injection or infusion contains 5 million IU of recombinant interferon alfa-2b produced in *E. coli* by recombinant DNA technology, in 0.5 mL of solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B
Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of DNA of hepatitis B virus (HBV-DNA) and hepatitis B antigen (HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic hepatitis C
Before initiating treatment with IntronA, consideration should be given to the results from clinical trials comparing IntronA with pegylated interferon (see section 5.1).

Adult patients
IntronA is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for hepatitis C virus RNA (HCV-RNA) (see section 4.4).

The best way to use IntronA in this indication is in combination with ribavirin.

Children 3 years of age and older and adolescents
IntronA is indicated, in a combination regimen with ribavirin, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients. The decision to treat should be made on a case by case basis (see section 4.4).

Hairy cell leukaemia
Treatment of patients with hairy cell leukaemia.

Chronic myelogenous leukaemia
Monotherapy
Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia.

Clinical experience indicates that a haematological and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is ≥ 34 %, but < 90 % Ph+ cells in the marrow.

Combination therapy
The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.

Multiple myeloma
As maintenance therapy in patients who have achieved objective remission (more than 50 % reduction in myeloma protein) following initial induction chemotherapy.
Current clinical experience indicates that maintenance therapy with interferon alfa-2b prolongs the plateau phase; however, effects on overall survival have not been conclusively demonstrated.

Follicular lymphoma
Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.

Carcinoid tumour
Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome".

Malignant melanoma
As adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement.

4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dose forms and strengths are appropriate for some indications. Appropriate dose form and strength must be selected.

If adverse events develop during the course of treatment with IntronA for any indication, modify the dose or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dose adjustment, or disease progresses, discontinue treatment with IntronA. At the discretion of the physician, the patient may self-administer the dose for maintenance dose regimens administered subcutaneously.

Chronic hepatitis B
The recommended dose is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/mm^3, granulocytes < 1,000/mm^3, thrombocytes < 100,000/mm^3). Treatment should be discontinued in case of severe leukopaenia (< 1,200/mm^3), severe neutropaenia (< 750/mm^3) or severe thrombocytopaenia (< 70,000/mm^3).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue IntronA therapy.

Chronic hepatitis C

Adults

IntronA is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

Children 3 years of age or older and adolescents

IntronA 3 MIU/m^2 is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsules SPC for dose of ribavirin capsules and dose modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC.)

Relapse patients (adults)

IntronA is given in combination with ribavirin. Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for 6 months.

Naïve patients (adults)

The efficacy of IntronA is enhanced when given in combination with ribavirin. IntronA should be given alone mainly in case of intolerance or contraindication to ribavirin.

- IntronA in combination with ribavirin

Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

- IntronA alone

The optimal duration of therapy with IntronA alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with IntronA alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

Naïve patients (children and adolescents)

The efficacy and safety of IntronA in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Duration of treatment for children and adolescents

- Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Therefore, it is recommended that children and adolescent

patients receiving IntronA/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 log_{10} compared to pretreatment, or if they have detectable HCV-RNA at treatment week 24.

- Genotype 2/3: The recommended duration of treatment is 24 weeks.

Hairy cell leukaemia
The recommended dose is 2 million IU/m^2 administered subcutaneously three times a week (every other day) for both splenectomised and non-splenectomised patients. For most patients with Hairy Cell Leukaemia, normalisation of one or more haematological variables occurs within one to two months of IntronA treatment. Improvement in all three haematological variables (granulocyte count, platelet count and haemoglobin level) may require six months or more. This regimen must be maintained unless the disease progresses rapidly or severe intolerance is manifested.

Chronic myelogenous leukaemia
The recommended dose of IntronA is 4 to 5 million IU/m^2 administered daily subcutaneously. Some patients have been shown to benefit from IntronA 5 million IU/m^2 administered daily subcutaneously in association with cytarabine (Ara-C) 20 mg/m^2 administered daily subcutaneously for 10 days per month (up to a maximum daily dose of 40 mg). When the white blood cell count is controlled, administer the maximum tolerated dose of IntronA (4 to 5 million IU/m^2 daily) to maintain haematological remission.

IntronA treatment must be discontinued after 8 to 12 weeks of treatment if at least a partial haematological remission or a clinically meaningful cytoreduction has not been achieved.

Multiple myeloma
Maintenance therapy
In patients who are in the plateau phase (more than 50 % reduction of myeloma protein) following initial induction chemotherapy, interferon alfa-2b may be administered as monotherapy, subcutaneously, at a dose of 3 million IU/m^2 three times a week (every other day).

Follicular lymphoma
Adjunctively with chemotherapy, interferon alfa-2b may be administered subcutaneously, at a dose of 5 million IU three times a week (every other day) for a duration of 18 months. CHOP-like regimens are advised, but clinical experience is available only with CHVP (combination of cyclophosphamide, doxorubicin, teniposide and prednisolone).

Carcinoid tumour
The usual dose is 5 million IU (3 to 9 million IU) administered subcutaneously three times a week (every other day). Patients with advanced disease may require a daily dose of 5 million IU. The treatment is to be temporarily discontinued during and after surgery. Therapy may continue for as long as the patient responds to interferon alfa-2b treatment.

Malignant melanoma
As induction therapy, interferon alfa-2b is administered intravenously at a dose of 20 million IU/m^2 daily for five days a week for a four-week period; the calculated interferon alfa-2b dose is added to sodium chloride 9 mg/mL (0.9 %) solution for injection and administered as a 20-minute infusion (see section 6.6). As maintenance treatment, the recommended dose is 10 million IU/m^2 administered subcutaneously three days a week (every other day) for 48 weeks.

If severe adverse events develop during interferon alfa-2b treatment, particularly if granulocytes decrease to < 500/mm^3 or alanine aminotransferase/aspartate aminotransferase (ALT/AST) rises to > 5 x upper limit of normal, discontinue treatment temporarily until the adverse event abates. Interferon alfa-2b treatment is to be restarted at 50 % of the previous dose. If intolerance persists after dose adjustment or if granulocytes decrease to < 250/mm^3 or ALT/AST rises to > 10 x upper limit of normal, discontinue interferon alfa-2b therapy.

Although the optimal (minimum) dose for full clinical benefit is unknown, patients must be treated at the recommended dose, with dose reduction for toxicity as described.

IntronA may be administered using either glass or plastic disposable injection syringes.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.
- Combination of IntronA with telbivudine.

Children and adolescents
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

4.4 Special warnings and precautions for use

Psychiatric and central nervous system (CNS)
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during IntronA therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents treated with IntronA in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation is identified, it is recommended that treatment with IntronA be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions:
If treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

Patients with substance use/abuse:
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Children and adolescent population: Growth and development (chronic hepatitis C)
During the course of interferon (standard and pegylated)/ribavirin combination therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children (n=20) despite being off treatment for more than 5 years. Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment.

Case by case benefit/risk assessment in children
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response, (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

Hypersensitivity reactions
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during IntronA therapy. If such a reaction develops, discontinue the medicine and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Adverse experiences including prolongation of coagulation markers and liver abnormalities
Moderate to severe adverse experiences may require modification of the patient's dose regimen, or in some cases, termination of IntronA therapy. IntronA increases the risk of liver decompensation and death in patients with cirrhosis.
Discontinue treatment with IntronA in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decomposition.
Any patient developing liver function abnormalities during treatment with IntronA must be monitored closely and treatment discontinued if signs and symptoms progress.
Liver enzymes and hepatic function should be closely monitored in cirrhotic patients.

Hypotension
Hypotension may occur during IntronA therapy or up to two days post-therapy and may require supportive treatment.

Need for adequate hydration
Adequate hydration must be maintained in patients undergoing IntronA therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Pyrexia
While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Patients with debilitating medical conditions
IntronA must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary conditions
Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events
Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, serous retinal detachment, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with IntronA, must have a prompt and complete eye examination. Periodic visual examinations during IntronA therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of IntronA should be considered in patients who develop new or worsening ophthalmological disorders.

Obtundation, coma and encephalopathy
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of IntronA.

Patients with pre-existing cardiac abnormalities
Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require IntronA therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of IntronA therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia
Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Patients with psoriasis and sarcoidosis
Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of IntronA in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Kidney and liver graft rejection
Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Auto-antibodies and autoimmune disorders
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Concomitant chemotherapy
Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered medicinal product. The most commonly reported potentially life-threatening or fatal adverse events include mucositis, diarrhoea, neutropaenia, renal impairment, and electrolyte disturbance. Because of the risk of increased toxicity, careful adjustments of doses are required for IntronA and for the concomitant chemotherapeutic agents (see section 4.5). When IntronA is used with hydroxyurea, the frequency and severity of cutaneous vasculitis may be increased.

Chronic hepatitis C
Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy
Infrequently, adult patients treated for chronic hepatitis C with IntronA developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using IntronA therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which IntronA may alter thyroid status is unknown. Prior to initiation of IntronA therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of IntronA therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, IntronA treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of IntronA therapy has not reversed thyroid dysfunction occurring during treatment (also see Thyroid supplemental monitoring specific for children and adolescents).

Thyroid supplemental monitoring specific for children and adolescents
Approximately 12 % of children treated with interferon alfa-2b and ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of IntronA therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding IntronA and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with IntronA and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of IntronA and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with IntronA.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during IntronA therapy to greater than or equal to 2 times baseline, IntronA therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, the following liver function tests must be monitored at two-week intervals: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin.

In patients treated for malignant melanoma, liver function and white blood cell (WBC) count and differential must be monitored weekly during the induction phase of therapy and monthly during the maintenance phase of therapy.

Effect on fertility
Interferon may impair fertility (see section 4.6 and section 5.3).

Important information about some of the ingredients of IntronA
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5 mL, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with IntronA.

Interactions between IntronA and other medicinal products have not been fully evaluated. Caution must be exercised when administering IntronA in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dose adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration) (see section 4.4).

Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see sections 4.3, 4.4 and 4.5 of the telbivudine SPC). Moreover, the safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated. Therefore, the combination of IntronA with telbivudine is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Women of childbearing potential have to use effective contraception during treatment. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

IntronA must be used with caution in fertile men.

Combination therapy with ribavirin
Ribavirin causes serious birth defects when administered during pregnancy. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking IntronA in combination with ribavirin. Females of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. IntronA is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Combination therapy with ribavirin
Ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with IntronA, and therefore it is recommended that they avoid driving or operating machinery.

4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/m^2/week in hairy cell leukaemia up to 100 MIU/m^2/week in melanoma), the most commonly reported undesirable effects were pyrexia, fatigue, headache and myalgia. Pyrexia and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

Adults
In clinical trials conducted in the hepatitis C population, patients were treated with IntronA alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of IntronA three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rarely (≥1/10,000 to <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported during clinical trials or following the marketing use of IntronA alone or in combination with ribavirin

System Organ Class	Adverse Reactions
Infections and infestations	
Very common:	Pharyngitis*, infection viral*
Common:	Bronchitis, sinusitis, herpes simplex (resistance), rhinitis
Uncommon:	Bacterial infection
Rarely:	Pneumonia§, sepsis
Blood and lymphatic system disorders	
Very common:	Leukopaenia
Common:	Thrombocytopaenia, lymphadenopathy, lymphopenia
Very rarely:	Aplastic anaemia
Not known**:**	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Immune system disorders§	
Very rarely:	Sarcoidosis, exacerbation of sarcoidosis
Not known:	Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis§

Endocrine disorders	
Common:	Hypothyroidism[§], hyperthyroidism[§]
Very rarely:	Diabetes, aggravated diabetes
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hypocalcaemia, dehydration, hyperuricemia, thirst
Very rarely:	Hyperglycaemia, hypertriglyceridaemia[§], increased appetite
Psychiatric disorders[§]	
Very common:	Depression, insomnia, anxiety, emotional lability*, agitation, nervousness
Common:	Confusion, sleep disorder, libido decreased
Rarely:	Suicide ideation
Very rarely:	Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations
Not known:	Homicidal ideation, mental status change[§], mania, bipolar disorders
Nervous system disorders[§]	
Very common:	Dizziness, headache, concentration impaired, mouth dry
Common:	Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion
Uncommon:	Peripheral neuropathy
Very rarely:	Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy
Not known:	Mononeuropathies, coma[§]
Eye disorders	
Very common:	Vision blurred
Common:	Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain
Rarely:	Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§]
Not known:	Serous retinal detachment
Ear and labyrinth	
Common:	Vertigo, tinnitus
Very rarely:	Hearing loss, hearing disorder
Cardiac disorders	
Common:	Palpitation, tachycardia
Rarely:	Cardiomyopathy
Very rarely:	Myocardial infarction, cardiac ischaemia
Not known:	Congestive heart failure, pericardial effusion, arrhythmia
Vascular disorders	
Common:	Hypertension
Very rarely:	Peripheral ischaemia, hypotension[§]
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea*, coughing*
Common:	Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive
Very rarely:	Pulmonary infiltrates[§], pneumonitis[§]
Not known:	Pulmonary fibrosis, pulmonary arterial hypertension[#]

Gastrointestinal disorders	
Very common:	Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia
Common:	Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools
Very rarely:	Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding
Not known:	Periodontal disorder NOS, dental disorder NOS[§]
Hepatobiliary disorders	
Common:	Hepatomegaly
Very rarely:	Hepatotoxicity, (including fatality)
Skin and subcutaneous tissue disorders	Alopecia, pruritus*, skin dry*, rash*, sweating increased
Very common:	Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder
Common:	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Very rarely:	
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, musculoskeletal pain
Common:	Arthritis
Very rarely:	Rhabdomyolysis, myositis, leg cramps, back pain
Renal and urinary disorders	
Common:	Micturition frequency
Very rarely:	Renal failure, renal insufficiency, nephrotic syndrome
Reproductive system and breast disorders	
Common:	Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction*, fatigue, rigors, pyrexia[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise
Common:	Injection site pain
Very rarely:	Injection site necrosis, face oedema
Investigations	
Very common:	Weight decrease

*These events were only common with IntronA alone
[§]See section 4.4
[#]Class label for interferon products, see below Pulmonary arterial hypertension

These undesirable effects have also been reported with IntronA alone.

The undesirable effects seen with hepatitis C are representative of those reported when IntronA is administered in other indications, with some anticipated dose-related increases in incidence. For example, in a trial of high-dose adjuvant IntronA treatment in patients with melanoma, incidences of fatigue, pyrexia, myalgia, neutropaenia/anaemia, anorexia, nausea and vomiting, diarrhoea, chills, flu-like symptoms, depression, alopecia, altered taste, and dizziness were greater than in the hepatitis C trials. Severity also increased with high dose therapy (WHO Grade 3 and 4, in 66 % and 14 % of patients, respectively), in comparison with the mild to moderate severity usually associated with lower doses. Undesirable effects were usually managed by dose adjustment.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4).

Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV-infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Moderate and usually reversible pancytopenia has been reported. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

Children and adolescent population

Chronic Hepatitis C - Combination therapy with ribavirin

In clinical trials of 118 children and adolescents (3 to 16 years of age), 6 % discontinued therapy due to adverse reactions. In general, the adverse reaction profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric- specific concern regarding growth inhibition as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile) were observed during treatment. Within the 5 years follow-up post-treatment period, the children had a mean height of 44^{th} percentile, which was below the median of the normative population and less than their mean baseline height (48^{th} percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years). Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment. During combination therapy for up to 48 weeks with IntronA and ribavirin, growth inhibition was observed that resulted in reduced final adult height in some patients. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from the two multicentre children and adolescent clinical trials. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Adverse reactions very commonly and commonly reported during clinical trials inchildren and adolescent patients treated with IntronA in combination with ribavirin	
System Organ Class	**Adverse Reactions**
Infection and infestations Very common: Common:	 Viral infection, pharyngitis Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Neoplasms benign, malignant and unspecified (including cysts and polyps) Common:	 Neoplasm (unspecified)
Blood and lymphatic system disorders Very common: Common:	 Anaemia, neutropaenia Thrombocytopaenia, lymphadenopathy
Endocrine disorders Very common: Common:	 Hypothyroidism[§], Hyperthyroidism[§], virilism
Metabolism and nutrition disorders Very common: Common:	 Anorexia Hypertriglyceridemia[§], hyperuricemia, increased appetite
Psychiatric disorders[§] Very common: Common:	 Depression, emotional lability, insomnia Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy
Nervous system disorders[§] Very common: Common:	 Headache, dizziness Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence
Eye disorders Common:	 Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Vascular disorders Common:	 Flushing, pallor
Respiratory, thoracic and mediastinal disorders Common:	 Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing
Gastrointestinal disorders Very common: Common:	 Diarrhoea, vomiting, nausea, abdominal pain Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder
Hepatobiliary disorders Common:	 Hepatic function abnormal
Skin and subcutaneous tissue disorders Very common: Common:	 Alopecia, rash Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased

Musculoskeletal and connective tissue disorders Very common:	Arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders Common:	Enuresis, micturition disorder, urinary incontinence
Reproductive system and breast disorders Common:	Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder Male: testicular pain
General disorders and administration site conditions Very common: Common:	Injection site inflammation, injection site reaction, fatigue, rigors, pyrexia[§], influenza-like symptoms[§], malaise, irritability Chest pain, asthenia, oedema, injection site pain
Investigations Very common:	Growth rate decrease (height and/or weight decrease for age)[§]
Injury and poisoning Common:	Skin laceration

[§]See section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: interferon alfa-2b, ATC code: L03A B05

IntronA is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of IntronA is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x 10^8 IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain

several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. IntronA has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/m^2 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C in adult patients
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

IntronA alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of IntronA used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/mL), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

IntronA was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained

virologic response. Sustained virologic response rates for treatment groups treated for one year with IntronA alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of IntronA with ribavirin increased the efficacy of IntronA by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of IntronA + ribavirin, compared with IntronA alone, is maintained across all subgroups. The relative benefit of combination therapy with IntronA + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received IntronA in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

Table 3 Sustained virologic response rates with IntronA + ribavirin (one year of treatment) by genotype and viral load

HCV Genotype	**I** **N=503** **C95-132/I95-143**	**I/R** **N=505** **C95-132/I95-143**	**I/R** **N=505** **C/I98-580**
All Genotypes	**16 %**	**41 %**	**47 %**
Genotype 1	9 %	29 %	33 %
Genotype 1 ≤ 2 million copies/mL	25 %	33 %	45 %
Genotype 1 > 2 million copies/mL	3 %	27 %	29 %
Genotype 2/3	31 %	65 %	79 %

I IntronA (3 MIU 3 times a week)
I/R IntronA (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

HCV/HIV Co-infected patients
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received IntronA plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or IntronA (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or IntronA (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/mL (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

Table 4	Sustained virological response based on genotype after IntronA in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients					
	Study 1[1]			**Study 2**[2]		
	pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg)	IntronA (3 MIU TIW) + ribavirin (800 mg)	p value[a]	pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d]	IntronA (3 MIU TIW) + ribavirin (800-1,200 mg)[d]	p value[b]
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients
A total of 345 interferon alpha relapse patients were treated in two clinical trials with IntronA monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to IntronA increased by as much as 10-fold the efficacy of IntronA used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/mL by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non-pegylated interferon alfa-2b or non-pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

<u>Chronic hepatitis C in children and adolescent population</u>
Three clinical trials have been conducted in children and adolescents; two with standard interferon and ribavirin and one with pegylated interferon and ribavirin. Patients who received IntronA plus ribavirin were less likely to respond than patients who received pegylated interferon alfa-2b and ribavirin.

Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received IntronA 3 MIU/m^2 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. In the two multicentre trials sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in these two multicentre trials for children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

Table 5 Sustained virological response in previously untreated children and adolescents

	IntronA 3 MIU/m^2 3 times a week + **ribavirin 15 mg/kg/day**
Overall Response[a] (n=118)	54 (46 %)*
Genotype 1 (n=92)	33 (36 %)*
Genotype 2/3/4 (n=26)	21 (81 %)*

*Number (%) of patients

[a] Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

Long-term efficacy data

A five-year long-term, observational, follow-up study enrolled 97 paediatric chronic hepatitis C patients after treatment in the standard interferon multicentre trials. Seventy percent (68/97) of all enrolled subjects completed this study of which 75 % (42/56) were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment of the 48-week interferon alfa-2b and ribavirin treatment. All but one of the paediatric subjects remained sustained virologic responders during long-term follow-up after completion of treatment with interferon alfa-2b plus ribavirin. The Kaplan-Meier estimate for continued sustained response over 5 years is 98 % [95 % CI: 95 %, 100 %] for paediatric patients treated with interferon alfa-2b and ribavirin. Additionally, 98 % (51/52) with normal ALT levels at follow-up week 24 maintained normal ALT levels at their last visit.

SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b with ribavirin results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Results from the clinical trial conducted with pegylated interferon alfa-2b and ribavirin

In a multicentre trial children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with peginterferon alfa-2b 60 μg/m^2 plus ribavirin 15 mg/kg per day once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of peginterferon alfa-2b with ribavirin needs to be carefully considered in this population (see peginterferon alfa-2b and ribavirin SPCs section 4.4). The study results are summarized in **Table 6.**

Table 6 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects n = 107		
	24 weeks	**48 weeks**
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment, lower limit of detection=125 IU/mL.

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/mL) were to receive 48 weeks of treatment.

5.2 Pharmacokinetic properties

The pharmacokinetics of IntronA were studied in healthy volunteers following single 5 million IU/m^2 and 10 million IU doses administered subcutaneously, at 5 million IU/m^2 administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. C_{max} occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/mL) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

Interferon neutralising factor assays were performed on serum samples of patients who received IntronA in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

Children and adolescent population
Multiple-dose pharmacokinetic properties for IntronA injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 7**. The pharmacokinetics of IntronA and ribavirin (dose-normalized) are similar in adults and children or adolescents.

Table 7 Mean (% CV) multiple-dose pharmacokinetic parameters for IntronA and ribavirin capsules when administered to children or adolescents with chronic hepatitis C		
Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**IntronA** 3 MIU/m^2 3 times a week (n = 54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3,275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	Not done

*AUC_{12} (ng.hr/mL) for ribavirin; AUC_{0-24} (IU.hr/mL) for IntronA

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x 10^6 IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x 10^6 IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

<u>IntronA plus ribavirin</u>
No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if IntronA is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate anhydrous
Sodium dihydrogen phosphate monohydrate
Edetate disodium
Sodium chloride

M-cresol
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

18 months.
Within its shelf-life, for the purpose of transport, the solution can be kept at or below 25ºC for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

0.5 mL of solution (corresponding to 5 MIU) is contained in a single dose vial (type I glass) with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene).

IntronA is supplied as:
- Pack of 1 vial
- Pack of 1 vial, 1 injection syringe of 1 mL, 1 injection needle and 1 cleansing swab
- Pack of 6 vials, 6 injection syringes of 1 mL, 6 injection needles and 6 cleansing swabs
- Pack of 12 vials, 12 injection syringes of 1 mL, 12 injection needles and 12 cleansing swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not all dose forms and strengths are appropriate for some indications. Please make sure to select an appropriate dose form and strength.

IntronA solution for injection or infusion may be injected directly after withdrawal of the appropriate doses from the vial with a sterile injection syringe.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to “How to self inject IntronA”).

Preparation of IntronA for intravenous infusion: The infusion is to be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

No other medicinal product can be infused concomitantly with IntronA.

As with all parenteral medicinal products, prior to administration inspect IntronA, solution for injection or infusion, visually for particulate matter and discolouration. The solution should be clear and colourless.

Any unused medicinal product must be discarded after withdrawal of the dose and in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/127/015
EU/1/99/127/016
EU/1/99/127/017
EU/1/99/127/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 March 2000
Date of latest renewal: 9 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

IntronA 10 million IU/mL solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of solution for injection or infusion contains 10 million IU of recombinant interferon alfa-2b produced in *E. coli* by recombinant DNA technology, in 1 mL of solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B
Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of DNA of hepatitis B virus (HBV-DNA) and hepatitis B antigen (HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic hepatitis C
Before initiating treatment with IntronA, consideration should be given to the results from clinical trials comparing IntronA with pegylated interferon (see section 5.1).

Adult patients
IntronA is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for hepatitis C virus RNA (HCV-RNA) (see section 4.4).

The best way to use IntronA in this indication is in combination with ribavirin.

Children 3 years of age and older and adolescents
IntronA is indicated, in a combination regimen with ribavirin, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients. The decision to treat should be made on a case by case basis (see section 4.4).

Hairy cell leukaemia
Treatment of patients with hairy cell leukaemia.

Chronic myelogenous leukaemia
Monotherapy
Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia.

Clinical experience indicates that a haematological and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is ≥ 34 %, but < 90 % Ph+ cells in the marrow.

Combination therapy
The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.

Multiple myeloma
As maintenance therapy in patients who have achieved objective remission (more than 50 % reduction in myeloma protein) following initial induction chemotherapy.
Current clinical experience indicates that maintenance therapy with interferon alfa-2b prolongs the plateau phase; however, effects on overall survival have not been conclusively demonstrated.

Follicular lymphoma
Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.

Carcinoid tumour
Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome".

Malignant melanoma
As adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement.

4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dose forms and strengths are appropriate for some indications. Appropriate dose form and strength must be selected.

If adverse events develop during the course of treatment with IntronA for any indication, modify the dose or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dose adjustment, or disease progresses, discontinue treatment with IntronA. At the discretion of the physician, the patient may self-administer the dose for maintenance dose regimens administered subcutaneously.

Chronic hepatitis B
The recommended dose is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/mm^3, granulocytes < 1,000/mm^3, thrombocytes < 100,000/mm^3). Treatment should be discontinued in case of severe leukopaenia (< 1,200/mm^3), severe neutropaenia (< 750/mm^3) or severe thrombocytopaenia (< 70,000/mm^3).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue IntronA therapy.

Chronic hepatitis C

Adults

IntronA is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

Children 3 years of age or older and adolescents

IntronA 3 MIU/m^2 is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsules SPC for dose of ribavirin capsules and dose modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC.)

Relapse patients (adults)

IntronA is given in combination with ribavirin. Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for 6 months.

Naïve patients (adults)

The efficacy of IntronA is enhanced when given in combination with ribavirin. IntronA should be given alone mainly in case of intolerance or contraindication to ribavirin.

- IntronA in combination with ribavirin

Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

- IntronA alone

The optimal duration of therapy with IntronA alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with IntronA alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

Naïve patients (children and adolescents)

The efficacy and safety of IntronA in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Duration of treatment for children and adolescents

- Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Therefore, it is recommended that children and adolescent

patients receiving IntronA/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 log_{10} compared to pretreatment, or if they have detectable HCV-RNA at treatment week 24.

- Genotype 2/3: The recommended duration of treatment is 24 weeks.

Hairy cell leukaemia
The recommended dose is 2 million IU/m^2 administered subcutaneously three times a week (every other day) for both splenectomised and non-splenectomised patients. For most patients with Hairy Cell Leukaemia, normalisation of one or more haematological variables occurs within one to two months of IntronA treatment. Improvement in all three haematological variables (granulocyte count, platelet count and haemoglobin level) may require six months or more. This regimen must be maintained unless the disease progresses rapidly or severe intolerance is manifested.

Chronic myelogenous leukaemia
The recommended dose of IntronA is 4 to 5 million IU/m^2 administered daily subcutaneously. Some patients have been shown to benefit from IntronA 5 million IU/m^2 administered daily subcutaneously in association with cytarabine (Ara-C) 20 mg/m^2 administered daily subcutaneously for 10 days per month (up to a maximum daily dose of 40 mg). When the white blood cell count is controlled, administer the maximum tolerated dose of IntronA (4 to 5 million IU/m^2 daily) to maintain haematological remission.

IntronA treatment must be discontinued after 8 to 12 weeks of treatment if at least a partial haematological remission or a clinically meaningful cytoreduction has not been achieved.

Multiple myeloma
Maintenance therapy
In patients who are in the plateau phase (more than 50 % reduction of myeloma protein) following initial induction chemotherapy, interferon alfa-2b may be administered as monotherapy, subcutaneously, at a dose of 3 million IU/m^2 three times a week (every other day).

Follicular lymphoma
Adjunctively with chemotherapy, interferon alfa-2b may be administered subcutaneously, at a dose of 5 million IU three times a week (every other day) for a duration of 18 months. CHOP-like regimens are advised, but clinical experience is available only with CHVP (combination of cyclophosphamide, doxorubicin, teniposide and prednisolone).

Carcinoid tumour
The usual dose is 5 million IU (3 to 9 million IU) administered subcutaneously three times a week (every other day). Patients with advanced disease may require a daily dose of 5 million IU. The treatment is to be temporarily discontinued during and after surgery. Therapy may continue for as long as the patient responds to interferon alfa-2b treatment.

Malignant melanoma
As induction therapy, interferon alfa-2b is administered intravenously at a dose of 20 million IU/m^2 daily for five days a week for a four-week period; the calculated interferon alfa-2b dose is added to sodium chloride 9 mg/mL (0.9 %) solution for injection and administered as a 20-minute infusion (see section 6.6). As maintenance treatment, the recommended dose is 10 million IU/m^2 administered subcutaneously three days a week (every other day) for 48 weeks.

If severe adverse events develop during interferon alfa-2b treatment, particularly if granulocytes decrease to < 500/mm^3 or alanine aminotransferase/aspartate aminotransferase (ALT/AST) rises to > 5 x upper limit of normal, discontinue treatment temporarily until the adverse event abates. Interferon alfa-2b treatment is to be restarted at 50 % of the previous dose. If intolerance persists after dose adjustment or if granulocytes decrease to < 250/mm^3 or ALT/AST rises to > 10 x upper limit of normal, discontinue interferon alfa-2b therapy.

Although the optimal (minimum) dose for full clinical benefit is unknown, patients must be treated at the recommended dose, with dose reduction for toxicity as described.

IntronA may be administered using either glass or plastic disposable injection syringes.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.
- Combination of IntronA with telbivudine.

Children and adolescents
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

4.4 Special warnings and precautions for use

Psychiatric and central nervous system (CNS)
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during IntronA therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents treated with IntronA in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation is identified, it is recommended that treatment with IntronA be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions:
If treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

Patients with substance use/abuse:
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Children and adolescent population: Growth and development (chronic hepatitis C)
During the course of interferon (standard and pegylated)/ribavirin combination therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children (n=20) despite being off treatment for more than 5 years. Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment.

Case by case benefit/risk assessment in children
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response, (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

Hypersensitivity reactions
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during IntronA therapy. If such a reaction develops, discontinue the medicine and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Adverse experiences including prolongation of coagulation markers and liver abnormalities
Moderate to severe adverse experiences may require modification of the patient's dose regimen, or in some cases, termination of IntronA therapy. IntronA increases the risk of liver decompensation and death in patients with cirrhosis.
Discontinue treatment with IntronA in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decomposition.
Any patient developing liver function abnormalities during treatment with IntronA must be monitored closely and treatment discontinued if signs and symptoms progress.
Liver enzymes and hepatic function should be closely monitored in cirrhotic patients.

Hypotension
Hypotension may occur during IntronA therapy or up to two days post-therapy and may require supportive treatment.

Need for adequate hydration
Adequate hydration must be maintained in patients undergoing IntronA therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Pyrexia
While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Patients with debilitating medical conditions
IntronA must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary conditions
Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events
Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, serous retinal detachment, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with IntronA, must have a prompt and complete eye examination. Periodic visual examinations during IntronA therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of IntronA should be considered in patients who develop new or worsening ophthalmological disorders.

Obtundation, coma and encephalopathy
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of IntronA.

Patients with pre-existing cardiac abnormalities
Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require IntronA therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of IntronA therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia
Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Patients with psoriasis and sarcoidosis
Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of IntronA in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Kidney and liver graft rejection
Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Auto-antibodies and autoimmune disorders
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Concomitant chemotherapy
Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered medicinal product. The most commonly reported potentially life-threatening or fatal adverse events include mucositis, diarrhoea, neutropaenia, renal impairment, and electrolyte disturbance. Because of the risk of increased toxicity, careful adjustments of doses are required for IntronA and for the concomitant chemotherapeutic agents (see section 4.5). When IntronA is used with hydroxyurea, the frequency and severity of cutaneous vasculitis may be increased.

Chronic hepatitis C
Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy
Infrequently, adult patients treated for chronic hepatitis C with IntronA developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using IntronA therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which IntronA may alter thyroid status is unknown. Prior to initiation of IntronA therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of IntronA therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, IntronA treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of IntronA therapy has not reversed thyroid dysfunction occurring during treatment (also see Thyroid supplemental monitoring specific for children and adolescents).

Thyroid supplemental monitoring specific for children and adolescents
Approximately 12 % of children treated with interferon alfa-2b and ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of IntronA therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding IntronA and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with IntronA and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of IntronA and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with IntronA.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during IntronA therapy to greater than or equal to 2 times baseline, IntronA therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, the following liver function tests must be monitored at two-week intervals: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin.

In patients treated for malignant melanoma, liver function and white blood cell (WBC) count and differential must be monitored weekly during the induction phase of therapy and monthly during the maintenance phase of therapy.

Effect on fertility
Interferon may impair fertility (see section 4.6 and section 5.3).

Important information about some of the ingredients of IntronA
This medicinal product contains less than 1 mmol sodium (23 mg) per 1 mL, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with IntronA.

Interactions between IntronA and other medicinal products have not been fully evaluated. Caution must be exercised when administering IntronA in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dose adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration) (see section 4.4).

Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see sections 4.3, 4.4 and 4.5 of the telbivudine SPC). Moreover, the safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated. Therefore, the combination of IntronA with telbivudine is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Women of childbearing potential have to use effective contraception during treatment. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

IntronA must be used with caution in fertile men.

Combination therapy with ribavirin
Ribavirin causes serious birth defects when administered during pregnancy. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking IntronA in combination with ribavirin. Females of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. IntronA is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Combination therapy with ribavirin
Ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with IntronA, and therefore it is recommended that they avoid driving or operating machinery.

4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/m^2/week in hairy cell leukaemia up to 100 MIU/m^2/week in melanoma), the most commonly reported undesirable effects were pyrexia, fatigue, headache and myalgia. Pyrexia and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

Adults
In clinical trials conducted in the hepatitis C population, patients were treated with IntronA alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of IntronA three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rarely (≥1/10,000 to <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported during clinical trials or following the marketing use of IntronA alone or in combination with ribavirin

System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Pharyngitis*, infection viral*
Common:	Bronchitis, sinusitis, herpes simplex (resistance), rhinitis
Uncommon:	Bacterial infection
Rarely:	Pneumonia§, sepsis
Blood and lymphatic system disorders	
Very common:	Leukopaenia
Common:	Thrombocytopaenia, lymphadenopathy, lymphopenia
Very rarely:	Aplastic anaemia
Not known**:**	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Immune system disorders§	
Very rarely:	Sarcoidosis, exacerbation of sarcoidosis
Not known:	Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis§

Endocrine disorders	
Common:	Hypothyroidism[§], hyperthyroidism[§]
Very rarely:	Diabetes, aggravated diabetes
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hypocalcaemia, dehydration, hyperuricemia, thirst
Very rarely:	Hyperglycaemia, hypertriglyceridaemia[§], increased appetite
Psychiatric disorders[§]	
Very common:	Depression, insomnia, anxiety, emotional lability*, agitation, nervousness
Common:	Confusion, sleep disorder, libido decreased
Rarely:	Suicide ideation
Very rarely:	Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations
Not known:	Homicidal ideation, mental status change[§], mania, bipolar disorders
Nervous system disorders[§]	
Very common:	Dizziness, headache, concentration impaired, mouth dry
Common:	Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion
Uncommon:	Peripheral neuropathy
Very rarely:	Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy
Not known:	Mononeuropathies, coma[§]
Eye disorders	
Very common:	Vision blurred
Common:	Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain
Rarely:	Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§]
Not known:	Serous retinal detachment
Ear and labyrinth	
Common:	Vertigo, tinnitus
Very rarely:	Hearing loss, hearing disorder
Cardiac disorders	
Common:	Palpitation, tachycardia
Rarely:	Cardiomyopathy
Very rarely:	Myocardial infarction, cardiac ischaemia
Not known:	Congestive heart failure, pericardial effusion, arrhythmia
Vascular disorders	
Common:	Hypertension
Very rarely:	Peripheral ischaemia, hypotension[§]
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea*, coughing*
Common:	Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive
Very rarely:	Pulmonary infiltrates[§], pneumonitis[§]
Not known:	Pulmonary fibrosis, pulmonary arterial hypertension[#]

Gastrointestinal disorders	
Very common:	Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia
Common:	Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools
Very rarely:	Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding
Not known:	Periodontal disorder NOS, dental disorder NOS[§]
Hepatobiliary disorders	
Common:	Hepatomegaly
Very rarely:	Hepatotoxicity, (including fatality)
Skin and subcutaneous tissue disorders	Alopecia, pruritus*, skin dry*, rash*, sweating increased
Very common:	Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder
Common:	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Very rarely:	
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, musculoskeletal pain
Common:	Arthritis
Very rarely:	Rhabdomyolysis, myositis, leg cramps, back pain
Renal and urinary disorders	
Common:	Micturition frequency
Very rarely:	Renal failure, renal insufficiency, nephrotic syndrome
Reproductive system and breast disorders	
Common:	Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction*, fatigue, rigors, pyrexia[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise
Common:	Injection site pain
Very rarely:	Injection site necrosis, face oedema
Investigations	
Very common:	Weight decrease

*These events were only common with IntronA alone
[§]See section 4.4
[#]Class label for interferon products, see below Pulmonary arterial hypertension

These undesirable effects have also been reported with IntronA alone.

The undesirable effects seen with hepatitis C are representative of those reported when IntronA is administered in other indications, with some anticipated dose-related increases in incidence. For example, in a trial of high-dose adjuvant IntronA treatment in patients with melanoma, incidences of fatigue, pyrexia, myalgia, neutropaenia/anaemia, anorexia, nausea and vomiting, diarrhoea, chills, flu-like symptoms, depression, alopecia, altered taste, and dizziness were greater than in the hepatitis C trials. Severity also increased with high dose therapy (WHO Grade 3 and 4, in 66 % and 14 % of patients, respectively), in comparison with the mild to moderate severity usually associated with lower doses. Undesirable effects were usually managed by dose adjustment.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4).

Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV-infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Moderate and usually reversible pancytopenia has been reported. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

Children and adolescent population

Chronic Hepatitis C - Combination therapy with ribavirin

In clinical trials of 118 children and adolescents (3 to 16 years of age), 6 % discontinued therapy due to adverse reactions. In general, the adverse reaction profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric- specific concern regarding growth inhibition as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile) were observed during treatment. Within the 5 years follow-up post-treatment period, the children had a mean height of 44th percentile, which was below the median of the normative population and less than their mean baseline height (48th percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years). Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment. During combination therapy for up to 48 weeks with IntronA and ribavirin, growth inhibition was observed that resulted in reduced final adult height in some patients. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from the two multicentre children and adolescent clinical trials. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Adverse reactions very commonly and commonly reported during clinical trials inchildren and adolescent patients treated with IntronA in combination with ribavirin	
System Organ Class	**Adverse Reactions**
Infection and infestations Very common: Common:	 Viral infection, pharyngitis Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Neoplasms benign, malignant and unspecified (including cysts and polyps) Common:	 Neoplasm (unspecified)
Blood and lymphatic system disorders Very common: Common:	 Anaemia, neutropaenia Thrombocytopaenia, lymphadenopathy
Endocrine disorders Very common: Common:	 Hypothyroidism[§], Hyperthyroidism[§], virilism
Metabolism and nutrition disorders Very common: Common:	 Anorexia Hypertriglyceridemia[§], hyperuricemia, increased appetite
Psychiatric disorders[§] Very common: Common:	 Depression, emotional lability, insomnia Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy
Nervous system disorders[§] Very common: Common:	 Headache, dizziness Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence
Eye disorders Common:	 Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Vascular disorders Common:	 Flushing, pallor
Respiratory, thoracic and mediastinal disorders Common:	 Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing
Gastrointestinal disorders Very common: Common:	 Diarrhoea, vomiting, nausea, abdominal pain Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder
Hepatobiliary disorders Common:	 Hepatic function abnormal
Skin and subcutaneous tissue disorders Very common: Common:	 Alopecia, rash Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased

Musculoskeletal and connective tissue disorders Very common:	Arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders Common:	Enuresis, micturition disorder, urinary incontinence
Reproductive system and breast disorders Common:	Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder Male: testicular pain
General disorders and administration site conditions Very common: Common:	Injection site inflammation, injection site reaction, fatigue, rigors, pyrexia[§], influenza-like symptoms[§], malaise, irritability Chest pain, asthenia, oedema, injection site pain
Investigations Very common:	Growth rate decrease (height and/or weight decrease for age)[§]
Injury and poisoning Common:	Skin laceration

[§]See section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: interferon alfa-2b, ATC code: L03A B05

IntronA is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of IntronA is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x 10^8 IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain

several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. IntronA has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/m^2 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C in adult patients
In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

IntronA alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of IntronA used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/mL), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

IntronA was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained

virologic response. Sustained virologic response rates for treatment groups treated for one year with IntronA alone or in combination with ribavirin (from two studies) are shown in **Table 3.**

Co-administration of IntronA with ribavirin increased the efficacy of IntronA by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of IntronA + ribavirin, compared with IntronA alone, is maintained across all subgroups. The relative benefit of combination therapy with IntronA + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received IntronA in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

Table 3 Sustained virologic response rates with IntronA + ribavirin (one year of treatment) by genotype and viral load

HCV Genotype	**I N=503 C95-132/I95-143**	**I/R N=505 C95-132/I95-143**	**I/R N=505 C/I98-580**
All Genotypes	**16 %**	**41 %**	**47 %**
Genotype 1	9 %	29 %	33 %
Genotype 1 ≤ 2 million copies/mL	25 %	33 %	45 %
Genotype 1 > 2 million copies/mL	3 %	27 %	29 %
Genotype 2/3	31 %	65 %	79 %

I IntronA (3 MIU 3 times a week)
I/R IntronA (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

HCV/HIV Co-infected patients
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received IntronA plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or IntronA (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or IntronA (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/mL (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

Table 4	Sustained virological response based on genotype after IntronA in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients					
	Study 1[1]			**Study 2**[2]		
	pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg)	IntronA (3 MIU TIW) + ribavirin (800 mg)	p value[a]	pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d]	IntronA (3 MIU TIW) + ribavirin (800-1,200 mg)[d]	p value[b]
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients
A total of 345 interferon alpha relapse patients were treated in two clinical trials with IntronA monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to IntronA increased by as much as 10-fold the efficacy of IntronA used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/mL by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non-pegylated interferon alfa-2b or non-pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

<u>Chronic hepatitis C in children and adolescent population</u>
Three clinical trials have been conducted in children and adolescents; two with standard interferon and ribavirin and one with pegylated interferon and ribavirin. Patients who received IntronA plus ribavirin were less likely to respond than patients who received pegylated interferon alfa-2b and ribavirin.

Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received IntronA 3 MIU/m^2 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. In the two multicentre trials sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in these two multicentre trials for children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

Table 5 Sustained virological response in previously untreated children and adolescents

	IntronA 3 MIU/m^2 3 times a week + **ribavirin 15 mg/kg/day**
Overall Response[a] (n=118)	54 (46 %)*
Genotype 1 (n=92)	33 (36 %)*
Genotype 2/3/4 (n=26)	21 (81 %)*

*Number (%) of patients

[a] Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

Long-term efficacy data

A five-year long-term, observational, follow-up study enrolled 97 paediatric chronic hepatitis C patients after treatment in the standard interferon multicentre trials. Seventy percent (68/97) of all enrolled subjects completed this study of which 75 % (42/56) were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment of the 48-week interferon alfa-2b and ribavirin treatment. All but one of the paediatric subjects remained sustained virologic responders during long-term follow-up after completion of treatment with interferon alfa-2b plus ribavirin. The Kaplan-Meier estimate for continued sustained response over 5 years is 98 % [95 % CI: 95 %, 100 %] for paediatric patients treated with interferon alfa-2b and ribavirin. Additionally, 98 % (51/52) with normal ALT levels at follow-up week 24 maintained normal ALT levels at their last visit.

SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b with ribavirin results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Results from the clinical trial conducted with pegylated interferon alfa-2b and ribavirin

In a multicentre trial children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with peginterferon alfa-2b 60 μg/m^2 plus ribavirin 15 mg/kg per day once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of peginterferon alfa-2b with ribavirin needs to be carefully considered in this population (see peginterferon alfa-2b and ribavirin SPCs section 4.4). The study results are summarized in **Table 6.**

Table 6 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects n = 107		
	24 weeks	**48 weeks**
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment, lower limit of detection=125 IU/mL.

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/mL) were to receive 48 weeks of treatment.

5.2 Pharmacokinetic properties

The pharmacokinetics of IntronA were studied in healthy volunteers following single 5 million IU/m^2 and 10 million IU doses administered subcutaneously, at 5 million IU/m^2 administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. C_{max} occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/mL) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

Interferon neutralising factor assays were performed on serum samples of patients who received IntronA in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

Children and adolescent population
Multiple-dose pharmacokinetic properties for IntronA injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 7**. The pharmacokinetics of IntronA and ribavirin (dose-normalized) are similar in adults and children or adolescents.

Table 7 Mean (% CV) multiple-dose pharmacokinetic parameters for IntronA and ribavirin capsules when administered to children or adolescents with chronic hepatitis C		
Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**IntronA** 3 MIU/m^2 3 times a week (n = 54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3,275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	Not done

*AUC_{12} (ng.hr/mL) for ribavirin; AUC_{0-24} (IU.hr/mL) for IntronA

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20×10^6 IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100×10^6 IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

<u>IntronA plus ribavirin</u>
No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if IntronA is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate anhydrous
Sodium dihydrogen phosphate monohydrate
Edetate disodium
Sodium chloride

M-cresol
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

18 months.
Within its shelf-life, for the purpose of transport, the solution can be kept at or below 25ºC for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1 mL of solution (corresponding to 10 MIU) is contained in a single dose vial (type I glass) with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene).

IntronA is supplied as:
- Pack of 1 vial
- Pack of 1 vial, 1 injection syringe of 2 mL, 1 injection needle and 1 cleansing swab
- Pack of 6 vials, 6 injection syringes of 2 mL, 6 injection needles and 6 cleansing swabs
- Pack of 12 vials, 12 injection syringes of 2 mL, 12 injection needles and 12 cleansing swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not all dose forms and strengths are appropriate for some indications. Please make sure to select an appropriate dose form and strength.

IntronA solution for injection or infusion may be injected directly after withdrawal of the appropriate doses from the vial with a sterile injection syringe.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to “How to self inject IntronA”).

Preparation of IntronA for intravenous infusion: The infusion is to be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

No other medicinal product can be infused concomitantly with IntronA.

As with all parenteral medicinal products, prior to administration inspect IntronA, solution for injection or infusion, visually for particulate matter and discolouration. The solution should be clear and colourless.

Any unused medicinal product must be discarded after withdrawal of the dose and in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/127/019
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EU/1/99/127/022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 March 2000
Date of latest renewal: 9 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

IntronA 18 million IU/3 mL solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of solution for injection or infusion contains 18 million IU of recombinant interferon alfa-2b produced in *E. coli* by recombinant DNA technology, in 3 mL of solution.

One mL of solution contains 6 million IU of interferon alfa-2b.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B
Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of DNA of hepatitis B virus (HBV-DNA) and hepatitis B antigen (HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic hepatitis C
Before initiating treatment with IntronA, consideration should be given to the results from clinical trials comparing IntronA with pegylated interferon (see section 5.1).

Adult patients
IntronA is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for hepatitis C virus RNA (HCV-RNA) (see section 4.4).

The best way to use IntronA in this indication is in combination with ribavirin.

Children 3 years of age and older and adolescents
IntronA is indicated, in a combination regimen with ribavirin, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients. The decision to treat should be made on a case by case basis (see section 4.4).

Hairy cell leukaemia
Treatment of patients with hairy cell leukaemia.

Chronic myelogenous leukaemia

Monotherapy

Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia.

Clinical experience indicates that a haematological and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is ≥ 34 %, but < 90 % Ph+ cells in the marrow.

Combination therapy

The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.

Multiple myeloma

As maintenance therapy in patients who have achieved objective remission (more than 50 % reduction in myeloma protein) following initial induction chemotherapy.

Current clinical experience indicates that maintenance therapy with interferon alfa-2b prolongs the plateau phase; however, effects on overall survival have not been conclusively demonstrated.

Follicular lymphoma

Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.

Carcinoid tumour

Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome".

Malignant melanoma

As adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement.

4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dose forms and strengths are appropriate for some indications. Appropriate dose form and strength must be selected.

If adverse events develop during the course of treatment with IntronA for any indication, modify the dose or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dose adjustment, or disease progresses, discontinue treatment with IntronA. At the discretion of the physician, the patient may self-administer the dose for maintenance dose regimens administered subcutaneously.

Chronic hepatitis B

The recommended dose is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/mm^3, granulocytes < 1,000/mm^3, thrombocytes < 100,000/mm^3). Treatment

should be discontinued in case of severe leukopaenia (< 1,200/mm^3), severe neutropaenia (< 750/mm^3) or severe thrombocytopaenia (< 70,000/mm^3).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue IntronA therapy.

Chronic hepatitis C

Adults

IntronA is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

Children 3 years of age or older and adolescents

IntronA 3 MIU/m^2 is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsules SPC for dose of ribavirin capsules and dose modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC.)

Relapse patients (adults)

IntronA is given in combination with ribavirin. Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for 6 months.

Naïve patients (adults)

The efficacy of IntronA is enhanced when given in combination with ribavirin. IntronA should be given alone mainly in case of intolerance or contraindication to ribavirin.

- IntronA in combination with ribavirin

Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

- IntronA alone

The optimal duration of therapy with IntronA alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with IntronA alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

Naïve patients (children and adolescents)

The efficacy and safety of IntronA in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Duration of treatment for children and adolescents

- Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Therefore, it is recommended that children and adolescent patients receiving IntronA/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment, or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2/3: The recommended duration of treatment is 24 weeks.

Hairy cell leukaemia

The recommended dose is 2 million IU/m^2 administered subcutaneously three times a week (every other day) for both splenectomised and non-splenectomised patients. For most patients with Hairy Cell Leukaemia, normalisation of one or more haematological variables occurs within one to two months of IntronA treatment. Improvement in all three haematological variables (granulocyte count, platelet count and haemoglobin level) may require six months or more. This regimen must be maintained unless the disease progresses rapidly or severe intolerance is manifested.

Chronic myelogenous leukaemia

The recommended dose of IntronA is 4 to 5 million IU/m^2 administered daily subcutaneously. Some patients have been shown to benefit from IntronA 5 million IU/m^2 administered daily subcutaneously in association with cytarabine (Ara-C) 20 mg/m^2 administered daily subcutaneously for 10 days per month (up to a maximum daily dose of 40 mg). When the white blood cell count is controlled, administer the maximum tolerated dose of IntronA (4 to 5 million IU/m^2 daily) to maintain haematological remission.

IntronA treatment must be discontinued after 8 to 12 weeks of treatment if at least a partial haematological remission or a clinically meaningful cytoreduction has not been achieved.

Multiple myeloma

Maintenance therapy

In patients who are in the plateau phase (more than 50 % reduction of myeloma protein) following initial induction chemotherapy, interferon alfa-2b may be administered as monotherapy, subcutaneously, at a dose of 3 million IU/m^2 three times a week (every other day).

Follicular lymphoma

Adjunctively with chemotherapy, interferon alfa-2b may be administered subcutaneously, at a dose of 5 million IU three times a week (every other day) for a duration of 18 months. CHOP-like regimens are advised, but clinical experience is available only with CHVP (combination of cyclophosphamide, doxorubicin, teniposide and prednisolone).

Carcinoid tumour

The usual dose is 5 million IU (3 to 9 million IU) administered subcutaneously three times a week (every other day). Patients with advanced disease may require a daily dose of 5 million IU. The treatment is to be temporarily discontinued during and after surgery. Therapy may continue for as long as the patient responds to interferon alfa-2b treatment.

Malignant melanoma

As induction therapy, interferon alfa-2b is administered intravenously at a dose of 20 million IU/m^2 daily for five days a week for a four-week period; the calculated interferon alfa-2b dose is added to sodium chloride 9 mg/mL (0.9 %) solution for injection and administered as a 20-minute infusion (see section 6.6). As maintenance treatment, the recommended dose is 10 million IU/m^2 administered subcutaneously three days a week (every other day) for 48 weeks.

If severe adverse events develop during interferon alfa-2b treatment, particularly if granulocytes decrease to < 500/mm^3 or alanine aminotransferase/aspartate aminotransferase (ALT/AST) rises to

> 5 x upper limit of normal, discontinue treatment temporarily until the adverse event abates. Interferon alfa-2b treatment is to be restarted at 50 % of the previous dose. If intolerance persists after dose adjustment or if granulocytes decrease to < 250/mm^3 or ALT/AST rises to > 10 x upper limit of normal, discontinue interferon alfa-2b therapy.

Although the optimal (minimum) dose for full clinical benefit is unknown, patients must be treated at the recommended dose, with dose reduction for toxicity as described.

IntronA may be administered using either glass or plastic disposable injection syringes.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.
- Combination of IntronA with telbivudine.

Children and adolescents
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

4.4 Special warnings and precautions for use

Psychiatric and central nervous system (CNS)
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during IntronA therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents treated with IntronA in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation is identified, it is recommended that treatment with IntronA be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions:
If treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.

- The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

Patients with substance use/abuse:
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Children and adolescent population: Growth and development (chronic hepatitis C)
During the course of interferon (standard and pegylated)/ribavirin combination therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children (n=20) despite being off treatment for more than 5 years. Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment.

Case by case benefit/risk assessment in children
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response, (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

Hypersensitivity reactions
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during IntronA therapy. If such a reaction develops, discontinue the medicine and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Adverse experiences including prolongation of coagulation markers and liver abnormalities
Moderate to severe adverse experiences may require modification of the patient's dose regimen, or in some cases, termination of IntronA therapy. IntronA increases the risk of liver decompensation and death in patients with cirrhosis.
Discontinue treatment with IntronA in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decomposition.
Any patient developing liver function abnormalities during treatment with IntronA must be monitored closely and treatment discontinued if signs and symptoms progress.
Liver enzymes and hepatic function should be closely monitored in cirrhotic patients.

Hypotension
Hypotension may occur during IntronA therapy or up to two days post-therapy and may require supportive treatment.

Need for adequate hydration
Adequate hydration must be maintained in patients undergoing IntronA therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Pyrexia
While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Patients with debilitating medical conditions
IntronA must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary conditions
Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events
Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, serous retinal detachment, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with IntronA, must have a prompt and complete eye examination. Periodic visual examinations during IntronA therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of IntronA should be considered in patients who develop new or worsening ophthalmological disorders.

Obtundation, coma and encephalopathy
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of IntronA.

Patients with pre-existing cardiac abnormalities
Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require IntronA therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of IntronA therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia
Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Patients with psoriasis and sarcoidosis
Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of IntronA in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Kidney and liver graft rejection
Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Auto-antibodies and autoimmune disorders
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Concomitant chemotherapy
Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered medicinal product. The most commonly reported potentially life-threatening or fatal adverse events include mucositis, diarrhoea, neutropaenia, renal impairment, and electrolyte disturbance. Because of the risk of increased toxicity, careful adjustments of doses are required for IntronA and for the concomitant chemotherapeutic agents (see section 4.5). When IntronA is used with hydroxyurea, the frequency and severity of cutaneous vasculitis may be increased.

Chronic hepatitis C
Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy
Infrequently, adult patients treated for chronic hepatitis C with IntronA developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using IntronA therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which IntronA may alter thyroid status is unknown. Prior to initiation of IntronA therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of IntronA therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, IntronA treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of IntronA therapy has not reversed thyroid

dysfunction occurring during treatment (also see Thyroid supplemental monitoring specific for children and adolescents).

Thyroid supplemental monitoring specific for children and adolescents
Approximately 12 % of children treated with interferon alfa-2b and ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of IntronA therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding IntronA and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with IntronA and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of IntronA and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with IntronA.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during IntronA therapy to greater than or equal to 2 times baseline, IntronA therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, the following liver function tests must be monitored at two-week intervals: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin.

In patients treated for malignant melanoma, liver function and white blood cell (WBC) count and differential must be monitored weekly during the induction phase of therapy and monthly during the maintenance phase of therapy.

Effect on fertility
Interferon may impair fertility (see section 4.6 and section 5.3).

Important information about some of the ingredients of IntronA
This medicinal product contains less than 1 mmol sodium (23 mg) per 3 mL, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with IntronA.

Interactions between IntronA and other medicinal products have not been fully evaluated. Caution must be exercised when administering IntronA in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dose adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration) (see section 4.4).

Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see sections 4.3, 4.4 and 4.5 of the telbivudine SPC). Moreover, the safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated. Therefore, the combination of IntronA with telbivudine is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Women of childbearing potential have to use effective contraception during treatment. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

IntronA must be used with caution in fertile men.

Combination therapy with ribavirin
Ribavirin causes serious birth defects when administered during pregnancy. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking IntronA in combination with ribavirin. Females of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. IntronA is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Combination therapy with ribavirin
Ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with IntronA, and therefore it is recommended that they avoid driving or operating machinery.

4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/m^2/week in hairy cell leukaemia up to 100 MIU/m^2/week in melanoma), the most commonly reported undesirable effects were pyrexia, fatigue, headache and myalgia. Pyrexia and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

Adults
In clinical trials conducted in the hepatitis C population, patients were treated with IntronA alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of IntronA three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rarely (≥1/10,000 to <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported during clinical trials or following the marketing use of IntronA alone or in combination with ribavirin

System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Pharyngitis*, infection viral*
Common:	Bronchitis, sinusitis, herpes simplex (resistance), rhinitis
Uncommon:	Bacterial infection
Rarely:	Pneumonia[§], sepsis
Blood and lymphatic system disorders	
Very common:	Leukopaenia
Common:	Thrombocytopaenia, lymphadenopathy, lymphopenia
Very rarely:	Aplastic anaemia
Not known**:**	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura

Immune system disorders[§]	
Very rarely:	Sarcoidosis, exacerbation of sarcoidosis
Not known:	Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§]
Endocrine disorders	
Common:	Hypothyroidism[§], hyperthyroidism[§]
Very rarely:	Diabetes, aggravated diabetes
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hypocalcaemia, dehydration, hyperuricemia, thirst
Very rarely:	Hyperglycaemia, hypertriglyceridaemia[§], increased appetite
Psychiatric disorders[§]	
Very common:	Depression, insomnia, anxiety, emotional lability*, agitation, nervousness
Common:	Confusion, sleep disorder, libido decreased
Rarely:	Suicide ideation
Very rarely:	Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations
Not known:	Homicidal ideation, mental status change[§], mania, bipolar disorders
Nervous system disorders[§]	
Very common:	Dizziness, headache, concentration impaired, mouth dry
Common:	Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion
Uncommon:	Peripheral neuropathy
Very rarely:	Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy
Not known:	Mononeuropathies, coma[§]
Eye disorders	
Very common:	Vision blurred
Common:	Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain
Rarely:	Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§]
Not known:	Serous retinal detachment
Ear and labyrinth	
Common:	Vertigo, tinnitus
Very rarely:	Hearing loss, hearing disorder
Cardiac disorders	
Common:	Palpitation, tachycardia
Rarely:	Cardiomyopathy
Very rarely:	Myocardial infarction, cardiac ischaemia
Not known:	Congestive heart failure, pericardial effusion, arrhythmia
Vascular disorders	
Common:	Hypertension
Very rarely:	Peripheral ischaemia, hypotension[§]

Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea*, coughing*
Common:	Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive
Very rarely:	Pulmonary infiltrates[§], pneumonitis[§]
Not known:	Pulmonary fibrosis, pulmonary arterial hypertension[#]
Gastrointestinal disorders	
Very common:	Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia
Common:	Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools
Very rarely:	Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding
Not known:	Periodontal disorder NOS, dental disorder NOS[§]
Hepatobiliary disorders	
Common:	Hepatomegaly
Very rarely:	Hepatotoxicity, (including fatality)
Skin and subcutaneous tissue disorders	Alopecia, pruritus*, skin dry*, rash*, sweating increased
Very common:	Psoriasis (new or aggravated)[§], rash maculopapular, rash
Common:	erythematous, eczema, erythema, skin disorder
Very rarely:	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, musculoskeletal pain
Common:	Arthritis
Very rarely:	Rhabdomyolysis, myositis, leg cramps, back pain
Renal and urinary disorders	
Common:	Micturition frequency
Very rarely:	Renal failure, renal insufficiency, nephrotic syndrome
Reproductive system and breast disorders	
Common:	Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction*, fatigue, rigors, pyrexia[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise
Common:	Injection site pain
Very rarely:	Injection site necrosis, face oedema
Investigations	
Very common:	Weight decrease

*These events were only common with IntronA alone
[§]See section 4.4
[#]Class label for interferon products, see below Pulmonary arterial hypertension

These undesirable effects have also been reported with IntronA alone.

The undesirable effects seen with hepatitis C are representative of those reported when IntronA is administered in other indications, with some anticipated dose-related increases in incidence. For example, in a trial of high-dose adjuvant IntronA treatment in patients with melanoma, incidences of fatigue, pyrexia, myalgia, neutropaenia/anaemia, anorexia, nausea and vomiting, diarrhoea, chills, flu-

like symptoms, depression, alopecia, altered taste, and dizziness were greater than in the hepatitis C trials. Severity also increased with high dose therapy (WHO Grade 3 and 4, in 66 % and 14 % of patients, respectively), in comparison with the mild to moderate severity usually associated with lower doses. Undesirable effects were usually managed by dose adjustment.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV-infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Moderate and usually reversible pancytopenia has been reported. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

Children and adolescent population

Chronic Hepatitis C - Combination therapy with ribavirin

In clinical trials of 118 children and adolescents (3 to 16 years of age), 6 % discontinued therapy due to adverse reactions. In general, the adverse reaction profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric- specific concern regarding growth inhibition as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile) were observed during treatment. Within the 5 years follow-up post-treatment period, the children had a mean height of 44th percentile, which was below the median of the normative population and less than their mean baseline height (48th percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years). Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment. During combination therapy for up to 48 weeks with IntronA and ribavirin, growth inhibition was observed that resulted in reduced final adult height in some patients. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from the two multicentre children and adolescent clinical trials. Within the organ system classes, adverse reactions are listed under headings

of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Adverse reactions very commonly and commonly reported during clinical trials inchildren and adolescent patients treated with IntronA in combination with ribavirin

System Organ Class	Adverse Reactions
Infection and infestations Very common: Common:	 Viral infection, pharyngitis Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Neoplasms benign, malignant and unspecified (including cysts and polyps) Common:	 Neoplasm (unspecified)
Blood and lymphatic system disorders Very common: Common:	 Anaemia, neutropaenia Thrombocytopaenia, lymphadenopathy
Endocrine disorders Very common: Common:	 Hypothyroidism[§], Hyperthyroidism[§], virilism
Metabolism and nutrition disorders Very common: Common:	 Anorexia Hypertriglyceridemia[§], hyperuricemia, increased appetite
Psychiatric disorders[§] Very common: Common:	 Depression, emotional lability, insomnia Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy
Nervous system disorders[§] Very common: Common:	 Headache, dizziness Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence
Eye disorders Common:	 Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Vascular disorders Common:	 Flushing, pallor
Respiratory, thoracic and mediastinal disorders Common:	 Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing
Gastrointestinal disorders Very common: Common:	 Diarrhoea, vomiting, nausea, abdominal pain Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder
Hepatobiliary disorders Common:	 Hepatic function abnormal

Skin and subcutaneous tissue disorders Very common: Common:	 Alopecia, rash Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased
Musculoskeletal and connective tissue disorders Very common:	 Arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders Common:	 Enuresis, micturition disorder, urinary incontinence
Reproductive system and breast disorders Common:	 Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder Male: testicular pain
General disorders and administration site conditions Very common: Common:	 Injection site inflammation, injection site reaction, fatigue, rigors, pyrexia[§], influenza-like symptoms[§], malaise, irritability Chest pain, asthenia, oedema, injection site pain
Investigations Very common:	 Growth rate decrease (height and/or weight decrease for age)[§]
Injury and poisoning Common:	 Skin laceration

[§]See section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: interferon alfa-2b, ATC code: L03A B05

IntronA is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of IntronA is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity

of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. IntronA has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B

Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/m^2 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C in adult patients

In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

IntronA alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of IntronA used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/mL), a liver

biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

IntronA was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with IntronA alone or in combination with ribavirin (from two studies) are shown in **Table 3.**

Co-administration of IntronA with ribavirin increased the efficacy of IntronA by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of IntronA + ribavirin, compared with IntronA alone, is maintained across all subgroups. The relative benefit of combination therapy with IntronA + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received IntronA in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

Table 3 Sustained virologic response rates with IntronA + ribavirin (one year of treatment) by genotype and viral load

HCV Genotype	**I N=503 C95-132/I95-143**	**I/R N=505 C95-132/I95-143**	**I/R N=505 C/I98-580**
All Genotypes	**16 %**	**41 %**	**47 %**
Genotype 1	9 %	29 %	33 %
Genotype 1 ≤ 2 million copies/mL	25 %	33 %	45 %
Genotype 1 > 2 million copies/mL	3 %	27 %	29 %
Genotype 2/3	31 %	65 %	79 %

I IntronA (3 MIU 3 times a week)
I/R IntronA (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

HCV/HIV Co-infected patients
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received IntronA plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or IntronA (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based

on weight) plus ribavirin (800-1,200 mg/day based on weight) or IntronA (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/mL (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

Table 4 Sustained virological response based on genotype after IntronA in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

	Study 1[1]			**Study 2**[2]		
	pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg)	IntronA (3 MIU TIW) + ribavirin (800 mg)	p value[a]	pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d]	IntronA (3 MIU TIW) + ribavirin (800-1,200 mg)[d]	p value[b]
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients
A total of 345 interferon alpha relapse patients were treated in two clinical trials with IntronA monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to IntronA increased by as much as 10-fold the efficacy of IntronA used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/mL by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non-pegylated interferon alfa-2b or non-pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Chronic hepatitis C in children and adolescent population

Three clinical trials have been conducted in children and adolescents; two with standard interferon and ribavirin and one with pegylated interferon and ribavirin. Patients who received IntronA plus ribavirin were less likely to respond than patients who received pegylated interferon alfa-2b and ribavirin.

Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received IntronA 3 MIU/m^2 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. In the two multicentre trials sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in these two multicentre trials for children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

Table 5 Sustained virological response in previously untreated children and adolescents

	IntronA 3 MIU/m^2 3 times a week + **ribavirin 15 mg/kg/day**
Overall Response[a] (n=118)	54 (46 %)*
Genotype 1 (n=92)	33 (36 %)*
Genotype 2/3/4 (n=26)	21 (81 %)*

*Number (%) of patients

[a] Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

Long-term efficacy data

A five-year long-term, observational, follow-up study enrolled 97 paediatric chronic hepatitis C patients after treatment in the standard interferon multicentre trials. Seventy percent (68/97) of all enrolled subjects completed this study of which 75 % (42/56) were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment of the 48-week interferon alfa-2b and ribavirin treatment. All but one of the paediatric subjects remained sustained virologic responders during long-term follow-up after completion of treatment with interferon alfa-2b plus ribavirin. The Kaplan-Meier estimate for continued sustained response over 5 years is 98 % [95 % CI: 95 %, 100 %] for paediatric patients treated with interferon alfa-2b and ribavirin. Additionally, 98 % (51/52) with normal ALT levels at follow-up week 24 maintained normal ALT levels at their last visit.

SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b with ribavirin results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Results from the clinical trial conducted with pegylated interferon alfa-2b and ribavirin

In a multicentre trial children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with peginterferon alfa-2b 60 μg/m^2 plus ribavirin 15 mg/kg per day once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received

treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of peginterferon alfa-2b with ribavirin needs to be carefully considered in this population (see peginterferon alfa-2b and ribavirin SPCs section 4.4). The study results are summarized in **Table 6.**

Table 6 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects
n = 107

	24 weeks	**48 weeks**
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment, lower limit of detection=125 IU/mL.

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/mL) were to receive 48 weeks of treatment.

5.2 Pharmacokinetic properties

The pharmacokinetics of IntronA were studied in healthy volunteers following single 5 million IU/m^2 and 10 million IU doses administered subcutaneously, at 5 million IU/m^2 administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. C_{max} occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/mL) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

Interferon neutralising factor assays were performed on serum samples of patients who received IntronA in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

Children and adolescent population
Multiple-dose pharmacokinetic properties for IntronA injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 7**. The pharmacokinetics of IntronA and ribavirin (dose-normalized) are similar in adults and children or adolescents.

Table 7 Mean (% CV) multiple-dose pharmacokinetic parameters for IntronA and ribavirin capsules when administered to children or adolescents with chronic hepatitis C		
Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**IntronA** 3 MIU/m^2 3 times a week (n = 54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3,275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	Not done

*AUC_{12} (ng.hr/mL) for ribavirin; AUC_{0-24} (IU.hr/mL) for IntronA

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20×10^6 IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100×10^6 IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

<u>IntronA plus ribavirin</u>
No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if IntronA is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate anhydrous
Sodium dihydrogen phosphate monohydrate
Edetate disodium
Sodium chloride

M-cresol
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

After first opening the container: Chemical and physical in-use stability has been demonstrated for 28 days at 2ºC – 8ºC.
From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.
Within its shelf-life, for the purpose of transport, the solution can be kept at or below 25ºC for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 mL of solution (corresponding to 18 MIU) is contained in a multidose vial (type I glass) with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene).

IntronA is supplied as:
- Pack of 1 vial
- Pack of 1 vial, 6 injection syringes of 1 mL, 6 injection needles and 12 cleansing swabs
- Pack of 1 vial, 6 injection syringes with attached needle and needle protection device of 1 mL and 12 cleansing swabs
- Pack of 2 vials
- Pack of 2 vials, 12 injection syringes of 1 mL, 12 injection needles and 24 cleansing swabs
- Pack of 2 vials, 12 injection syringes with attached needle and needle protection device of 1 mL and 24 cleansing swabs
- Pack of 12 vials
- Pack of 12 vials, 72 injection syringes of 1 mL, 72 injection needles and 144 cleansing swabs
- Pack of 12 vials, 72 injection syringes with attached needle and needle protection device of 1 mL and 144 cleansing swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not all dose forms and strengths are appropriate for some indications. Please make sure to select an appropriate dose form and strength.

IntronA solution for injection or infusion may be injected directly after withdrawal of the appropriate doses from the vial with a sterile injection syringe.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to “How to self inject IntronA”).

Preparation of IntronA for intravenous infusion: The infusion is to be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

No other medicinal product can be infused concomitantly with IntronA.

As with all parenteral medicinal products, prior to administration inspect IntronA, solution for injection or infusion, visually for particulate matter and discolouration. The solution should be clear and colourless.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/127/023
EU/1/99/127/024
EU/1/99/127/025
EU/1/99/127/026
EU/1/99/127/041
EU/1/99/127/042
EU/1/99/127/045
EU/1/99/127/046
EU/1/99/127/047

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 March 2000
Date of latest renewal: 9 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

IntronA 25 million IU/2.5 mL solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of solution for injection or infusion contains 25 million IU of recombinant interferon alfa-2b produced in *E. coli* by recombinant DNA technology, in 2.5 mL of solution.

One mL of solution contains 10 million IU of interferon alfa-2b.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B
Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of DNA of hepatitis B virus (HBV-DNA) and hepatitis B antigen (HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic hepatitis C
Before initiating treatment with IntronA, consideration should be given to the results from clinical trials comparing IntronA with pegylated interferon (see section 5.1).

Adult patients
IntronA is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for hepatitis C virus RNA (HCV-RNA) (see section 4.4).

The best way to use IntronA in this indication is in combination with ribavirin.

Children 3 years of age and older and adolescents
IntronA is indicated, in a combination regimen with ribavirin, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
The decision to treat should be made on a case by case basis (see section 4.4).

Hairy cell leukaemia
Treatment of patients with hairy cell leukaemia.

Chronic myelogenous leukaemia

Monotherapy

Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia.

Clinical experience indicates that a haematological and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is ≥ 34 %, but < 90 % Ph+ cells in the marrow.

Combination therapy

The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.

Multiple myeloma

As maintenance therapy in patients who have achieved objective remission (more than 50 % reduction in myeloma protein) following initial induction chemotherapy.

Current clinical experience indicates that maintenance therapy with interferon alfa-2b prolongs the plateau phase; however, effects on overall survival have not been conclusively demonstrated.

Follicular lymphoma

Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.

Carcinoid tumour

Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome".

Malignant melanoma

As adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement.

4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Not all dose forms and strengths are appropriate for some indications. Appropriate dose form and strength must be selected.

If adverse events develop during the course of treatment with IntronA for any indication, modify the dose or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dose adjustment, or disease progresses, discontinue treatment with IntronA. At the discretion of the physician, the patient may self-administer the dose for maintenance dose regimens administered subcutaneously.

Chronic hepatitis B

The recommended dose is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/mm^3, granulocytes < 1,000/mm^3, thrombocytes < 100,000/mm^3). Treatment

should be discontinued in case of severe leukopaenia (< 1,200/mm^3), severe neutropaenia (< 750/mm^3) or severe thrombocytopaenia (< 70,000/mm^3).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue IntronA therapy.

Chronic hepatitis C

Adults

IntronA is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

Children 3 years of age or older and adolescents

IntronA 3 MIU/m^2 is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsules SPC for dose of ribavirin capsules and dose modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC.)

Relapse patients (adults)

IntronA is given in combination with ribavirin. Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for 6 months.

Naïve patients (adults)

The efficacy of IntronA is enhanced when given in combination with ribavirin. IntronA should be given alone mainly in case of intolerance or contraindication to ribavirin.

- IntronA in combination with ribavirin

Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

- IntronA alone

The optimal duration of therapy with IntronA alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with IntronA alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

Naïve patients (children and adolescents)

The efficacy and safety of IntronA in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Duration of treatment for children and adolescents

- Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Therefore, it is recommended that children and adolescent patients receiving IntronA/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment, or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2/3: The recommended duration of treatment is 24 weeks.

Hairy cell leukaemia

The recommended dose is 2 million IU/m^2 administered subcutaneously three times a week (every other day) for both splenectomised and non-splenectomised patients. For most patients with Hairy Cell Leukaemia, normalisation of one or more haematological variables occurs within one to two months of IntronA treatment. Improvement in all three haematological variables (granulocyte count, platelet count and haemoglobin level) may require six months or more. This regimen must be maintained unless the disease progresses rapidly or severe intolerance is manifested.

Chronic myelogenous leukaemia

The recommended dose of IntronA is 4 to 5 million IU/m^2 administered daily subcutaneously. Some patients have been shown to benefit from IntronA 5 million IU/m^2 administered daily subcutaneously in association with cytarabine (Ara-C) 20 mg/m^2 administered daily subcutaneously for 10 days per month (up to a maximum daily dose of 40 mg). When the white blood cell count is controlled, administer the maximum tolerated dose of IntronA (4 to 5 million IU/m^2 daily) to maintain haematological remission.

IntronA treatment must be discontinued after 8 to 12 weeks of treatment if at least a partial haematological remission or a clinically meaningful cytoreduction has not been achieved.

Multiple myeloma

Maintenance therapy

In patients who are in the plateau phase (more than 50 % reduction of myeloma protein) following initial induction chemotherapy, interferon alfa-2b may be administered as monotherapy, subcutaneously, at a dose of 3 million IU/m^2 three times a week (every other day).

Follicular lymphoma

Adjunctively with chemotherapy, interferon alfa-2b may be administered subcutaneously, at a dose of 5 million IU three times a week (every other day) for a duration of 18 months. CHOP-like regimens are advised, but clinical experience is available only with CHVP (combination of cyclophosphamide, doxorubicin, teniposide and prednisolone).

Carcinoid tumour

The usual dose is 5 million IU (3 to 9 million IU) administered subcutaneously three times a week (every other day). Patients with advanced disease may require a daily dose of 5 million IU. The treatment is to be temporarily discontinued during and after surgery. Therapy may continue for as long as the patient responds to interferon alfa-2b treatment.

Malignant melanoma

As induction therapy, interferon alfa-2b is administered intravenously at a dose of 20 million IU/m^2 daily for five days a week for a four-week period; the calculated interferon alfa-2b dose is added to sodium chloride 9 mg/mL (0.9 %) solution for injection and administered as a 20-minute infusion (see section 6.6). As maintenance treatment, the recommended dose is 10 million IU/m^2 administered subcutaneously three days a week (every other day) for 48 weeks.

If severe adverse events develop during interferon alfa-2b treatment, particularly if granulocytes decrease to < 500/mm^3 or alanine aminotransferase/aspartate aminotransferase (ALT/AST) rises to

> 5 x upper limit of normal, discontinue treatment temporarily until the adverse event abates. Interferon alfa-2b treatment is to be restarted at 50 % of the previous dose. If intolerance persists after dose adjustment or if granulocytes decrease to < 250/mm^3 or ALT/AST rises to > 10 x upper limit of normal, discontinue interferon alfa-2b therapy.

Although the optimal (minimum) dose for full clinical benefit is unknown, patients must be treated at the recommended dose, with dose reduction for toxicity as described.

IntronA may be administered using either glass or plastic disposable injection syringes.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.
- Combination of IntronA with telbivudine.

Children and adolescents
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

4.4 Special warnings and precautions for use

Psychiatric and central nervous system (CNS)
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during IntronA therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents treated with IntronA in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation is identified, it is recommended that treatment with IntronA be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions:
If treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.

- The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

Patients with substance use/abuse:
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Children and adolescent population: Growth and development (chronic hepatitis C)
During the course of interferon (standard and pegylated)/ribavirin combination therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children (n=20) despite being off treatment for more than 5 years. Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment.

Case by case benefit/risk assessment in children
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response, (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

Hypersensitivity reactions
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during IntronA therapy. If such a reaction develops, discontinue the medicine and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Adverse experiences including prolongation of coagulation markers and liver abnormalities
Moderate to severe adverse experiences may require modification of the patient's dose regimen, or in some cases, termination of IntronA therapy. IntronA increases the risk of liver decompensation and death in patients with cirrhosis.
Discontinue treatment with IntronA in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decomposition.
Any patient developing liver function abnormalities during treatment with IntronA must be monitored closely and treatment discontinued if signs and symptoms progress.
Liver enzymes and hepatic function should be closely monitored in cirrhotic patients.

Hypotension
Hypotension may occur during IntronA therapy or up to two days post-therapy and may require supportive treatment.

Need for adequate hydration
Adequate hydration must be maintained in patients undergoing IntronA therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Pyrexia
While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Patients with debilitating medical conditions
IntronA must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary conditions
Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events
Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, serous retinal detachment, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with IntronA, must have a prompt and complete eye examination. Periodic visual examinations during IntronA therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of IntronA should be considered in patients who develop new or worsening ophthalmological disorders.

Obtundation, coma and encephalopathy
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of IntronA.

Patients with pre-existing cardiac abnormalities
Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require IntronA therapy, must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of IntronA therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia
Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Patients with psoriasis and sarcoidosis
Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of IntronA in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Kidney and liver graft rejection
Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Auto-antibodies and autoimmune disorders
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

<u>Concomitant chemotherapy</u>
Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered medicinal product. The most commonly reported potentially life-threatening or fatal adverse events include mucositis, diarrhoea, neutropaenia, renal impairment, and electrolyte disturbance. Because of the risk of increased toxicity, careful adjustments of doses are required for IntronA and for the concomitant chemotherapeutic agents (see section 4.5). When IntronA is used with hydroxyurea, the frequency and severity of cutaneous vasculitis may be increased.

<u>Chronic hepatitis C</u>
Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy
Infrequently, adult patients treated for chronic hepatitis C with IntronA developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using IntronA therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which IntronA may alter thyroid status is unknown. Prior to initiation of IntronA therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of IntronA therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, IntronA treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of IntronA therapy has not reversed thyroid

dysfunction occurring during treatment (also see Thyroid supplemental monitoring specific for children and adolescents).

Thyroid supplemental monitoring specific for children and adolescents
Approximately 12 % of children treated with interferon alfa-2b and ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of IntronA therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding IntronA and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with IntronA and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of IntronA and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with IntronA.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during IntronA therapy to greater than or equal to 2 times baseline, IntronA therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, the following liver function tests must be monitored at two-week intervals: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin.

In patients treated for malignant melanoma, liver function and white blood cell (WBC) count and differential must be monitored weekly during the induction phase of therapy and monthly during the maintenance phase of therapy.

Effect on fertility
Interferon may impair fertility (see section 4.6 and section 5.3).

Important information about some of the ingredients of IntronA
This medicinal product contains less than 1 mmol sodium (23 mg) per 2.5 mL, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with IntronA.

Interactions between IntronA and other medicinal products have not been fully evaluated. Caution must be exercised when administering IntronA in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dose adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration) (see section 4.4).

Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see sections 4.3, 4.4 and 4.5 of the telbivudine SPC). Moreover, the safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated. Therefore, the combination of IntronA with telbivudine is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Women of childbearing potential have to use effective contraception during treatment. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

IntronA must be used with caution in fertile men.

Combination therapy with ribavirin
Ribavirin causes serious birth defects when administered during pregnancy. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking IntronA in combination with ribavirin. Females of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. IntronA is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Combination therapy with ribavirin
Ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with IntronA, and therefore it is recommended that they avoid driving or operating machinery.

4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/m^2/week in hairy cell leukaemia up to 100 MIU/m^2/week in melanoma), the most commonly reported undesirable effects were pyrexia, fatigue, headache and myalgia. Pyrexia and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

Adults
In clinical trials conducted in the hepatitis C population, patients were treated with IntronA alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of IntronA three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rarely (≥1/10,000 to <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported during clinical trials or following the marketing use of IntronA alone or in combination with ribavirin

System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Pharyngitis*, infection viral*
Common:	Bronchitis, sinusitis, herpes simplex (resistance), rhinitis
Uncommon:	Bacterial infection
Rarely:	Pneumonia[§], sepsis
Blood and lymphatic system disorders	
Very common:	Leukopaenia
Common:	Thrombocytopaenia, lymphadenopathy, lymphopenia
Very rarely:	Aplastic anaemia
Not known**:**	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura

Immune system disorders[§]	
Very rarely:	Sarcoidosis, exacerbation of sarcoidosis
Not known:	Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§]
Endocrine disorders	
Common:	Hypothyroidism[§], hyperthyroidism[§]
Very rarely:	Diabetes, aggravated diabetes
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hypocalcaemia, dehydration, hyperuricemia, thirst
Very rarely:	Hyperglycaemia, hypertriglyceridaemia[§], increased appetite
Psychiatric disorders[§]	
Very common:	Depression, insomnia, anxiety, emotional lability*, agitation, nervousness
Common:	Confusion, sleep disorder, libido decreased
Rarely:	Suicide ideation
Very rarely:	Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations
Not known:	Homicidal ideation, mental status change[§], mania, bipolar disorders
Nervous system disorders[§]	
Very common:	Dizziness, headache, concentration impaired, mouth dry
Common:	Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion
Uncommon:	Peripheral neuropathy
Very rarely:	Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy
Not known:	Mononeuropathies, coma[§]
Eye disorders	
Very common:	Vision blurred
Common:	Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain
Rarely:	Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§]
Not known:	Serous retinal detachment
Ear and labyrinth	
Common:	Vertigo, tinnitus
Very rarely:	Hearing loss, hearing disorder
Cardiac disorders	
Common:	Palpitation, tachycardia
Rarely:	Cardiomyopathy
Very rarely:	Myocardial infarction, cardiac ischaemia
Not known:	Congestive heart failure, pericardial effusion, arrhythmia
Vascular disorders	
Common:	Hypertension
Very rarely:	Peripheral ischaemia, hypotension[§]

Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea*, coughing*
Common:	Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive
Very rarely:	Pulmonary infiltrates[§], pneumonitis[§]
Not known:	Pulmonary fibrosis, pulmonary arterial hypertension[#]
Gastrointestinal disorders	
Very common:	Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia
Common:	Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools
Very rarely:	Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding
Not known:	Periodontal disorder NOS, dental disorder NOS[§]
Hepatobiliary disorders	
Common:	Hepatomegaly
Very rarely:	Hepatotoxicity, (including fatality)
Skin and subcutaneous tissue disorders	Alopecia, pruritus*, skin dry*, rash*, sweating increased
Very common:	Psoriasis (new or aggravated)[§], rash maculopapular, rash
Common:	erythematous, eczema, erythema, skin disorder
Very rarely:	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, musculoskeletal pain
Common:	Arthritis
Very rarely:	Rhabdomyolysis, myositis, leg cramps, back pain
Renal and urinary disorders	
Common:	Micturition frequency
Very rarely:	Renal failure, renal insufficiency, nephrotic syndrome
Reproductive system and breast disorders	
Common:	Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction*, fatigue, rigors, pyrexia[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise
Common:	Injection site pain
Very rarely:	Injection site necrosis, face oedema
Investigations	
Very common:	Weight decrease

*These events were only common with IntronA alone
[§]See section 4.4
[#]Class label for interferon products, see below Pulmonary arterial hypertension

These undesirable effects have also been reported with IntronA alone.

The undesirable effects seen with hepatitis C are representative of those reported when IntronA is administered in other indications, with some anticipated dose-related increases in incidence. For example, in a trial of high-dose adjuvant IntronA treatment in patients with melanoma, incidences of fatigue, pyrexia, myalgia, neutropaenia/anaemia, anorexia, nausea and vomiting, diarrhoea, chills, flu-

like symptoms, depression, alopecia, altered taste, and dizziness were greater than in the hepatitis C trials. Severity also increased with high dose therapy (WHO Grade 3 and 4, in 66 % and 14 % of patients, respectively), in comparison with the mild to moderate severity usually associated with lower doses. Undesirable effects were usually managed by dose adjustment.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV-infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Moderate and usually reversible pancytopenia has been reported. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

Children and adolescent population

Chronic Hepatitis C - Combination therapy with ribavirin

In clinical trials of 118 children and adolescents (3 to 16 years of age), 6 % discontinued therapy due to adverse reactions. In general, the adverse reaction profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric- specific concern regarding growth inhibition as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile) were observed during treatment. Within the 5 years follow-up post-treatment period, the children had a mean height of 44th percentile, which was below the median of the normative population and less than their mean baseline height (48th percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years). Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment. During combination therapy for up to 48 weeks with IntronA and ribavirin, growth inhibition was observed that resulted in reduced final adult height in some patients. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from the two multicentre children and adolescent clinical trials. Within the organ system classes, adverse reactions are listed under headings

of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Adverse reactions very commonly and commonly reported during clinical trials inchildren and adolescent patients treated with IntronA in combination with ribavirin

System Organ Class	Adverse Reactions
Infection and infestations Very common: Common:	 Viral infection, pharyngitis Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Neoplasms benign, malignant and unspecified (including cysts and polyps) Common:	 Neoplasm (unspecified)
Blood and lymphatic system disorders Very common: Common:	 Anaemia, neutropaenia Thrombocytopaenia, lymphadenopathy
Endocrine disorders Very common: Common:	 Hypothyroidism[§], Hyperthyroidism[§], virilism
Metabolism and nutrition disorders Very common: Common:	 Anorexia Hypertriglyceridemia[§], hyperuricemia, increased appetite
Psychiatric disorders[§] Very common: Common:	 Depression, emotional lability, insomnia Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy
Nervous system disorders[§] Very common: Common:	 Headache, dizziness Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence
Eye disorders Common:	 Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Vascular disorders Common:	 Flushing, pallor
Respiratory, thoracic and mediastinal disorders Common:	 Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing
Gastrointestinal disorders Very common: Common:	 Diarrhoea, vomiting, nausea, abdominal pain Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder
Hepatobiliary disorders Common:	 Hepatic function abnormal

Skin and subcutaneous tissue disorders Very common: Common:	 Alopecia, rash Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased
Musculoskeletal and connective tissue disorders Very common:	 Arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders Common:	 Enuresis, micturition disorder, urinary incontinence
Reproductive system and breast disorders Common:	 Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder Male: testicular pain
General disorders and administration site conditions Very common: Common:	 Injection site inflammation, injection site reaction, fatigue, rigors, pyrexia[§], influenza-like symptoms[§], malaise, irritability Chest pain, asthenia, oedema, injection site pain
Investigations Very common:	 Growth rate decrease (height and/or weight decrease for age)[§]
Injury and poisoning Common:	 Skin laceration

[§]See section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: interferon alfa-2b, ATC code: L03A B05

IntronA is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of IntronA is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity

of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. IntronA has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B

Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/m^2 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C in adult patients

In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

IntronA alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of IntronA used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/mL), a liver

biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

IntronA was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with IntronA alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of IntronA with ribavirin increased the efficacy of IntronA by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of IntronA + ribavirin, compared with IntronA alone, is maintained across all subgroups. The relative benefit of combination therapy with IntronA + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received IntronA in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

Table 3 Sustained virologic response rates with IntronA + ribavirin (one year of treatment) by genotype and viral load

HCV Genotype	**I N=503 C95-132/I95-143**	**I/R N=505 C95-132/I95-143**	**I/R N=505 C/I98-580**
All Genotypes	**16 %**	**41 %**	**47 %**
Genotype 1	9 %	29 %	33 %
Genotype 1 ≤ 2 million copies/mL	25 %	33 %	45 %
Genotype 1 > 2 million copies/mL	3 %	27 %	29 %
Genotype 2/3	31 %	65 %	79 %

I IntronA (3 MIU 3 times a week)
I/R IntronA (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

HCV/HIV Co-infected patients
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received IntronA plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or IntronA (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based

on weight) plus ribavirin (800-1,200 mg/day based on weight) or IntronA (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/mL (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

Table 4 Sustained virological response based on genotype after IntronA in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

	Study 1[1]			**Study 2**[2]		
	pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg)	IntronA (3 MIU TIW) + ribavirin (800 mg)	p value[a]	pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d]	IntronA (3 MIU TIW) + ribavirin (800-1,200 mg)[d]	p value[b]
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients
A total of 345 interferon alpha relapse patients were treated in two clinical trials with IntronA monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to IntronA increased by as much as 10-fold the efficacy of IntronA used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/mL by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non-pegylated interferon alfa-2b or non-pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Chronic hepatitis C in children and adolescent population

Three clinical trials have been conducted in children and adolescents; two with standard interferon and ribavirin and one with pegylated interferon and ribavirin. Patients who received IntronA plus ribavirin were less likely to respond than patients who received pegylated interferon alfa-2b and ribavirin.

Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received IntronA 3 MIU/m^2 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. In the two multicentre trials sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in these two multicentre trials for children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

Table 5 Sustained virological response in previously untreated children and adolescents

	IntronA 3 MIU/m^2 3 times a week + **ribavirin 15 mg/kg/day**
Overall Response[a] (n=118)	54 (46 %)*
Genotype 1 (n=92)	33 (36 %)*
Genotype 2/3/4 (n=26)	21 (81 %)*

*Number (%) of patients

[a] Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

Long-term efficacy data

A five-year long-term, observational, follow-up study enrolled 97 paediatric chronic hepatitis C patients after treatment in the standard interferon multicentre trials. Seventy percent (68/97) of all enrolled subjects completed this study of which 75 % (42/56) were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment of the 48-week interferon alfa-2b and ribavirin treatment. All but one of the paediatric subjects remained sustained virologic responders during long-term follow-up after completion of treatment with interferon alfa-2b plus ribavirin. The Kaplan-Meier estimate for continued sustained response over 5 years is 98 % [95 % CI: 95 %, 100 %] for paediatric patients treated with interferon alfa-2b and ribavirin. Additionally, 98 % (51/52) with normal ALT levels at follow-up week 24 maintained normal ALT levels at their last visit.

SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b with ribavirin results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Results from the clinical trial conducted with pegylated interferon alfa-2b and ribavirin

In a multicentre trial children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with peginterferon alfa-2b 60 μg/m^2 plus ribavirin 15 mg/kg per day once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received

treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of peginterferon alfa-2b with ribavirin needs to be carefully considered in this population (see peginterferon alfa-2b and ribavirin SPCs section 4.4). The study results are summarized in **Table 6.**

Table 6 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects
n = 107

	24 weeks	**48 weeks**
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment, lower limit of detection=125 IU/mL.

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/mL) were to receive 48 weeks of treatment.

5.2 Pharmacokinetic properties

The pharmacokinetics of IntronA were studied in healthy volunteers following single 5 million IU/m^2 and 10 million IU doses administered subcutaneously, at 5 million IU/m^2 administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. C_{max} occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/mL) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

Interferon neutralising factor assays were performed on serum samples of patients who received IntronA in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

Children and adolescent population
Multiple-dose pharmacokinetic properties for IntronA injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 7**. The pharmacokinetics of IntronA and ribavirin (dose-normalized) are similar in adults and children or adolescents.

Table 7 Mean (% CV) multiple-dose pharmacokinetic parameters for IntronA and ribavirin capsules when administered to children or adolescents with chronic hepatitis C		
Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**IntronA** 3 MIU/m^2 3 times a week (n = 54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3,275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	Not done

*AUC_{12} (ng.hr/mL) for ribavirin; AUC_{0-24} (IU.hr/mL) for IntronA

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20×10^6 IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100×10^6 IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

<u>IntronA plus ribavirin</u>
No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if IntronA is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate anhydrous
Sodium dihydrogen phosphate monohydrate
Edetate disodium
Sodium chloride

M-cresol
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

After first opening the container: Chemical and physical in-use stability has been demonstrated for 28 days at 2ºC – 8ºC.
From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.
Within its shelf-life, for the purpose of transport, the solution can be kept at or below 25ºC for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2.5 mL of solution (corresponding to 25 MIU) is contained in a multidose vial (type I glass) with a stopper (halobutyl rubber) in a flip-off seal (aluminium) with a bonnet (polypropylene).

IntronA is supplied as:
- Pack of 1 vial
- Pack of 1 vial, 6 injection syringes of 1 mL, 6 injection needles and 12 cleansing swabs
- Pack of 1 vial, 6 injection syringes with attached needle and needle protection device of 1 mL and 12 cleansing swabs
- Pack of 1 vial, 6 injection syringes with attached needle of 1 mL and 12 cleansing swabs
- Pack of 2 vials
- Pack of 2 vials, 12 injection syringes of 1 mL, 12 injection needles and 24 cleansing swabs
- Pack of 2 vials, 12 injection syringes with attached needle and needle protection device of 1 mL and 24 cleansing swabs
- Pack of 2 vials, 12 injection syringes with attached needle of 1 mL and 24 cleansing swabs
- Pack of 12 vials
- Pack of 12 vials, 72 injection syringes of 1 mL, 72 injection needles and 144 cleansing swabs
- Pack of 12 vials, 72 injection syringes with attached needle and needle protection device of 1 mL and 144 cleansing swabs
- Pack of 12 vials, 72 injection syringes with attached needle of 1 mL and 144 cleansing swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not all dose forms and strengths are appropriate for some indications. Please make sure to select an appropriate dose form and strength.

IntronA solution for injection or infusion may be injected directly after withdrawal of the appropriate doses from the vial with a sterile injection syringe.

Detailed instructions for the subcutaneous use of the product are provided with the package leaflet (refer to “How to self inject IntronA”).

Preparation of IntronA for intravenous infusion: The infusion is to be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

No other medicinal product can be infused concomitantly with IntronA.

As with all parenteral medicinal products, prior to administration inspect IntronA, solution for injection or infusion, visually for particulate matter and discolouration. The solution should be clear and colourless.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/127/027
EU/1/99/127/028
EU/1/99/127/029
EU/1/99/127/030
EU/1/99/127/043
EU/1/99/127/044
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EU/1/99/127/049
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EU/1/99/127/053

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 March 2000
Date of latest renewal: 9 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

IntronA 18 million IU solution for injection in multidose pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pen contains 18 million IU of recombinant interferon alfa-2b produced in *E. coli* by recombinant DNA technology, in 1.2 mL solution.

One mL contains 15 million IU of interferon alfa-2b.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B
Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of DNA of hepatitis B virus (HBV-DNA) and hepatitis B antigen (HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic hepatitis C
Before initiating treatment with IntronA, consideration should be given to the results from clinical trials comparing IntronA with pegylated interferon (see section 5.1).

Adult patients
IntronA is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for hepatitis C virus RNA (HCV-RNA) (see section 4.4).

The best way to use IntronA in this indication is in combination with ribavirin.

Children 3 years of age and older and adolescents
IntronA is indicated, in a combination regimen with ribavirin, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
The decision to treat should be made on a case by case basis (see section 4.4).

Hairy cell leukaemia
Treatment of patients with hairy cell leukaemia.

Chronic myelogenous leukaemia

Monotherapy

Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia.

Clinical experience indicates that a haematological and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is ≥ 34 %, but < 90 % Ph+ cells in the marrow.

Combination therapy

The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.

Multiple myeloma

As maintenance therapy in patients who have achieved objective remission (more than 50 % reduction in myeloma protein) following initial induction chemotherapy.

Current clinical experience indicates that maintenance therapy with interferon alfa-2b prolongs the plateau phase; however, effects on overall survival have not been conclusively demonstrated.

Follicular lymphoma

Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.

Carcinoid tumour

Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome".

Malignant melanoma

As adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement.

4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Multidose presentations must be for individual patient use only.

The pen is designed to deliver its contents of 18 million IU in doses ranging from 1.5 to 6 million IU. The pen will deliver a maximum of 12 doses of 1.5 million IU over a period not to exceed 4 weeks.

Not all dose forms and strengths are appropriate for some indications. Appropriate dose form and strength must be selected.

If adverse events develop during the course of treatment with IntronA for any indication, modify the dose or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dose adjustment, or disease progresses, discontinue treatment with IntronA. At the discretion of the physician, the patient may self-administer the dose for maintenance dose regimens administered subcutaneously.

Chronic hepatitis B
The recommended dose is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/mm^3, granulocytes < 1,000/mm^3, thrombocytes < 100,000/mm^3). Treatment should be discontinued in case of severe leukopaenia (< 1,200/mm^3), severe neutropaenia (< 750/mm^3) or severe thrombocytopaenia (< 70,000/mm^3).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue IntronA therapy.

Chronic hepatitis C
Adults
IntronA is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

Children 3 years of age or older and adolescents
IntronA 3 MIU/m^2 is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsules SPC for dose of ribavirin capsules and dose modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC.)

Relapse patients (adults)
IntronA is given in combination with ribavirin. Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for 6 months.

Naïve patients (adults)
The efficacy of IntronA is enhanced when given in combination with ribavirin. IntronA should be given alone mainly in case of intolerance or contraindication to ribavirin.

- IntronA in combination with ribavirin
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

- IntronA alone
The optimal duration of therapy with IntronA alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with IntronA alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

Naïve patients (children and adolescents)
The efficacy and safety of IntronA in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Duration of treatment for children and adolescents

- Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Therefore, it is recommended that children and adolescent patients receiving IntronA/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment, or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2/3: The recommended duration of treatment is 24 weeks.

Hairy cell leukaemia
The recommended dose is 2 million IU/m^2 administered subcutaneously three times a week (every other day) for both splenectomised and non-splenectomised patients. For most patients with Hairy Cell Leukaemia, normalisation of one or more haematological variables occurs within one to two months of IntronA treatment. Improvement in all three haematological variables (granulocyte count, platelet count and haemoglobin level) may require six months or more. This regimen must be maintained unless the disease progresses rapidly or severe intolerance is manifested.

Chronic myelogenous leukaemia
The recommended dose of IntronA is 4 to 5 million IU/m^2 administered daily subcutaneously. Some patients have been shown to benefit from IntronA 5 million IU/m^2 administered daily subcutaneously in association with cytarabine (Ara-C) 20 mg/m^2 administered daily subcutaneously for 10 days per month (up to a maximum daily dose of 40 mg). When the white blood cell count is controlled, administer the maximum tolerated dose of IntronA (4 to 5 million IU/m^2 daily) to maintain haematological remission.

IntronA treatment must be discontinued after 8 to 12 weeks of treatment if at least a partial haematological remission or a clinically meaningful cytoreduction has not been achieved.

Multiple myeloma
Maintenance therapy
In patients who are in the plateau phase (more than 50 % reduction of myeloma protein) following initial induction chemotherapy, interferon alfa-2b may be administered as monotherapy, subcutaneously, at a dose of 3 million IU/m^2 three times a week (every other day).

Follicular lymphoma
Adjunctively with chemotherapy, interferon alfa-2b may be administered subcutaneously, at a dose of 5 million IU three times a week (every other day) for a duration of 18 months. CHOP-like regimens are advised, but clinical experience is available only with CHVP (combination of cyclophosphamide, doxorubicin, teniposide and prednisolone).

Carcinoid tumour
The usual dose is 5 million IU (3 to 9 million IU) administered subcutaneously three times a week (every other day). Patients with advanced disease may require a daily dose of 5 million IU. The treatment is to be temporarily discontinued during and after surgery. Therapy may continue for as long as the patient responds to interferon alfa-2b treatment.

Malignant melanoma
As induction therapy, interferon alfa-2b is administered intravenously at a dose of 20 million IU/m^2 daily for five days a week for a four-week period; the calculated interferon alfa-2b dose is added to sodium chloride 9 mg/mL (0.9 %) solution for injection and administered as a 20-minute infusion (see section 6.6). As maintenance treatment, the recommended dose is 10 million IU/m^2 administered subcutaneously three days a week (every other day) for 48 weeks.

If severe adverse events develop during interferon alfa-2b treatment, particularly if granulocytes decrease to < 500/mm^3 or alanine aminotransferase/aspartate aminotransferase (ALT/AST) rises to > 5 x upper limit of normal, discontinue treatment temporarily until the adverse event abates. Interferon alfa-2b treatment is to be restarted at 50 % of the previous dose. If intolerance persists after dose adjustment or if granulocytes decrease to < 250/mm^3 or ALT/AST rises to > 10 x upper limit of normal, discontinue interferon alfa-2b therapy.

Although the optimal (minimum) dose for full clinical benefit is unknown, patients must be treated at the recommended dose, with dose reduction for toxicity as described.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.
- Combination of IntronA with telbivudine.

Children and adolescents
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

4.4 Special warnings and precautions for use

Psychiatric and central nervous system (CNS)
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during IntronA therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents treated with IntronA in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or

suicidal or homicidal ideation is identified, it is recommended that treatment with IntronA be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions:
If treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

Patients with substance use/abuse:
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Children and adolescent population: Growth and development (chronic hepatitis C)
During the course of interferon (standard and pegylated)/ribavirin combination therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children (n=20) despite being off treatment for more than 5 years. Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment.

Case by case benefit/risk assessment in children
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response, (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

Hypersensitivity reactions
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during IntronA therapy. If such a reaction develops, discontinue the medicine and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Adverse experiences including prolongation of coagulation markers and liver abnormalities
Moderate to severe adverse experiences may require modification of the patient's dose regimen, or in some cases, termination of IntronA therapy. IntronA increases the risk of liver decompensation and death in patients with cirrhosis.

Discontinue treatment with IntronA in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decomposition.
Any patient developing liver function abnormalities during treatment with IntronA must be monitored closely and treatment discontinued if signs and symptoms progress.
Liver enzymes and hepatic function should be closely monitored in cirrhotic patients.

Hypotension
Hypotension may occur during IntronA therapy or up to two days post-therapy and may require supportive treatment.

Need for adequate hydration
Adequate hydration must be maintained in patients undergoing IntronA therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Pyrexia
While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Patients with debilitating medical conditions
IntronA must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary conditions
Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events
Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, serous retinal detachment, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with IntronA, must have a prompt and complete eye examination. Periodic visual examinations during IntronA therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of IntronA should be considered in patients who develop new or worsening ophthalmological disorders.

Obtundation, coma and encephalopathy
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of IntronA.

Patients with pre-existing cardiac abnormalities
Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require IntronA therapy, must be closely monitored. It is

recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of IntronA therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia
Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Patients with psoriasis and sarcoidosis
Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of IntronA in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Kidney and liver graft rejection
Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Auto-antibodies and autoimmune disorders
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Concomitant chemotherapy
Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered medicinal product. The most commonly reported potentially life-threatening or fatal adverse events include mucositis, diarrhoea, neutropaenia, renal impairment, and electrolyte disturbance. Because of the risk of increased toxicity, careful adjustments of doses are required for IntronA and for the concomitant chemotherapeutic agents (see section 4.5). When IntronA is used with hydroxyurea, the frequency and severity of cutaneous vasculitis may be increased.

Chronic hepatitis C
Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy
Infrequently, adult patients treated for chronic hepatitis C with IntronA developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using IntronA therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which IntronA may alter thyroid status is unknown. Prior to initiation of IntronA therapy for the treatment of chronic hepatitis C,

evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of IntronA therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, IntronA treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of IntronA therapy has not reversed thyroid dysfunction occurring during treatment (also see Thyroid supplemental monitoring specific for children and adolescents).

Thyroid supplemental monitoring specific for children and adolescents
Approximately 12 % of children treated with interferon alfa-2b and ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of IntronA therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding IntronA and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with IntronA and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of IntronA and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with IntronA.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during IntronA therapy to greater than or equal to 2 times baseline, IntronA therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, the following liver function tests must be monitored at two-week intervals: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin.

In patients treated for malignant melanoma, liver function and white blood cell (WBC) count and differential must be monitored weekly during the induction phase of therapy and monthly during the maintenance phase of therapy.

Effect on fertility
Interferon may impair fertility (see section 4.6 and section 5.3).

Important information about some of the ingredients of IntronA
This medicinal product contains less than 1 mmol sodium (23 mg) per 1.2 mL, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with IntronA.

Interactions between IntronA and other medicinal products have not been fully evaluated. Caution must be exercised when administering IntronA in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dose adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration) (see section 4.4).

Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C) .

A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see sections 4.3, 4.4 and 4.5 of the telbivudine SPC). Moreover, the safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated. Therefore, the combination of IntronA with telbivudine is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Women of childbearing potential have to use effective contraception during treatment. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

IntronA must be used with caution in fertile men.

Combination therapy with ribavirin
Ribavirin causes serious birth defects when administered during pregnancy. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking IntronA in combination with ribavirin. Females of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female

partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. IntronA is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Combination therapy with ribavirin
Ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with IntronA, and therefore it is recommended that they avoid driving or operating machinery.

4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/m^2/week in hairy cell leukaemia up to 100 MIU/m^2/week in melanoma), the most commonly reported undesirable effects were pyrexia, fatigue, headache and myalgia. Pyrexia and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

Adults
In clinical trials conducted in the hepatitis C population, patients were treated with IntronA alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of IntronA three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rarely (≥1/10,000 to <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported during clinical trials or following the marketing use of IntronA alone or in combination with ribavirin

System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Pharyngitis*, infection viral*
Common:	Bronchitis, sinusitis, herpes simplex (resistance), rhinitis
Uncommon:	Bacterial infection
Rarely:	Pneumonia[§], sepsis

Blood and lymphatic system disorders	
Very common:	Leukopaenia
Common:	Thrombocytopaenia, lymphadenopathy, lymphopenia
Very rarely:	Aplastic anaemia
Not known**:**	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Immune system disorders[§]	
Very rarely:	Sarcoidosis, exacerbation of sarcoidosis
Not known:	Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§]
Endocrine disorders	
Common:	Hypothyroidism[§], hyperthyroidism[§]
Very rarely:	Diabetes, aggravated diabetes
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hypocalcaemia, dehydration, hyperuricemia, thirst
Very rarely:	Hyperglycaemia, hypertriglyceridaemia[§], increased appetite
Psychiatric disorders[§]	
Very common:	Depression, insomnia, anxiety, emotional lability*, agitation, nervousness
Common:	Confusion, sleep disorder, libido decreased
Rarely:	Suicide ideation
Very rarely:	Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations
Not known:	Homicidal ideation, mental status change[§], mania, bipolar disorders
Nervous system disorders[§]	
Very common:	Dizziness, headache, concentration impaired, mouth dry
Common:	Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion
Uncommon:	Peripheral neuropathy
Very rarely:	Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy
Not known:	Mononeuropathies, coma[§]
Eye disorders	
Very common:	Vision blurred
Common:	Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain
Rarely:	Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§]
Not known:	Serous retinal detachment
Ear and labyrinth	
Common:	Vertigo, tinnitus
Very rarely:	Hearing loss, hearing disorder
Cardiac disorders	
Common:	Palpitation, tachycardia
Rarely:	Cardiomyopathy
Very rarely:	Myocardial infarction, cardiac ischaemia
Not known:	Congestive heart failure, pericardial effusion, arrhythmia

Vascular disorders	
Common:	Hypertension
Very rarely:	Peripheral ischaemia, hypotension[§]
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea*, coughing*
Common:	Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive
Very rarely:	Pulmonary infiltrates[§], pneumonitis[§]
Not known:	Pulmonary fibrosis, pulmonary arterial hypertension[#]
Gastrointestinal disorders	
Very common:	Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia
Common:	Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools
Very rarely:	Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding
Not known:	Periodontal disorder NOS, dental disorder NOS[§]
Hepatobiliary disorders	
Common:	Hepatomegaly
Very rarely:	Hepatotoxicity, (including fatality)
Skin and subcutaneous tissue disorders	Alopecia, pruritus*, skin dry*, rash*, sweating increased
Very common:	Psoriasis (new or aggravated)[§], rash maculopapular, rash
Common:	erythematous, eczema, erythema, skin disorder
Very rarely:	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, musculoskeletal pain
Common:	Arthritis
Very rarely:	Rhabdomyolysis, myositis, leg cramps, back pain
Renal and urinary disorders	
Common:	Micturition frequency
Very rarely:	Renal failure, renal insufficiency, nephrotic syndrome
Reproductive system and breast disorders	
Common:	Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction*, fatigue, rigors, pyrexia[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise
Common:	Injection site pain
Very rarely:	Injection site necrosis, face oedema
Investigations	
Very common:	Weight decrease

*These events were only common with IntronA alone

[§]See section 4.4

[#]Class label for interferon products, see below Pulmonary arterial hypertension

These undesirable effects have also been reported with IntronA alone.

The undesirable effects seen with hepatitis C are representative of those reported when IntronA is administered in other indications, with some anticipated dose-related increases in incidence. For example, in a trial of high-dose adjuvant IntronA treatment in patients with melanoma, incidences of fatigue, pyrexia, myalgia, neutropaenia/anaemia, anorexia, nausea and vomiting, diarrhoea, chills, flu-like symptoms, depression, alopecia, altered taste, and dizziness were greater than in the hepatitis C trials. Severity also increased with high dose therapy (WHO Grade 3 and 4, in 66 % and 14 % of patients, respectively), in comparison with the mild to moderate severity usually associated with lower doses. Undesirable effects were usually managed by dose adjustment.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV-infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Moderate and usually reversible pancytopenia has been reported. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

Children and adolescent population

Chronic Hepatitis C - Combination therapy with ribavirin

In clinical trials of 118 children and adolescents (3 to 16 years of age), 6 % discontinued therapy due to adverse reactions. In general, the adverse reaction profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric- specific concern regarding growth inhibition as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile) were observed during treatment. Within the 5 years follow-up post-treatment period, the children had a mean height of 44th percentile, which was below the median of the normative population and less than their mean baseline height (48th percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years). Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment. During combination therapy for up to 48 weeks with IntronA and ribavirin, growth inhibition was observed that resulted in reduced final adult height in some patients. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from the two multicentre children and adolescent clinical trials. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Adverse reactions very commonly and commonly reported during clinical trials inchildren and adolescent patients treated with IntronA in combination with ribavirin

System Organ Class	Adverse Reactions
Infection and infestations Very common: Common:	 Viral infection, pharyngitis Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Neoplasms benign, malignant and unspecified (including cysts and polyps) Common:	 Neoplasm (unspecified)
Blood and lymphatic system disorders Very common: Common:	 Anaemia, neutropaenia Thrombocytopaenia, lymphadenopathy
Endocrine disorders Very common: Common:	 Hypothyroidism[§], Hyperthyroidism[§], virilism
Metabolism and nutrition disorders Very common: Common:	 Anorexia Hypertriglyceridemia[§], hyperuricemia, increased appetite
Psychiatric disorders[§] Very common: Common:	 Depression, emotional lability, insomnia Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy
Nervous system disorders[§] Very common: Common:	 Headache, dizziness Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence
Eye disorders Common:	 Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Vascular disorders Common:	 Flushing, pallor
Respiratory, thoracic and mediastinal disorders Common:	 Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing
Gastrointestinal disorders Very common: Common:	 Diarrhoea, vomiting, nausea, abdominal pain Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder
Hepatobiliary disorders Common:	 Hepatic function abnormal

Skin and subcutaneous tissue disorders Very common: Common:	 Alopecia, rash Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased
Musculoskeletal and connective tissue disorders Very common:	 Arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders Common:	 Enuresis, micturition disorder, urinary incontinence
Reproductive system and breast disorders Common:	 Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder Male: testicular pain
General disorders and administration site conditions Very common: Common:	 Injection site inflammation, injection site reaction, fatigue, rigors, pyrexia[§], influenza-like symptoms[§], malaise, irritability Chest pain, asthenia, oedema, injection site pain
Investigations Very common:	 Growth rate decrease (height and/or weight decrease for age)[§]
Injury and poisoning Common:	 Skin laceration

[§]See section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: interferon alfa-2b, ATC code: L03A B05

IntronA is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of IntronA is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity

of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. IntronA has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B

Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/m^2 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C in adult patients

In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

IntronA alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of IntronA used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/mL), a liver

biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

IntronA was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with IntronA alone or in combination with ribavirin (from two studies) are shown in **Table 3.**

Co-administration of IntronA with ribavirin increased the efficacy of IntronA by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of IntronA + ribavirin, compared with IntronA alone, is maintained across all subgroups. The relative benefit of combination therapy with IntronA + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received IntronA in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

Table 3 Sustained virologic response rates with IntronA + ribavirin (one year of treatment) by genotype and viral load

HCV Genotype	**I N=503 C95-132/I95-143**	**I/R N=505 C95-132/I95-143**	**I/R N=505 C/I98-580**
All Genotypes	**16 %**	**41 %**	**47 %**
Genotype 1	9 %	29 %	33 %
Genotype 1 ≤ 2 million copies/mL	25 %	33 %	45 %
Genotype 1 > 2 million copies/mL	3 %	27 %	29 %
Genotype 2/3	31 %	65 %	79 %

I IntronA (3 MIU 3 times a week)
I/R IntronA (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

HCV/HIV Co-infected patients
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received IntronA plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or IntronA (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based

on weight) plus ribavirin (800-1,200 mg/day based on weight) or IntronA (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/mL (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

Table 4 Sustained virological response based on genotype after IntronA in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

	Study 1[1]			**Study 2**[2]		
	pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg)	IntronA (3 MIU TIW) + ribavirin (800 mg)	p value[a]	pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d]	IntronA (3 MIU TIW) + ribavirin (800-1,200 mg)[d]	p value[b]
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients
A total of 345 interferon alpha relapse patients were treated in two clinical trials with IntronA monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to IntronA increased by as much as 10-fold the efficacy of IntronA used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/mL by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non-pegylated interferon alfa-2b or non-pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Chronic hepatitis C in children and adolescent population

Three clinical trials have been conducted in children and adolescents; two with standard interferon and ribavirin and one with pegylated interferon and ribavirin. Patients who received IntronA plus ribavirin were less likely to respond than patients who received pegylated interferon alfa-2b and ribavirin.

Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received IntronA 3 MIU/m^2 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. In the two multicentre trials sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in these two multicentre trials for children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

Table 5 Sustained virological response in previously untreated children and adolescents

	IntronA 3 MIU/m^2 3 times a week + **ribavirin 15 mg/kg/day**
Overall Response[a] (n=118)	54 (46 %)*
Genotype 1 (n=92)	33 (36 %)*
Genotype 2/3/4 (n=26)	21 (81 %)*

*Number (%) of patients

[a] Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

Long-term efficacy data

A five-year long-term, observational, follow-up study enrolled 97 paediatric chronic hepatitis C patients after treatment in the standard interferon multicentre trials. Seventy percent (68/97) of all enrolled subjects completed this study of which 75 % (42/56) were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment of the 48-week interferon alfa-2b and ribavirin treatment. All but one of the paediatric subjects remained sustained virologic responders during long-term follow-up after completion of treatment with interferon alfa-2b plus ribavirin. The Kaplan-Meier estimate for continued sustained response over 5 years is 98 % [95 % CI: 95 %, 100 %] for paediatric patients treated with interferon alfa-2b and ribavirin. Additionally, 98 % (51/52) with normal ALT levels at follow-up week 24 maintained normal ALT levels at their last visit.

SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b with ribavirin results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Results from the clinical trial conducted with pegylated interferon alfa-2b and ribavirin

In a multicentre trial children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with peginterferon alfa-2b 60 μg/m^2 plus ribavirin 15 mg/kg per day once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received

treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of peginterferon alfa-2b with ribavirin needs to be carefully considered in this population (see peginterferon alfa-2b and ribavirin SPCs section 4.4). The study results are summarized in **Table 6.**

Table 6 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects
n = 107

	24 weeks	**48 weeks**
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment, lower limit of detection=125 IU/mL.

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/mL) were to receive 48 weeks of treatment.

5.2 Pharmacokinetic properties

The pharmacokinetics of IntronA were studied in healthy volunteers following single 5 million IU/m^2 and 10 million IU doses administered subcutaneously, at 5 million IU/m^2 administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. C_{max} occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/mL) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

Interferon neutralising factor assays were performed on serum samples of patients who received IntronA in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

Children and adolescent population
Multiple-dose pharmacokinetic properties for IntronA injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 7**. The pharmacokinetics of IntronA and ribavirin (dose-normalized) are similar in adults and children or adolescents.

Table 7 Mean (% CV) multiple-dose pharmacokinetic parameters for IntronA and ribavirin capsules when administered to children or adolescents with chronic hepatitis C		
Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**IntronA** 3 MIU/m^2 3 times a week (n = 54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3,275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	Not done

*AUC_{12} (ng.hr/mL) for ribavirin; AUC_{0-24} (IU.hr/mL) for IntronA

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20×10^6 IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100×10^6 IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

<u>IntronA plus ribavirin</u>
No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if IntronA is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate anhydrous
Sodium dihydrogen phosphate monohydrate
Edetate disodium
Sodium chloride

M-cresol
Polysorbate 80
Water for injections q.s.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

15 months.

Chemical and physical in-use stability has been demonstrated for 27 days at 2ºC – 8ºC.
From a microbiological point of view, once opened, the product may be stored for a maximum of 27 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1.2 mL of solution (corresponding to 18 MIU) is contained in a pen made of a cartridge (type I glass) sealed at one end with a cap (aluminium) containing a liner (bromobutyl rubber) and at the other end by a plunger (bromobutyl rubber).

IntronA is supplied as:
- Pack of 1 pen, 12 injection needles and 12 cleansing swabs
- Pack of 2 pens, 24 injection needles and 24 cleansing swabs
- Pack of 8 pens, 96 injection needles and 96 cleansing swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not all dose forms and strengths are appropriate for some indications. Please make sure to select an appropriate dose form and strength.

IntronA, solution for injection in multidose pen is injected subcutaneously after attaching an injection needle and dialing the prescribed dose.

Remove the pen from the refrigerator approximately 30 minutes before administration to allow the injectable solution to reach room temperature (not more than 25°C).

Detailed instructions for the use of the product are provided with the package leaflet (refer to “How to self inject IntronA”).

Each pen is intended for a maximum four-week use period and must then be discarded. A new injection needle must be used for each dose. After each use, the injection needle must be discarded safely and the pen must be returned immediately to the refrigerator. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week use period to cover accidental delays in returning the pen to the refrigerator.

Sufficient needles and swabs are provided to use the IntronA pen for administering the smallest measurable doses. Instruct the patient that any extra needles and swabs that remain after the final dose has been taken from the pen must be discarded appropriately and safely.

As with all parenteral medicinal products, prior to administration inspect IntronA, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/127/031
EU/1/99/127/032
EU/1/99/127/033

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 March 2000
Date of latest renewal: 9 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

IntronA 30 million IU solution for injection in multidose pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pen contains 30 million IU of recombinant interferon alfa-2b produced in *E. coli* by recombinant DNA technology, in 1.2 mL solution.

One mL contains 25 million IU of interferon alfa-2b.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B
Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of DNA of hepatitis B virus (HBV-DNA) and hepatitis B antigen (HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic hepatitis C
Before initiating treatment with IntronA, consideration should be given to the results from clinical trials comparing IntronA with pegylated interferon (see section 5.1).

Adult patients
IntronA is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for hepatitis C virus RNA (HCV-RNA) (see section 4.4).

The best way to use IntronA in this indication is in combination with ribavirin.

Children 3 years of age and older and adolescents
IntronA is indicated, in a combination regimen with ribavirin, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
The decision to treat should be made on a case by case basis (see section 4.4).

Hairy cell leukaemia
Treatment of patients with hairy cell leukaemia.

Chronic myelogenous leukaemia

Monotherapy

Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia.

Clinical experience indicates that a haematological and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is ≥ 34 %, but < 90 % Ph+ cells in the marrow.

Combination therapy

The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.

Multiple myeloma

As maintenance therapy in patients who have achieved objective remission (more than 50 % reduction in myeloma protein) following initial induction chemotherapy.

Current clinical experience indicates that maintenance therapy with interferon alfa-2b prolongs the plateau phase; however, effects on overall survival have not been conclusively demonstrated.

Follicular lymphoma

Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.

Carcinoid tumour

Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome".

Malignant melanoma

As adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement.

4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Multidose presentations must be for individual patient use only.

The pen is designed to deliver its contents of 30 million IU in doses ranging from 2.5 to 10 million IU. The pen will deliver a maximum of 12 doses of 2.5 million IU over a period not to exceed 4 weeks.

Not all dose forms and strengths are appropriate for some indications. Appropriate dose form and strength must be selected.

If adverse events develop during the course of treatment with IntronA for any indication, modify the dose or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dose adjustment, or disease progresses, discontinue treatment with IntronA. At the discretion of the physician, the patient may self-administer the dose for maintenance dose regimens administered subcutaneously.

Chronic hepatitis B
The recommended dose is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/mm^3, granulocytes < 1,000/mm^3, thrombocytes < 100,000/mm^3). Treatment should be discontinued in case of severe leukopaenia (< 1,200/mm^3), severe neutropaenia (< 750/mm^3) or severe thrombocytopaenia (< 70,000/mm^3).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue IntronA therapy.

Chronic hepatitis C
Adults
IntronA is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

Children 3 years of age or older and adolescents
IntronA 3 MIU/m^2 is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsules SPC for dose of ribavirin capsules and dose modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC.)

Relapse patients (adults)
IntronA is given in combination with ribavirin. Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for 6 months.

Naïve patients (adults)
The efficacy of IntronA is enhanced when given in combination with ribavirin. IntronA should be given alone mainly in case of intolerance or contraindication to ribavirin.

- IntronA in combination with ribavirin
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

- IntronA alone
The optimal duration of therapy with IntronA alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with IntronA alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

Naïve patients (children and adolescents)
The efficacy and safety of IntronA in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Duration of treatment for children and adolescents

- Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Therefore, it is recommended that children and adolescent patients receiving IntronA/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment, or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2/3: The recommended duration of treatment is 24 weeks.

Hairy cell leukaemia
The recommended dose is 2 million IU/m^2 administered subcutaneously three times a week (every other day) for both splenectomised and non-splenectomised patients. For most patients with Hairy Cell Leukaemia, normalisation of one or more haematological variables occurs within one to two months of IntronA treatment. Improvement in all three haematological variables (granulocyte count, platelet count and haemoglobin level) may require six months or more. This regimen must be maintained unless the disease progresses rapidly or severe intolerance is manifested.

Chronic myelogenous leukaemia
The recommended dose of IntronA is 4 to 5 million IU/m^2 administered daily subcutaneously. Some patients have been shown to benefit from IntronA 5 million IU/m^2 administered daily subcutaneously in association with cytarabine (Ara-C) 20 mg/m^2 administered daily subcutaneously for 10 days per month (up to a maximum daily dose of 40 mg). When the white blood cell count is controlled, administer the maximum tolerated dose of IntronA (4 to 5 million IU/m^2 daily) to maintain haematological remission.

IntronA treatment must be discontinued after 8 to 12 weeks of treatment if at least a partial haematological remission or a clinically meaningful cytoreduction has not been achieved.

Multiple myeloma
Maintenance therapy
In patients who are in the plateau phase (more than 50 % reduction of myeloma protein) following initial induction chemotherapy, interferon alfa-2b may be administered as monotherapy, subcutaneously, at a dose of 3 million IU/m^2 three times a week (every other day).

Follicular lymphoma
Adjunctively with chemotherapy, interferon alfa-2b may be administered subcutaneously, at a dose of 5 million IU three times a week (every other day) for a duration of 18 months. CHOP-like regimens are advised, but clinical experience is available only with CHVP (combination of cyclophosphamide, doxorubicin, teniposide and prednisolone).

Carcinoid tumour
The usual dose is 5 million IU (3 to 9 million IU) administered subcutaneously three times a week (every other day). Patients with advanced disease may require a daily dose of 5 million IU. The treatment is to be temporarily discontinued during and after surgery. Therapy may continue for as long as the patient responds to interferon alfa-2b treatment.

Malignant melanoma
As induction therapy, interferon alfa-2b is administered intravenously at a dose of 20 million IU/m^2 daily for five days a week for a four-week period; the calculated interferon alfa-2b dose is added to sodium chloride 9 mg/mL (0.9 %) solution for injection and administered as a 20-minute infusion (see section 6.6). As maintenance treatment, the recommended dose is 10 million IU/m^2 administered subcutaneously three days a week (every other day) for 48 weeks.

If severe adverse events develop during interferon alfa-2b treatment, particularly if granulocytes decrease to < 500/mm^3 or alanine aminotransferase/aspartate aminotransferase (ALT/AST) rises to > 5 x upper limit of normal, discontinue treatment temporarily until the adverse event abates. Interferon alfa-2b treatment is to be restarted at 50 % of the previous dose. If intolerance persists after dose adjustment or if granulocytes decrease to < 250/mm^3 or ALT/AST rises to > 10 x upper limit of normal, discontinue interferon alfa-2b therapy.

Although the optimal (minimum) dose for full clinical benefit is unknown, patients must be treated at the recommended dose, with dose reduction for toxicity as described.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.
- Combination of IntronA with telbivudine.

Children and adolescents
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

4.4 Special warnings and precautions for use

Psychiatric and central nervous system (CNS)
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during IntronA therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents treated with IntronA in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or

suicidal or homicidal ideation is identified, it is recommended that treatment with IntronA be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions:
If treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

Patients with substance use/abuse:
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Children and adolescent population: Growth and development (chronic hepatitis C)
During the course of interferon (standard and pegylated)/ribavirin combination therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children (n=20) despite being off treatment for more than 5 years. Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment.

Case by case benefit/risk assessment in children
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response, (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

Hypersensitivity reactions
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during IntronA therapy. If such a reaction develops, discontinue the medicine and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Adverse experiences including prolongation of coagulation markers and liver abnormalities
Moderate to severe adverse experiences may require modification of the patient's dose regimen, or in some cases, termination of IntronA therapy. IntronA increases the risk of liver decompensation and death in patients with cirrhosis.

Discontinue treatment with IntronA in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decomposition.
Any patient developing liver function abnormalities during treatment with IntronA must be monitored closely and treatment discontinued if signs and symptoms progress.
Liver enzymes and hepatic function should be closely monitored in cirrhotic patients.

Hypotension
Hypotension may occur during IntronA therapy or up to two days post-therapy and may require supportive treatment.

Need for adequate hydration
Adequate hydration must be maintained in patients undergoing IntronA therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Pyrexia
While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Patients with debilitating medical conditions
IntronA must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary conditions
Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events
Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, serous retinal detachment, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with IntronA, must have a prompt and complete eye examination. Periodic visual examinations during IntronA therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of IntronA should be considered in patients who develop new or worsening ophthalmological disorders.

Obtundation, coma and encephalopathy
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of IntronA.

Patients with pre-existing cardiac abnormalities
Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require IntronA therapy, must be closely monitored. It is

recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of IntronA therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia
Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Patients with psoriasis and sarcoidosis
Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of IntronA in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Kidney and liver graft rejection
Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Auto-antibodies and autoimmune disorders
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

<u>Concomitant chemotherapy</u>
Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered medicinal product. The most commonly reported potentially life-threatening or fatal adverse events include mucositis, diarrhoea, neutropaenia, renal impairment, and electrolyte disturbance. Because of the risk of increased toxicity, careful adjustments of doses are required for IntronA and for the concomitant chemotherapeutic agents (see section 4.5). When IntronA is used with hydroxyurea, the frequency and severity of cutaneous vasculitis may be increased.

<u>Chronic hepatitis C</u>
Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy
Infrequently, adult patients treated for chronic hepatitis C with IntronA developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using IntronA therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which IntronA may alter thyroid status is unknown. Prior to initiation of IntronA therapy for the treatment of chronic hepatitis C,

evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of IntronA therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, IntronA treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of IntronA therapy has not reversed thyroid dysfunction occurring during treatment (also see *Thyroid supplemental monitoring specific for children and adolescents*).

Thyroid supplemental monitoring specific for children and adolescents
Approximately 12 % of children treated with interferon alfa-2b and ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of IntronA therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding IntronA and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with IntronA and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of IntronA and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with IntronA.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during IntronA therapy to greater than or equal to 2 times baseline, IntronA therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, the following liver function tests must be monitored at two-week intervals: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin.

In patients treated for malignant melanoma, liver function and white blood cell (WBC) count and differential must be monitored weekly during the induction phase of therapy and monthly during the maintenance phase of therapy.

Effect on fertility
Interferon may impair fertility (see section 4.6 and section 5.3).

Important information about some of the ingredients of IntronA
This medicinal product contains less than 1 mmol sodium (23 mg) per 1.2 mL, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with IntronA.

Interactions between IntronA and other medicinal products have not been fully evaluated. Caution must be exercised when administering IntronA in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration) (see section 4.4).

Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see sections 4.3, 4.4 and 4.5 of the telbivudine SPC). Moreover, the safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated. Therefore, the combination of IntronA with telbivudine is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Women of childbearing potential have to use effective contraception during treatment. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

IntronA must be used with caution in fertile men.

Combination therapy with ribavirin
Ribavirin causes serious birth defects when administered during pregnancy. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking IntronA in combination with ribavirin. Females of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female

partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. IntronA is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Combination therapy with ribavirin
Ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with IntronA, and therefore it is recommended that they avoid driving or operating machinery.

4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/m^2/week in hairy cell leukaemia up to 100 MIU/m^2/week in melanoma), the most commonly reported undesirable effects were pyrexia, fatigue, headache and myalgia. Pyrexia and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

Adults
In clinical trials conducted in the hepatitis C population, patients were treated with IntronA alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of IntronA three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rarely (≥1/10,000 to <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported during clinical trials or following the marketing use of IntronA alone or in combination with ribavirin

System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Pharyngitis*, infection viral*
Common:	Bronchitis, sinusitis, herpes simplex (resistance), rhinitis
Uncommon:	Bacterial infection
Rarely:	Pneumonia[§], sepsis

Blood and lymphatic system disorders	
Very common:	Leukopaenia
Common:	Thrombocytopaenia, lymphadenopathy, lymphopenia
Very rarely:	Aplastic anaemia
Not known**:**	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Immune system disorders[§]	
Very rarely:	Sarcoidosis, exacerbation of sarcoidosis
Not known:	Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§]
Endocrine disorders	
Common:	Hypothyroidism[§], hyperthyroidism[§]
Very rarely:	Diabetes, aggravated diabetes
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hypocalcaemia, dehydration, hyperuricemia, thirst
Very rarely:	Hyperglycaemia, hypertriglyceridaemia[§], increased appetite
Psychiatric disorders[§]	
Very common:	Depression, insomnia, anxiety, emotional lability*, agitation, nervousness
Common:	Confusion, sleep disorder, libido decreased
Rarely:	Suicide ideation
Very rarely:	Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations
Not known:	Homicidal ideation, mental status change[§], mania, bipolar disorders
Nervous system disorders[§]	
Very common:	Dizziness, headache, concentration impaired, mouth dry
Common:	Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion
Uncommon:	Peripheral neuropathy
Very rarely:	Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy
Not known:	Mononeuropathies, coma[§]
Eye disorders	
Very common:	Vision blurred
Common:	Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain
Rarely:	Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§]
Not known:	Serous retinal detachment
Ear and labyrinth	
Common:	Vertigo, tinnitus
Very rarely:	Hearing loss, hearing disorder
Cardiac disorders	
Common:	Palpitation, tachycardia
Rarely:	Cardiomyopathy
Very rarely:	Myocardial infarction, cardiac ischaemia
Not known:	Congestive heart failure, pericardial effusion, arrhythmia

Vascular disorders	
Common:	Hypertension
Very rarely:	Peripheral ischaemia, hypotension[§]
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea*, coughing*
Common:	Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive
Very rarely:	Pulmonary infiltrates[§], pneumonitis[§]
Not known:	Pulmonary fibrosis, pulmonary arterial hypertension[#]
Gastrointestinal disorders	
Very common:	Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia
Common:	Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools
Very rarely:	Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding
Not known:	Periodontal disorder NOS, dental disorder NOS[§]
Hepatobiliary disorders	
Common:	Hepatomegaly
Very rarely:	Hepatotoxicity, (including fatality)
Skin and subcutaneous tissue disorders	Alopecia, pruritus*, skin dry*, rash*, sweating increased
Very common:	Psoriasis (new or aggravated)[§], rash maculopapular, rash
Common:	erythematous, eczema, erythema, skin disorder
Very rarely:	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, musculoskeletal pain
Common:	Arthritis
Very rarely:	Rhabdomyolysis, myositis, leg cramps, back pain
Renal and urinary disorders	
Common:	Micturition frequency
Very rarely:	Renal failure, renal insufficiency, nephrotic syndrome
Reproductive system and breast disorders	
Common:	Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction*, fatigue, rigors, pyrexia[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise
Common:	Injection site pain
Very rarely:	Injection site necrosis, face oedema
Investigations	
Very common:	Weight decrease

*These events were only common with IntronA alone

[§]See section 4.4

[#]Class label for interferon products, see below Pulmonary arterial hypertension

These undesirable effects have also been reported with IntronA alone.

The undesirable effects seen with hepatitis C are representative of those reported when IntronA is administered in other indications, with some anticipated dose-related increases in incidence. For example, in a trial of high-dose adjuvant IntronA treatment in patients with melanoma, incidences of fatigue, pyrexia, myalgia, neutropaenia/anaemia, anorexia, nausea and vomiting, diarrhoea, chills, flu-like symptoms, depression, alopecia, altered taste, and dizziness were greater than in the hepatitis C trials. Severity also increased with high dose therapy (WHO Grade 3 and 4, in 66 % and 14 % of patients, respectively), in comparison with the mild to moderate severity usually associated with lower doses. Undesirable effects were usually managed by dose adjustment.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV-infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Moderate and usually reversible pancytopenia has been reported. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

Children and adolescent population

Chronic Hepatitis C - Combination therapy with ribavirin

In clinical trials of 118 children and adolescents (3 to 16 years of age), 6 % discontinued therapy due to adverse reactions. In general, the adverse reaction profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric- specific concern regarding growth inhibition as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile) were observed during treatment. Within the 5 years follow-up post-treatment period, the children had a mean height of 44th percentile, which was below the median of the normative population and less than their mean baseline height (48th percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years). Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment. During combination therapy for up to 48 weeks with IntronA and ribavirin, growth inhibition was observed that resulted in reduced final adult height in some patients. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from the two multicentre children and adolescent clinical trials. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Adverse reactions very commonly and commonly reported during clinical trials inchildren and adolescent patients treated with IntronA in combination with ribavirin

System Organ Class	Adverse Reactions
Infection and infestations Very common: Common:	 Viral infection, pharyngitis Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Neoplasms benign, malignant and unspecified (including cysts and polyps) Common:	 Neoplasm (unspecified)
Blood and lymphatic system disorders Very common: Common:	 Anaemia, neutropaenia Thrombocytopaenia, lymphadenopathy
Endocrine disorders Very common: Common:	 Hypothyroidism[§], Hyperthyroidism[§], virilism
Metabolism and nutrition disorders Very common: Common:	 Anorexia Hypertriglyceridemia[§], hyperuricemia, increased appetite
Psychiatric disorders[§] Very common: Common:	 Depression, emotional lability, insomnia Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy
Nervous system disorders[§] Very common: Common:	 Headache, dizziness Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence
Eye disorders Common:	 Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Vascular disorders Common:	 Flushing, pallor
Respiratory, thoracic and mediastinal disorders Common:	 Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing
Gastrointestinal disorders Very common: Common:	 Diarrhoea, vomiting, nausea, abdominal pain Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder
Hepatobiliary disorders Common:	 Hepatic function abnormal

Skin and subcutaneous tissue disorders Very common: Common:	 Alopecia, rash Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased
Musculoskeletal and connective tissue disorders Very common:	 Arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders Common:	 Enuresis, micturition disorder, urinary incontinence
Reproductive system and breast disorders Common:	 Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder Male: testicular pain
General disorders and administration site conditions Very common: Common:	 Injection site inflammation, injection site reaction, fatigue, rigors, pyrexia[§], influenza-like symptoms[§], malaise, irritability Chest pain, asthenia, oedema, injection site pain
Investigations Very common:	 Growth rate decrease (height and/or weight decrease for age)[§]
Injury and poisoning Common:	 Skin laceration

[§]See section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: interferon alfa-2b, ATC code: L03A B05

IntronA is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of IntronA is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity

of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. IntronA has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B

Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/m^2 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C in adult patients

In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

IntronA alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of IntronA used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/mL), a liver

biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

IntronA was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with IntronA alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of IntronA with ribavirin increased the efficacy of IntronA by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of IntronA + ribavirin, compared with IntronA alone, is maintained across all subgroups. The relative benefit of combination therapy with IntronA + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received IntronA in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

Table 3 Sustained virologic response rates with IntronA + ribavirin (one year of treatment) by genotype and viral load

HCV Genotype	**I N=503 C95-132/I95-143**	**I/R N=505 C95-132/I95-143**	**I/R N=505 C/I98-580**
All Genotypes	**16 %**	**41 %**	**47 %**
Genotype 1	9 %	29 %	33 %
Genotype 1 ≤ 2 million copies/mL	25 %	33 %	45 %
Genotype 1 > 2 million copies/mL	3 %	27 %	29 %
Genotype 2/3	31 %	65 %	79 %

I IntronA (3 MIU 3 times a week)
I/R IntronA (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

HCV/HIV Co-infected patients
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received IntronA plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or IntronA (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based

on weight) plus ribavirin (800-1,200 mg/day based on weight) or IntronA (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/mL (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

Table 4 Sustained virological response based on genotype after IntronA in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

	Study 1[1]			**Study 2**[2]		
	pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg)	IntronA (3 MIU TIW) + ribavirin (800 mg)	p value[a]	pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d]	IntronA (3 MIU TIW) + ribavirin (800-1,200 mg)[d]	p value[b]
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients
A total of 345 interferon alpha relapse patients were treated in two clinical trials with IntronA monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to IntronA increased by as much as 10-fold the efficacy of IntronA used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/mL by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non-pegylated interferon alfa-2b or non-pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Chronic hepatitis C in children and adolescent population
Three clinical trials have been conducted in children and adolescents; two with standard interferon and ribavirin and one with pegylated interferon and ribavirin. Patients who received IntronA plus ribavirin were less likely to respond than patients who received pegylated interferon alfa-2b and ribavirin.

Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received IntronA 3 MIU/m^2 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. In the two multicentre trials sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in these two multicentre trials for children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

Table 5 Sustained virological response in previously untreated children and adolescents

	IntronA 3 MIU/m^2 3 times a week + **ribavirin 15 mg/kg/day**
Overall Response[a] (n=118)	54 (46 %)*
Genotype 1 (n=92)	33 (36 %)*
Genotype 2/3/4 (n=26)	21 (81 %)*

*Number (%) of patients
[a] Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

Long-term efficacy data
A five-year long-term, observational, follow-up study enrolled 97 paediatric chronic hepatitis C patients after treatment in the standard interferon multicentre trials. Seventy percent (68/97) of all enrolled subjects completed this study of which 75 % (42/56) were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment of the 48-week interferon alfa-2b and ribavirin treatment. All but one of the paediatric subjects remained sustained virologic responders during long-term follow-up after completion of treatment with interferon alfa-2b plus ribavirin. The Kaplan-Meier estimate for continued sustained response over 5 years is 98 % [95 % CI: 95 %, 100 %] for paediatric patients treated with interferon alfa-2b and ribavirin. Additionally, 98 % (51/52) with normal ALT levels at follow-up week 24 maintained normal ALT levels at their last visit.
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b with ribavirin results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Results from the clinical trial conducted with pegylated interferon alfa-2b and ribavirin
In a multicentre trial children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with peginterferon alfa-2b 60 μg/m^2 plus ribavirin 15 mg/kg per day once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received

treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of peginterferon alfa-2b with ribavirin needs to be carefully considered in this population (see peginterferon alfa-2b and ribavirin SPCs section 4.4). The study results are summarized in **Table 6.**

Table 6 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects
n = 107

	24 weeks	**48 weeks**
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment, lower limit of detection=125 IU/mL.

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/mL) were to receive 48 weeks of treatment.

5.2 Pharmacokinetic properties

The pharmacokinetics of IntronA were studied in healthy volunteers following single 5 million IU/m^2 and 10 million IU doses administered subcutaneously, at 5 million IU/m^2 administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. C_{max} occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/mL) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

Interferon neutralising factor assays were performed on serum samples of patients who received IntronA in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

Children and adolescent population
Multiple-dose pharmacokinetic properties for IntronA injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 7**. The pharmacokinetics of IntronA and ribavirin (dose-normalized) are similar in adults and children or adolescents.

Table 7 Mean (% CV) multiple-dose pharmacokinetic parameters for IntronA and ribavirin capsules when administered to children or adolescents with chronic hepatitis C		
Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**IntronA** 3 MIU/m^2 3 times a week (n = 54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3,275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	Not done

*AUC_{12} (ng.hr/mL) for ribavirin; AUC_{0-24} (IU.hr/mL) for IntronA

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x 10^6 IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x 10^6 IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

<u>IntronA plus ribavirin</u>
No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if IntronA is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate anhydrous
Sodium dihydrogen phosphate monohydrate
Edetate disodium
Sodium chloride

M-cresol
Polysorbate 80
Water for injections q.s.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

15 months.

Chemical and physical in-use stability has been demonstrated for 27 days at 2ºC – 8ºC.
From a microbiological point of view, once opened, the product may be stored for a maximum of 27 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1.2 mL of solution (corresponding to 30 MIU) is contained in a pen made of a cartridge (type I glass) sealed at one end with a cap (aluminium) containing a liner (bromobutyl rubber) and at the other end by a plunger (bromobutyl rubber).

IntronA is supplied as:
- Pack of 1 pen, 12 injection needles and 12 cleansing swabs
- Pack of 2 pens, 24 injection needles and 24 cleansing swabs
- Pack of 8 pens, 96 injection needles and 96 cleansing swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not all dose forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

IntronA, solution for injection in multidose pen is injected subcutaneously after attaching an injection needle and dialing the prescribed dose.

Remove the pen from the refrigerator approximately 30 minutes before administration to allow the injectable solution to reach room temperature (not more than 25°C).

Detailed instructions for the use of the product are provided with the package leaflet (refer to “How to self inject IntronA”).

Each pen is intended for a maximum four-week use period and must then be discarded. A new injection needle must be used for each dose. After each use, the injection needle must be discarded safely and the pen must be returned immediately to the refrigerator. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week use period to cover accidental delays in returning the pen to the refrigerator.

Sufficient needles and swabs are provided to use the IntronA pen for administering the smallest measurable doses. Instruct the patient that any extra needles and swabs that remain after the final dose has been taken from the pen must be discarded appropriately and safely.

As with all parenteral medicinal products, prior to administration inspect IntronA, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/127/034
EU/1/99/127/035
EU/1/99/127/036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 March 2000
Date of latest renewal: 9 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

IntronA 60 million IU solution for injection in multidose pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pen contains 60 million IU of recombinant interferon alfa-2b produced in *E. coli* by recombinant DNA technology, in 1.2 mL solution.

One mL contains 50 million IU of interferon alfa-2b.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B
Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of DNA of hepatitis B virus (HBV-DNA) and hepatitis B antigen (HBeAg), elevated alanine aminotransferase (ALT) and histologically proven active liver inflammation and/or fibrosis.

Chronic hepatitis C
Before initiating treatment with IntronA, consideration should be given to the results from clinical trials comparing IntronA with pegylated interferon (see section 5.1).

Adult patients
IntronA is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for hepatitis C virus RNA (HCV-RNA) (see section 4.4).

The best way to use IntronA in this indication is in combination with ribavirin.

Children 3 years of age and older and adolescents
IntronA is indicated, in a combination regimen with ribavirin, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
The decision to treat should be made on a case by case basis (see section 4.4).

Hairy cell leukaemia
Treatment of patients with hairy cell leukaemia.

Chronic myelogenous leukaemia

Monotherapy

Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia.

Clinical experience indicates that a haematological and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is ≥ 34 %, but < 90 % Ph+ cells in the marrow.

Combination therapy

The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.

Multiple myeloma

As maintenance therapy in patients who have achieved objective remission (more than 50 % reduction in myeloma protein) following initial induction chemotherapy.

Current clinical experience indicates that maintenance therapy with interferon alfa-2b prolongs the plateau phase; however, effects on overall survival have not been conclusively demonstrated.

Follicular lymphoma

Treatment of high tumour burden follicular lymphoma as adjunct to appropriate combination induction chemotherapy such as a CHOP-like regimen. High tumour burden is defined as having at least one of the following: bulky tumour mass (> 7 cm), involvement of three or more nodal sites (each > 3 cm), systemic symptoms (weight loss > 10 %, pyrexia > 38°C for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.

Carcinoid tumour

Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome".

Malignant melanoma

As adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement.

4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of the disease.

Multidose presentations must be for individual patient use only.

The pen is designed to deliver its contents of 60 million IU in doses ranging from 5 to 20 million IU. The pen will deliver a maximum of 12 doses of 5 million IU over a period not to exceed 4 weeks.

Not all dose forms and strengths are appropriate for some indications. Appropriate dose form and strength must be selected.

If adverse events develop during the course of treatment with IntronA for any indication, modify the dosage or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, discontinue treatment with IntronA. At the discretion of the physician, the patient may self-administer the dose for maintenance dosage regimens administered subcutaneously.

Chronic hepatitis B
The recommended dosage is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/mm^3, granulocytes < 1,000/mm^3, thrombocytes < 100,000/mm^3). Treatment should be discontinued in case of severe leukopaenia (< 1,200/mm^3), severe neutropaenia (< 750/mm^3) or severe thrombocytopaenia (< 70,000/mm^3).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue IntronA therapy.

Chronic hepatitis C
Adults
IntronA is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

Children 3 years of age or older and adolescents
IntronA 3 MIU/m^2 is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or oral solution administered orally in two divided doses daily with food (morning and evening).

(See ribavirin capsules SPC for dose of ribavirin capsules and dose modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC.)

Relapse patients (adults)
IntronA is given in combination with ribavirin. Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for 6 months.

Naïve patients (adults)
The efficacy of IntronA is enhanced when given in combination with ribavirin. IntronA should be given alone mainly in case of intolerance or contraindication to ribavirin.

- IntronA in combination with ribavirin
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with IntronA in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

- IntronA alone
The optimal duration of therapy with IntronA alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with IntronA alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

Naïve patients (children and adolescents)
The efficacy and safety of IntronA in combination with ribavirin has been studied in children and adolescents who have not been previously treated for chronic hepatitis C.

Duration of treatment for children and adolescents

- Genotype 1: The recommended duration of treatment is one year. Patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders (negative predictive value 96 %). Therefore, it is recommended that children and adolescent patients receiving IntronA/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment, or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2/3: The recommended duration of treatment is 24 weeks.

Hairy cell leukaemia
The recommended dose is 2 million IU/m^2 administered subcutaneously three times a week (every other day) for both splenectomised and non-splenectomised patients. For most patients with Hairy Cell Leukaemia, normalisation of one or more haematological variables occurs within one to two months of IntronA treatment. Improvement in all three haematological variables (granulocyte count, platelet count and haemoglobin level) may require six months or more. This regimen must be maintained unless the disease progresses rapidly or severe intolerance is manifested.

Chronic myelogenous leukaemia
The recommended dose of IntronA is 4 to 5 million IU/m^2 administered daily subcutaneously. Some patients have been shown to benefit from IntronA 5 million IU/m^2 administered daily subcutaneously in association with cytarabine (Ara-C) 20 mg/m^2 administered daily subcutaneously for 10 days per month (up to a maximum daily dose of 40 mg). When the white blood cell count is controlled, administer the maximum tolerated dose of IntronA (4 to 5 million IU/m^2 daily) to maintain haematological remission.

IntronA treatment must be discontinued after 8 to 12 weeks of treatment if at least a partial haematological remission or a clinically meaningful cytoreduction has not been achieved.

Multiple myeloma
Maintenance therapy
In patients who are in the plateau phase (more than 50 % reduction of myeloma protein) following initial induction chemotherapy, interferon alfa-2b may be administered as monotherapy, subcutaneously, at a dose of 3 million IU/m^2 three times a week (every other day).

Follicular lymphoma
Adjunctively with chemotherapy, interferon alfa-2b may be administered subcutaneously, at a dose of 5 million IU three times a week (every other day) for a duration of 18 months. CHOP-like regimens are advised, but clinical experience is available only with CHVP (combination of cyclophosphamide, doxorubicin, teniposide and prednisolone).

Carcinoid tumour
The usual dose is 5 million IU (3 to 9 million IU) administered subcutaneously three times a week (every other day). Patients with advanced disease may require a daily dose of 5 million IU. The treatment is to be temporarily discontinued during and after surgery. Therapy may continue for as long as the patient responds to interferon alfa-2b treatment.

Malignant melanoma
As induction therapy, interferon alfa-2b is administered intravenously at a dose of 20 million IU/m^2 daily for five days a week for a four-week period; the calculated interferon alfa-2b dose is added to sodium chloride 9 mg/mL (0.9 %) solution for injection and administered as a 20-minute infusion (see section 6.6). As maintenance treatment, the recommended dose is 10 million IU/m^2 administered subcutaneously three days a week (every other day) for 48 weeks.

If severe adverse events develop during interferon alfa-2b treatment, particularly if granulocytes decrease to < 500/mm^3 or alanine aminotransferase/aspartate aminotransferase (ALT/AST) rises to > 5 x upper limit of normal, discontinue treatment temporarily until the adverse event abates. Interferon alfa-2b treatment is to be restarted at 50 % of the previous dose. If intolerance persists after dose adjustment or if granulocytes decrease to < 250/mm^3 or ALT/AST rises to > 10 x upper limit of normal, discontinue interferon alfa-2b therapy.

Although the optimal (minimum) dose for full clinical benefit is unknown, patients must be treated at the recommended dose, with dose reduction for toxicity as described.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.
- Combination of IntronA with telbivudine.

Children and adolescents
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

4.4 Special warnings and precautions for use

Psychiatric and central nervous system (CNS)
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during IntronA therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents treated with IntronA in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or

suicidal or homicidal ideation is identified, it is recommended that treatment with IntronA be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions:
If treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

Patients with substance use/abuse:
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Children and adolescent population: Growth and development (chronic hepatitis C)
During the course of interferon (standard and pegylated)/ribavirin combination therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children (n=20) despite being off treatment for more than 5 years. Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment.

Case by case benefit/risk assessment in children
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition that resulted in reduced final adult height in some patients.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response, (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

Hypersensitivity reactions
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during IntronA therapy. If such a reaction develops, discontinue the medicine and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Adverse experiences including prolongation of coagulation markers and liver abnormalities
Moderate to severe adverse experiences may require modification of the patient's dose regimen, or in some cases, termination of IntronA therapy. IntronA increases the risk of liver decompensation and death in patients with cirrhosis.

Discontinue treatment with IntronA in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decomposition.
Any patient developing liver function abnormalities during treatment with IntronA must be monitored closely and treatment discontinued if signs and symptoms progress.
Liver enzymes and hepatic function should be closely monitored in cirrhotic patients.

Hypotension
Hypotension may occur during IntronA therapy or up to two days post-therapy and may require supportive treatment.

Need for adequate hydration
Adequate hydration must be maintained in patients undergoing IntronA therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Pyrexia
While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Patients with debilitating medical conditions
IntronA must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary conditions
Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.5). Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events
Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, serous retinal detachment, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with IntronA, must have a prompt and complete eye examination. Periodic visual examinations during IntronA therapy are recommended particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of IntronA should be considered in patients who develop new or worsening ophthalmological disorders.

Obtundation, coma and encephalopathy
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of IntronA.

Patients with pre-existing cardiac abnormalities
Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, who require IntronA therapy, must be closely monitored. It is

recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of IntronA therapy. There are no data in children or adolescents with a history of cardiac disease.

Hypertriglyceridemia
Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Patients with psoriasis and sarcoidosis
Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of IntronA in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Kidney and liver graft rejection
Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Auto-antibodies and autoimmune disorders
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Concomitant chemotherapy
Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered medicinal product. The most commonly reported potentially life-threatening or fatal adverse events include mucositis, diarrhoea, neutropaenia, renal impairment, and electrolyte disturbance. Because of the risk of increased toxicity, careful adjustments of doses are required for IntronA and for the concomitant chemotherapeutic agents (see section 4.5). When IntronA is used with hydroxyurea, the frequency and severity of cutaneous vasculitis may be increased.

Chronic hepatitis C
Combination therapy with ribavirin
Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy
Infrequently, adult patients treated for chronic hepatitis C with IntronA developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using IntronA therapy, 2.8 % patients overall developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which IntronA may alter thyroid status is unknown. Prior to initiation of IntronA therapy for the treatment of chronic hepatitis C,

evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of IntronA therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, IntronA treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of IntronA therapy has not reversed thyroid dysfunction occurring during treatment (also see Thyroid supplemental monitoring specific for children and adolescents).

Thyroid supplemental monitoring specific for children and adolescents
Approximately 12 % of children treated with interferon alfa-2b and ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another 4 % had a transient decrease below the lower limit of normal. Prior to initiation of IntronA therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding IntronA and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with IntronA and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of IntronA and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with IntronA.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during IntronA therapy to greater than or equal to 2 times baseline, IntronA therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, the following liver function tests must be monitored at two-week intervals: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin.

In patients treated for malignant melanoma, liver function and white blood cell (WBC) count and differential must be monitored weekly during the induction phase of therapy and monthly during the maintenance phase of therapy.

Effect on fertility
Interferon may impair fertility (see section 4.6 and section 5.3).

Important information about some of the ingredients of IntronA
This medicinal product contains less than 1 mmol sodium (23 mg) per 1.2 mL, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with IntronA.

Interactions between IntronA and other medicinal products have not been fully evaluated. Caution must be exercised when administering IntronA in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dosage adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients, including those treated with IntronA. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alpha (see section 4.4).

Administration of IntronA in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration) (see section 4.4).

Also see ribavirin SPC if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see sections 4.3, 4.4 and 4.5 of the telbivudine SPC). Moreover, the safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated. Therefore, the combination of IntronA with telbivudine is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Women of childbearing potential have to use effective contraception during treatment. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

IntronA must be used with caution in fertile men.

Combination therapy with ribavirin
Ribavirin causes serious birth defects when administered during pregnancy. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking IntronA in combination with ribavirin. Females of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female

partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. IntronA is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Combination therapy with ribavirin
Ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with IntronA, and therefore it is recommended that they avoid driving or operating machinery.

4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if IntronA is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/m^2/week in hairy cell leukaemia up to 100 MIU/m^2/week in melanoma), the most commonly reported undesirable effects were pyrexia, fatigue, headache and myalgia. Pyrexia and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

Adults
In clinical trials conducted in the hepatitis C population, patients were treated with IntronA alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of IntronA three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rarely (≥1/10,000 to <1/1,000); very rarely (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported during clinical trials or following the marketing use of IntronA alone or in combination with ribavirin

System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Pharyngitis*, infection viral*
Common:	Bronchitis, sinusitis, herpes simplex (resistance), rhinitis
Uncommon:	Bacterial infection
Rarely:	Pneumonia[§], sepsis

Blood and lymphatic system disorders	
Very common:	Leukopaenia
Common:	Thrombocytopaenia, lymphadenopathy, lymphopenia
Very rarely:	Aplastic anaemia
Not known**:**	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Immune system disorders[§]	
Very rarely:	Sarcoidosis, exacerbation of sarcoidosis
Not known:	Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§]
Endocrine disorders	
Common:	Hypothyroidism[§], hyperthyroidism[§]
Very rarely:	Diabetes, aggravated diabetes
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hypocalcaemia, dehydration, hyperuricemia, thirst
Very rarely:	Hyperglycaemia, hypertriglyceridaemia[§], increased appetite
Psychiatric disorders[§]	
Very common:	Depression, insomnia, anxiety, emotional lability*, agitation, nervousness
Common:	Confusion, sleep disorder, libido decreased
Rarely:	Suicide ideation
Very rarely:	Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations
Not known:	Homicidal ideation, mental status change[§], mania, bipolar disorders
Nervous system disorders[§]	
Very common:	Dizziness, headache, concentration impaired, mouth dry
Common:	Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion
Uncommon:	Peripheral neuropathy
Very rarely:	Cerebrovascular haemorrhage, cerbrovascular ischaemia, seizure, impaired consciousness, encephalopathy
Not known:	Mononeuropathies, coma[§]
Eye disorders	
Very common:	Vision blurred
Common:	Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain
Rarely:	Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§]
Not known:	Serous retinal detachment
Ear and labyrinth	
Common:	Vertigo, tinnitus
Very rarely:	Hearing loss, hearing disorder
Cardiac disorders	
Common:	Palpitation, tachycardia
Rarely:	Cardiomyopathy
Very rarely:	Myocardial infarction, cardiac ischaemia
Not known:	Congestive heart failure, pericardial effusion, arrhythmia

Vascular disorders	
Common:	Hypertension
Very rarely:	Peripheral ischaemia, hypotension[§]
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea*, coughing*
Common:	Epistaxis, respiratory disorder, nasal congestion, rhinorrhea, cough nonproductive
Very rarely:	Pulmonary infiltrates[§], pneumonitis[§]
Not known:	Pulmonary fibrosis, pulmonary arterial hypertension[#]
Gastrointestinal disorders	
Very common:	Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia
Common:	Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools
Very rarely:	Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding
Not known:	Periodontal disorder NOS, dental disorder NOS[§]
Hepatobiliary disorders	
Common:	Hepatomegaly
Very rarely:	Hepatotoxicity, (including fatality)
Skin and subcutaneous tissue disorders	Alopecia, pruritus*, skin dry*, rash*, sweating increased
Very common:	Psoriasis (new or aggravated)[§], rash maculopapular, rash
Common:	erythematous, eczema, erythema, skin disorder
Very rarely:	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, musculoskeletal pain
Common:	Arthritis
Very rarely:	Rhabdomyolysis, myositis, leg cramps, back pain
Renal and urinary disorders	
Common:	Micturition frequency
Very rarely:	Renal failure, renal insufficiency, nephrotic syndrome
Reproductive system and breast disorders	
Common:	Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction*, fatigue, rigors, pyrexia[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise
Common:	Injection site pain
Very rarely:	Injection site necrosis, face oedema
Investigations	
Very common:	Weight decrease

*These events were only common with IntronA alone
[§]See section 4.4
[#]Class label for interferon products, see below Pulmonary arterial hypertension

These undesirable effects have also been reported with IntronA alone.

The undesirable effects seen with hepatitis C are representative of those reported when IntronA is administered in other indications, with some anticipated dose-related increases in incidence. For example, in a trial of high-dose adjuvant IntronA treatment in patients with melanoma, incidences of fatigue, pyrexia, myalgia, neutropaenia/anaemia, anorexia, nausea and vomiting, diarrhoea, chills, flu-like symptoms, depression, alopecia, altered taste, and dizziness were greater than in the hepatitis C trials. Severity also increased with high dose therapy (WHO Grade 3 and 4, in 66 % and 14 % of patients, respectively), in comparison with the mild to moderate severity usually associated with lower doses. Undesirable effects were usually managed by dose adjustment.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV-infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, LDH, serum creatinine and serum urea nitrogen levels. Moderate and usually reversible pancytopenia has been reported. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

Children and adolescent population

Chronic Hepatitis C - Combination therapy with ribavirin

In clinical trials of 118 children and adolescents (3 to 16 years of age), 6 % discontinued therapy due to adverse reactions. In general, the adverse reaction profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric- specific concern regarding growth inhibition as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile) were observed during treatment. Within the 5 years follow-up post-treatment period, the children had a mean height of 44th percentile, which was below the median of the normative population and less than their mean baseline height (48th percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years). Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment. During combination therapy for up to 48 weeks with IntronA and ribavirin, growth inhibition was observed that resulted in reduced final adult height in some patients. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropaenia.

The adverse reactions listed in **Table 2** are based on experience from the two multicentre children and adolescent clinical trials. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Adverse reactions very commonly and commonly reported during clinical trials inchildren and adolescent patients treated with IntronA in combination with ribavirin

System Organ Class	Adverse Reactions
Infection and infestations Very common: Common:	 Viral infection, pharyngitis Fungal infection, bacterial infection, pulmonary infection, otitis media, tooth abscess, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Neoplasms benign, malignant and unspecified (including cysts and polyps) Common:	 Neoplasm (unspecified)
Blood and lymphatic system disorders Very common: Common:	 Anaemia, neutropaenia Thrombocytopaenia, lymphadenopathy
Endocrine disorders Very common: Common:	 Hypothyroidism[§], Hyperthyroidism[§], virilism
Metabolism and nutrition disorders Very common: Common:	 Anorexia Hypertriglyceridemia[§], hyperuricemia, increased appetite
Psychiatric disorders[§] Very common: Common:	 Depression, emotional lability, insomnia Suicidal ideation, aggressive reaction, confusion, behaviour disorder, agitation, somnambulism, anxiety, nervousness, sleep disorder, abnormal dreaming, apathy
Nervous system disorders[§] Very common: Common:	 Headache, dizziness Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence
Eye disorders Common:	 Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Vascular disorders Common:	 Flushing, pallor
Respiratory, thoracic and mediastinal disorders Common:	 Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhea, sneezing
Gastrointestinal disorders Very common: Common:	 Diarrhoea, vomiting, nausea, abdominal pain Mouth ulceration, stomatitis ulcerative, stomatitis, right upper quadrant pain, dyspepsia, glossitis, gastroesophogeal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder
Hepatobiliary disorders Common:	 Hepatic function abnormal

Skin and subcutaneous tissue disorders Very common: Common:	 Alopecia, rash Photosensitivity reaction, maculopapular rash, eczema, acne, skin disorder, nail disorder, skin discolouration, pruritus, dry skin, erythema, bruise, sweating increased
Musculoskeletal and connective tissue disorders Very common:	 Arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders Common:	 Enuresis, micturition disorder, urinary incontinence
Reproductive system and breast disorders Common:	 Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder Male: testicular pain
General disorders and administration site conditions Very common: Common:	 Injection site inflammation, injection site reaction, fatigue, rigors, pyrexia[§], influenza-like symptoms[§], malaise, irritability Chest pain, asthenia, oedema, injection site pain
Investigations Very common:	 Growth rate decrease (height and/or weight decrease for age)[§]
Injury and poisoning Common:	 Skin laceration

[§]See section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: interferon alfa-2b, ATC code: L03A B05

IntronA is a sterile, stable, formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water-soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of E. coli, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of IntronA is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ IU. International Units are determined by comparison of the activity

of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alpha interferons have been identified. IntronA has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

The results of several studies suggest that, once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B

Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/m^2 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C in adult patients

In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47 %. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61 % achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

IntronA alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of IntronA used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/mL), a liver

biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

IntronA was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with IntronA alone or in combination with ribavirin (from two studies) are shown in **Table 3**.

Co-administration of IntronA with ribavirin increased the efficacy of IntronA by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of IntronA + ribavirin, compared with IntronA alone, is maintained across all subgroups. The relative benefit of combination therapy with IntronA + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table 3**).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received IntronA in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

Table 3 Sustained virologic response rates with IntronA + ribavirin (one year of treatment) by genotype and viral load

HCV Genotype	**I N=503 C95-132/I95-143**	**I/R N=505 C95-132/I95-143**	**I/R N=505 C/I98-580**
All Genotypes	**16 %**	**41 %**	**47 %**
Genotype 1	9 %	29 %	33 %
Genotype 1 ≤ 2 million copies/mL	25 %	33 %	45 %
Genotype 1 > 2 million copies/mL	3 %	27 %	29 %
Genotype 2/3	31 %	65 %	79 %

I IntronA (3 MIU 3 times a week)
I/R IntronA (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

HCV/HIV Co-infected patients
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received IntronA plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 4.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or IntronA (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based

on weight) plus ribavirin (800-1,200 mg/day based on weight) or IntronA (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/mL (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

Table 4 Sustained virological response based on genotype after IntronA in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

	Study 1[1]			**Study 2**[2]		
	pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg)	IntronA (3 MIU TIW) + ribavirin (800 mg)	p value[a]	pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d]	IntronA (3 MIU TIW) + ribavirin (800-1,200 mg)[d]	p value[b]
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients
A total of 345 interferon alpha relapse patients were treated in two clinical trials with IntronA monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to IntronA increased by as much as 10-fold the efficacy of IntronA used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/mL by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non-pegylated interferon alfa-2b or non-pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Chronic hepatitis C in children and adolescent population
Three clinical trials have been conducted in children and adolescents; two with standard interferon and ribavirin and one with pegylated interferon and ribavirin. Patients who received IntronA plus ribavirin were less likely to respond than patients who received pegylated interferon alfa-2b and ribavirin.

Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received IntronA 3 MIU/m^2 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1,64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. In the two multicentre trials sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in these two multicentre trials for children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

Study results are summarized in **Table 5**.

Table 5 Sustained virological response in previously untreated children and adolescents

	IntronA 3 MIU/m^2 3 times a week + **ribavirin 15 mg/kg/day**
Overall Response[a] (n=118)	54 (46 %)*
Genotype 1 (n=92)	33 (36 %)*
Genotype 2/3/4 (n=26)	21 (81 %)*

*Number (%) of patients
[a] Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period

Long-term efficacy data
A five-year long-term, observational, follow-up study enrolled 97 paediatric chronic hepatitis C patients after treatment in the standard interferon multicentre trials. Seventy percent (68/97) of all enrolled subjects completed this study of which 75 % (42/56) were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment of the 48-week interferon alfa-2b and ribavirin treatment. All but one of the paediatric subjects remained sustained virologic responders during long-term follow-up after completion of treatment with interferon alfa-2b plus ribavirin. The Kaplan-Meier estimate for continued sustained response over 5 years is 98 % [95 % CI: 95 %, 100 %] for paediatric patients treated with interferon alfa-2b and ribavirin. Additionally, 98 % (51/52) with normal ALT levels at follow-up week 24 maintained normal ALT levels at their last visit.
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b with ribavirin results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Results from the clinical trial conducted with pegylated interferon alfa-2b and ribavirin
In a multicentre trial children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with peginterferon alfa-2b 60 μg/m^2 plus ribavirin 15 mg/kg per day once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received

treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of peginterferon alfa-2b with ribavirin needs to be carefully considered in this population (see peginterferon alfa-2b and ribavirin SPCs section 4.4). The study results are summarized in **Table 6.**

Table 6 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects
n = 107

	24 weeks	**48 weeks**
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment, lower limit of detection=125 IU/mL.

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/mL) were to receive 48 weeks of treatment.

5.2 Pharmacokinetic properties

The pharmacokinetics of IntronA were studied in healthy volunteers following single 5 million IU/m^2 and 10 million IU doses administered subcutaneously, at 5 million IU/m^2 administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. C_{max} occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively. Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous administration, serum interferon levels peaked (135 to 273 IU/mL) by the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

Urine levels of interferon were below the detection limit following each of the three routes of administration.

Interferon neutralising factor assays were performed on serum samples of patients who received IntronA in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9 % and in chronic hepatitis patients is 6.2 %. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

Children and adolescent population
Multiple-dose pharmacokinetic properties for IntronA injection and ribavirin capsules in children and adolescents with chronic hepatitis C, between 5 and 16 years of age, are summarized in **Table 7**. The pharmacokinetics of IntronA and ribavirin (dose-normalized) are similar in adults and children or adolescents.

Table 7 Mean (% CV) multiple-dose pharmacokinetic parameters for IntronA and ribavirin capsules when administered to children or adolescents with chronic hepatitis C		
Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**IntronA** 3 MIU/m^2 3 times a week (n = 54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3,275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	Not done

*AUC_{12} (ng.hr/mL) for ribavirin; AUC_{0-24} (IU.hr/mL) for IntronA

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x 10^6 IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x 10^6 IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

Mutagenicity studies with interferon alfa-2b revealed no adverse events.

<u>IntronA plus ribavirin</u>
No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if IntronA is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate anhydrous
Sodium dihydrogen phosphate monohydrate
Edetate disodium
Sodium chloride

M-cresol
Polysorbate 80
Water for injections q.s.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

15 months.

Chemical and physical in-use stability has been demonstrated for 27 days at 2ºC – 8ºC.
From a microbiological point of view, once opened, the product may be stored for a maximum of 27 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1.2 mL of solution (corresponding to 60 MIU) is contained in a pen made of a cartridge (type I glass) sealed at one end with a cap (aluminium) containing a liner (bromobutyl rubber) and at the other end by a plunger (bromobutyl rubber).

IntronA is supplied as:
- Pack of 1 pen, 12 injection needles and 12 cleansing swabs
- Pack of 2 pens, 24 injection needles and 24 cleansing swabs
- Pack of 8 pens, 96 injection needles and 96 cleansing swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not all dose forms and strengths are appropriate for some indications. Please make sure to select an appropriate dosage form and strength.

IntronA, solution for injection in multidose pen is injected subcutaneously after attaching an injection needle and dialing the prescribed dose.

Remove the pen from the refrigerator approximately 30 minutes before administration to allow the injectable solution to reach room temperature (not more than 25°C).

Detailed instructions for the use of the product are provided with the package leaflet (refer to “How to self inject IntronA”).

Each pen is intended for a maximum four-week use period and must then be discarded. A new injection needle must be used for each dose. After each use, the injection needle must be discarded safely and the pen must be returned immediately to the refrigerator. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week use period to cover accidental delays in returning the pen to the refrigerator.

Sufficient needles and swabs are provided to use the IntronA pen for administering the smallest measurable doses. Instruct the patient that any extra needles and swabs that remain after the final dose has been taken from the pen must be discarded appropriately and safely.

As with all parenteral medicinal products, prior to administration inspect IntronA, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/127/037
EU/1/99/127/038
EU/1/99/127/039

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 March 2000
Date of latest renewal: 9 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

SP (Brinny) Company
Innishannon - County Cork
Ireland

Name and address of the manufacturer responsible for batch release

SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

IntronA 3 million IU/0.5 mL solution for injection or infusion
interferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 3 million IU of interferon alfa-2b in 0.5 mL of solution.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

3 million IU/0.5 mL solution for injection or infusion
1 single dose vial
1 single dose vial, 1 injection syringe of 1 mL, 1 injection needle and 1 cleansing swab
6 single dose vials, 6 injection syringes of 1 mL, 6 injection needles and 6 cleansing swabs
12 single dose vials, 12 injection syringes of 1 mL, 12 injection needles and 12 cleansing swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use.
Dilute prior to intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/127/011 1 single dose vial
EU/1/99/127/012 1 single dose vial, 1 injection syringe of 1 mL, 1 injection needle and 1 cleansing swab
EU/1/99/127/013 6 single dose vials, 6 injection syringes of 1 mL, 6 injection needles and 6 cleansing swabs
EU/1/99/127/014 12 single dose vials, 12 injection syringes of 1 mL, 12 injection needles and 12 cleansing swabs

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IntronA 3 MIU solution

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IntronA 3 million IU/0.5 mL solution for injection or infusion
interferon alfa-2b
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 million IU/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

IntronA 5 million IU/0.5 mL solution for injection or infusion
interferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 5 million IU of interferon alfa-2b in 0.5 mL of solution.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

5 million IU/0.5 mL solution for injection or infusion
1 single dose vial
1 single dose vial, 1 injection syringe of 1 mL, 1 injection needle and 1 cleansing swab
6 single dose vials, 6 injection syringes of 1 mL, 6 injection needles and 6 cleansing swabs
12 single dose vials, 12 injection syringes of 1 mL, 12 injection needles and 12 cleansing swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use.
Dilute prior to intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/127/015 1 single dose vial
EU/1/99/127/016 1 single dose vial, 1 injection syringe of 1 mL, 1 injection needle and 1 cleansing swab
EU/1/99/127/017 6 single dose vials, 6 injection syringes of 1 mL, 6 injection needles and 6 cleansing swabs
EU/1/99/127/018 12 single dose vials, 12 injection syringes of 1 mL, 12 injection needles and 12 cleansing swabs

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IntronA 5 MIU solution

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IntronA 5 million IU/0.5 mL solution for injection or infusion
interferon alfa-2b
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 million IU/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

IntronA 10 million IU/mL solution for injection or infusion
interferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 10 million IU of interferon alfa-2b in 1 mL of solution.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

10 million IU/mL solution for injection or infusion
1 single dose vial
1 single dose vial, 1 injection syringe of 2 mL, 1 injection needle and 1 cleansing swab
6 single dose vials, 6 injection syringes of 2 mL, 6 injection needles and 6 cleansing swabs
12 single dose vials, 12 injection syringes of 2 mL, 12 injection needles and 12 cleansing swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use.
Dilute prior to intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/127/019 1 single dose vial
EU/1/99/127/020 1 single dose vial, 1 injection syringe of 2 mL, 1 injection needle and 1 cleansing swab
EU/1/99/127/021 6 single dose vials, 6 injection syringes of 2 mL, 6 injection needles and 6 cleansing swabs
EU/1/99/127/022 12 single dose vials, 12 injection syringes of 2 mL, 12 injection needles and 12 cleansing swabs

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IntronA 10 MIU solution

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IntronA 10 million IU/mL solution for injection or infusion
interferon alfa-2b
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 million IU/mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

IntronA 18 million IU/3 mL solution for injection or infusion
interferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 18 million IU of interferon alfa-2b in 3 mL of solution.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

18 million IU/3 mL solution for injection or infusion
1 multiple dose vial
1 multiple dose vial, 6 injection syringes of 1 mL, 6 injection needles and 12 cleansing swabs
1 multiple dose vial, 6 injection syringes with attached needle and needle protection device of 1 mL and 12 cleansing swabs
2 multiple dose vials
2 multiple dose vials, 12 injection syringes of 1 mL, 12 injection needles and 24 cleansing swabs
2 multiple dose vials, 12 injection syringes with attached needle and needle protection device of 1 mL and 24 cleansing swabs
12 multiple dose vials
12 multiple dose vials, 72 injection syringes of 1 mL, 72 injection needles and 144 cleansing swabs
12 multiple dose vials, 72 injection syringes with attached needle and needle protection device of 1 mL and 144 cleansing swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use.
Dilute prior to intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/127/023 1 multiple dose vial
EU/1/99/127/024 1 multiple dose vial 6 injection syringes of 1 mL, 6 injection needles and 12 cleansing swabs
EU/1/99/127/045 1 multiple dose vial, 6 injection syringes with attached needle and needle protection device of 1 mL and 12 cleansing swabs
EU/1/99/127/025 2 multiple dose vials
EU/1/99/127/041 2 multiple dose vials, 12 injection syringes of 1 mL, 12 injection needles and 24 cleansing swabs
EU/1/99/127/046 2 multiple dose vial, 12 injection syringes with attached needle and needle protection device of 1 mL and 24 cleansing swabs
EU/1/99/127/026 12 multiple dose vials
EU/1/99/127/042 12 multiple dose vials, 72 injection syringes of 1 mL, 72 injection needles and 144 cleansing swabs
EU/1/99/127/047 12 multiple dose vial, 72 injection syringes with attached needle and needle protection device of 1 mL and 144 cleansing swabs

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IntronA 18 MIU solution

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IntronA 18 million IU/3 mL solution for injection or infusion
interferon alfa-2b
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

18 million IU/3 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

IntronA 25 million IU/2.5 mL solution for injection or infusion
interferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 25 million IU of interferon alfa-2b in 2.5 mL of solution.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

25 million IU/2.5 mL solution for injection or infusion
1 multiple dose vial
1 multiple dose vial, 6 injection syringes of 1 mL, 6 injection needles and 12 cleansing swabs
1 multiple dose vial, 6 injection syringes with attached needle and needle protection device of 1 mL and 12 cleansing swabs
1 multiple dose vial, 6 injection syringes with attached needle of 1 mL and 12 cleansing swabs
2 multiple dose vials
2 multiple dose vials, 12 injection syringes of 1 mL, 12 injection needles and 24 cleansing swabs
2 multiple dose vial, 12 injection syringes with attached needle and needle protection device of 1 mL and 24 cleansing swabs
2 multiple dose vial, 12 injection syringes with attached needle of 1 mL and 24 cleansing swabs
12 multiple dose vials
12 multiple dose vials, 72 injection syringes of 1 mL, 72 injection needles and 144 cleansing swabs
12 multiple dose vial, 72 injection syringes with attached needle and needle protection device of 1 mL and 144 cleansing swabs
12 multiple dose vial, 72 injection syringes with attached needle of 1 mL and 144 cleansing swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use.
Dilute prior to intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/127/027 1 multiple dose vial
EU/1/99/127/028 1 multiple dose vial, 6 injection syringes of 1 mL, 6 injection needles and 12 cleansing swabs
EU/1/99/127/048 1 multiple dose vial, 6 injection syringes with attached needle and needle protection device of 1 mL and 12 cleansing swabs
EU/1/99/127/051 1 multiple dose vial, 6 injection syringes with attached needle of 1 mL and 12 cleansing swabs
EU/1/99/127/029 2 multiple dose vials
EU/1/99/127/043 2 multiple dose vials, 12 injection syringes of 1 mL, 12 injection needles and 24 cleansing swabs
EU/1/99/127/049 2 multiple dose vial, 12 injection syringes with attached needle and needle protection device of 1 mL and 24 cleansing swabs
EU/1/99/127/052 2 multiple dose vial, 12 injection syringes with attached needle of 1 mL and 24 cleansing swabs
EU/1/99/127/030 12 multiple dose vials
EU/1/99/127/044 12 multiple dose vials, 72 injection syringes of 1 mL, 72 injection needles and 144 cleansing swabs
EU/1/99/127/050 12 multiple dose vial, 72 injection syringes with attached needle and needle protection device of 1 mL and 144 cleansing swabs
EU/1/99/127/053 12 multiple dose vial, 72 injection syringes with attached needle of 1 mL and 144 cleansing swabs

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IntronA 25 MIU solution

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IntronA 25 million IU/2.5 mL solution for injection or infusion
interferon alfa-2b
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

25 million IU/2.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

IntronA 18 million IU solution for injection in multidose pen
interferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pen contains 18 million IU of interferon alfa-2b in 1.2 mL of solution.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

18 million IU solution for injection in multidose pen
1 pen, 12 injection needles and 12 cleansing swabs
2 pens, 24 injection needles and 24 cleansing swabs
8 pens, 96 injection needles and 96 cleansing swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/127/031 1 pen, 12 injection needles and 12 cleansing swabs
EU/1/99/127/032 2 pens, 24 injection needles and 24 cleansing swabs
EU/1/99/127/033 8 pens, 96 injection needles and 96 cleansing swabs

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IntronA 18 MIU pen

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pen label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IntronA 18 million IU solution for injection in multidose pen
interferon alfa-2b
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

18 million IU/pen

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

IntronA 30 million IU solution for injection in multidose pen
interferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pen contains 30 million IU of interferon alfa-2b in 1.2 mL of solution.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

30 million IU solution for injection in multidose pen
1 pen, 12 injection needles and 12 cleansing swabs
2 pens, 24 injection needles and 24 cleansing swabs
8 pens, 96 injection needles and 96 cleansing swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/127/034 1 pen, 12 injection needles and 12 cleansing swabs
EU/1/99/127/035 2 pens, 24 injection needles and 24 cleansing swabs
EU/1/99/127/036 8 pens, 96 injection needles and 96 cleansing swabs

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IntronA 30 MIU pen

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pen label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IntronA 30 million IU solution for injection in multidose pen
interferon alfa-2b
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 million IU/pen

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

IntronA 60 million IU solution for injection in multidose pen
interferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pen contains 60 million IU of interferon alfa-2b in 1.2 mL of solution.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

60 million IU solution for injection in multidose pen
1 pen, 12 injection needles and 12 cleansing swabs
2 pens, 24 injection needles and 24 cleansing swabs
8 pens, 96 injection needles and 96 cleansing swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/127/037 1 pen, 12 injection needles and 12 cleansing swabs
EU/1/99/127/038 2 pens, 24 injection needles and 24 cleansing swabs
EU/1/99/127/039 8 pens, 96 injection needles and 96 cleansing swabs

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IntronA 60 MIU pen

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pen label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IntronA 60 million IU solution for injection in multidose pen
interferon alfa-2b
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 million IU/pen

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

IntronA 3 million IU/0.5 mL solution for injection or infusion
Interferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IntronA is and what it is used for

IntronA (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases.

IntronA is used in adult patients to treat certain disorders that affect the blood, bone marrow, lymph glands, or skin and may extend into the body. Included are hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, and malignant melanoma.

IntronA is also used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

IntronA is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

2. What you need to know before you use IntronA

Do not use IntronA
- if you are allergic to interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medicines that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.
- if you are being treated with telbivudine (see section "Other medicines and IntronA").

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using IntronA
- if you are pregnant or planning to become pregnant (see section "Pregnancy and breast-feeding").
- if you are being treated for mental illness or had treatment in the past for any other nervous or mental disorder, including depression (such as feelings of sadness, dejection) or suicidal or homicidal behaviour (see section 4 "Possible side effects"). The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section "Do not use IntronA").
- if you have cirrhosis or other liver problems (other than hepatitis B or C).
- if you have psoriasis, it may get worse during treatment with IntronA.
- when receiving IntronA, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medicine seek medical help immediately.
- if you are also being treated for HIV (see section "Other medicines and IntronA").
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of IntronA with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs).

Be sure to tell your doctor if you are taking the Chinese herbal medicine Shosaikoto.

Other medicines and IntronA
IntronA will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medicines.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medicines you are taking, or have taken recently, even those not prescribed, as the dose of some medicines may have to be adjusted while you are treated with IntronA.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of IntronA and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with IntronA and

ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

If you take telbivudine with a pegylated interferon alfa-2a or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, the combination of IntronA with telbivudine is contraindicated.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

IntronA with food and drink and alcohol
While being treated with IntronA, your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed IntronA in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you a or your partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking IntronA. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Driving and using machines
Do not drive or use machines if you become drowsy, tired, or confused from using this medicine.

IntronA contains less than 1 mmol sodium (23 mg) per 0.5 mL, i.e., essentially "sodium-free".

3. How to use IntronA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor has prescribed IntronA specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of IntronA according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting IntronA yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/m^2 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Hairy Cell Leukaemia: 2 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic Myelogenous Leukaemia: 4-5 million IU/m^2 daily injected subcutaneously (under the skin).

Multiple myeloma: 3 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Follicular lymphoma: Adjunctively with chemotherapy, 5 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Carcinoid tumour: 5 million IU, 3 times a week (every other day) injected subcutaneously (under the skin).

Malignant melanoma, induction therapy: 20 million IU/m^2, intravenously, given daily for 5 days a week for a 4 week period. Maintenance treatment: 10 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Your doctor may prescribe a different dose of IntronA alone or in combination with other medicines (e.g., cytarabine, ribavirin). If you are prescribed IntronA in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of IntronA is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
IntronA is usually intended for subcutaneous use. This means that IntronA is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see section “HOW TO SELF INJECT INTRONA” at the end of the leaflet).

Intravenous infusion:
The infusion must be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

No other medicinal product can be infused concomitantly with IntronA.

One dose of IntronA is given on each scheduled day. IntronA is given either daily (5 or 7 times a week), or three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use IntronA exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take IntronA for as long as prescribed.

If you use more IntronA than you should
Contact your doctor or healthcare professional as soon as possible.

If you forget to use IntronA
If you are self-administering treatment, or if you are the caregiver of a child taking IntronA in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this medicine every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Psychiatric and central nervous system:
Some people get depressed when taking IntronA alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with IntronA and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with IntronA in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 10-12 years after completing treatment.

If any of the following side effects happen, stop taking IntronA and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to IntronA. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels. Moderate and usually reversible reduction in all three blood elements-white blood cells, red blood cells and platelets, has been reported.

At the beginning of treatment with IntronA, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Possible side effects listed below are grouped by frequency of occurrence:

Very common	(affects more than 1 user in 10)
Common	(affects 1 to 10 users in 100)
Uncommon	(affects 1 to 10 users in 1,000)
Rare	(affects 1 to 10 users in 10,000)
Very rare	(affects less than 1 user in 10,000)
Not known	(frequency cannot be estimated from the available data)

The following side effects have been reported:

Very commonly reported side effects:
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects:
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis (“pink eye”), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Uncommonly reported side effects:
bacterial infection and feeling of pins and needles.

Rarely reported side effects:
pneumonia.

Very rarely reported side effects:
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.

Not known side effects:
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.
Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, mania (excessive or unreasonable enthusiasm), bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement), congestive heart failure, pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), and pulmonary fibrosis (scarring of the lungs) have been reported with IntronA use.

Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with IntronA.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can also help provide more information on the safety of this medicine.

5. How to store IntronA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the medicine is not used during the seven-day period, it should be discarded.

Do not use this medicine if you notice changes in the appearance of IntronA.

Any unused medicine must be discarded after withdrawal of the dose.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IntronA contains

- The active substance is recombinant interferon alfa-2b. Each vial contains 3 million IU in 0.5 mL of solution.
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

What IntronA looks like and contents of the pack

IntronA is presented as a solution for injection or infusion.
The clear and colourless solution is contained in a glass vial.

IntronA is available in four different pack sizes:
- Pack of 1 vial
- Pack of 1 vial, 1 injection syringe of 1 mL, 1 injection needle and 1 cleansing swab
- Pack of 6 vials, 6 injection syringes of 1 mL, 6 injection needles and 6 cleansing swabs
- Pack of 12 vials, 12 injection syringes of 1 mL, 12 injection needles and 12 cleansing swabs

Not all pack sizes may be marketed.

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United Kingdom

Manufacturer:
SP Labo N.V.
Industriepark 30
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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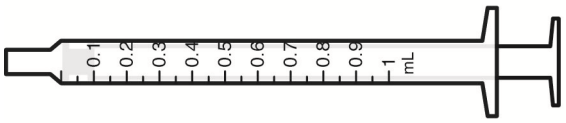
This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

HOW TO SELF INJECT INTRONA
Syringe with an unattached needle



The following instructions explain how to inject IntronA yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject IntronA. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of IntronA solution for injection;
- a syringe (for example 1 mL);
- a needle for the subcutaneous injection (for example 0.4 x 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of IntronA
Remove the cap from the vial. Clean the rubber stopper on the top of the vial containing the IntronA solution with a cleansing swab.
Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.
Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.
Hold the IntronA vial upright without touching the cleaned top of the vial with your hands.
Insert the needle into the vial containing the IntronA solution and inject air into the vial.
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the IntronA solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container.

Package leaflet: Information for the user

IntronA 5 million IU/0.5 mL solution for injection or infusion
Interferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IntronA is and what it is used for

IntronA (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases.

IntronA is used in adult patients to treat certain disorders that affect the blood, bone marrow, lymph glands, or skin and may extend into the body. Included are hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, and malignant melanoma.

IntronA is also used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

IntronA is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

2. What you need to know before you use IntronA

Do not use IntronA
- if you are allergic to interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medicines that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.
- if you are being treated with telbivudine (see section "Other medicines and IntronA").

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using IntronA
- if you are pregnant or planning to become pregnant (see section "Pregnancy and breast-feeding").
- if you are being treated for mental illness or had treatment in the past for any other nervous or mental disorder, including depression (such as feelings of sadness, dejection) or suicidal or homicidal behaviour (see section 4 "Possible side effects"). The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section "Do not use IntronA").
- if you have cirrhosis or other liver problems (other than hepatitis B or C).
- if you have psoriasis, it may get worse during treatment with IntronA.
- when receiving IntronA, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medicine seek medical help immediately.
- if you are also being treated for HIV (see section "Other medicines and IntronA").
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of IntronA with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs).

Be sure to tell your doctor if you are taking the Chinese herbal medicine Shosaikoto.

Other medicines and IntronA
IntronA will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medicines.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medicines you are taking, or have taken recently, even those not prescribed, as the dose of some medicines may have to be adjusted while you are treated with IntronA.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of IntronA and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with IntronA and

ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

If you take telbivudine with a pegylated interferon alfa-2a or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, the combination of IntronA with telbivudine is contraindicated.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

IntronA with food and drink and alcohol
While being treated with IntronA, your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed IntronA in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you or your partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking IntronA. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Driving and using machines
Do not drive or use machines if you become drowsy, tired, or confused from using this medicine.

IntronA contains less than 1 mmol sodium (23 mg) per 0.5 mL, i.e., essentially "sodium-free".

3. How to use IntronA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor has prescribed IntronA specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of IntronA according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting IntronA yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/m^2 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Hairy Cell Leukaemia: 2 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic Myelogenous Leukaemia: 4-5 million IU/m^2 daily injected subcutaneously (under the skin).

Multiple myeloma: 3 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Follicular lymphoma: Adjunctively with chemotherapy, 5 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Carcinoid tumour: 5 million IU, 3 times a week (every other day) injected subcutaneously (under the skin).

Malignant melanoma, induction therapy: 20 million IU/m^2, intravenously, given daily for 5 days a week for a 4 week period. Maintenance treatment: 10 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Your doctor may prescribe a different dose of IntronA alone or in combination with other medicines (e.g., cytarabine, ribavirin). If you are prescribed IntronA in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of IntronA is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
IntronA is usually intended for subcutaneous use. This means that IntronA is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see section “HOW TO SELF INJECT INTRONA” at the end of the leaflet).

Intravenous infusion:
The infusion must be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

No other medicinal product can be infused concomitantly with IntronA.

One dose of IntronA is given on each scheduled day. IntronA is given either daily (5 or 7 times a week), or three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use IntronA exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take IntronA for as long as prescribed.

If you use more IntronA than you should
Contact your doctor or healthcare professional as soon as possible.

If you forget to use IntronA
If you are self-administering treatment, or if you are the caregiver of a child taking IntronA in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this medicine every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Psychiatric and central nervous system:
Some people get depressed when taking IntronA alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with IntronA and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with IntronA in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 10-12 years after completing treatment.

If any of the following side effects happen, stop taking IntronA and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to IntronA. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels. Moderate and usually reversible reduction in all three blood elements-white blood cells, red blood cells and platelets, has been reported.

At the beginning of treatment with IntronA, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Possible side effects listed below are grouped by frequency of occurrence:

Very common	(affects more than 1 user in 10)
Common	(affects 1 to 10 users in 100)
Uncommon	(affects 1 to 10 users in 1,000)
Rare	(affects 1 to 10 users in 10,000)
Very rare	(affects less than 1 user in 10,000)
Not known	(frequency cannot be estimated from the available data)

The following side effects have been reported:

Very commonly reported side effects:
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects:
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis (“pink eye”), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Uncommonly reported side effects:
bacterial infection and feeling of pins and needles.

Rarely reported side effects:
pneumonia.

Very rarely reported side effects:
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.

Not known side effects:
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.
Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, mania (excessive or unreasonable enthusiasm), bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement), congestive heart failure, pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), and pulmonary fibrosis (scarring of the lungs) have been reported with IntronA use.

Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with IntronA.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can also help provide more information on the safety of this medicine.

5. How to store IntronA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the medicine is not used during the seven-day period, it should be discarded.

Do not use this medicine if you notice changes in the appearance of IntronA.

Any unused medicine must be discarded after withdrawal of the dose.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IntronA contains

- The active substance is recombinant interferon alfa-2b. Each vial contains 5 million IU in 0.5 mL of solution.
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

What IntronA looks like and contents of the pack

IntronA is presented as a solution for injection or infusion.
The clear and colourless solution is contained in a glass vial.

IntronA is available in four different pack sizes:
- Pack of 1 vial
- Pack of 1 vial, 1 injection syringe of 1 mL, 1 injection needle and 1 cleansing swab
- Pack of 6 vials, 6 injection syringes of 1 mL, 6 injection needles and 6 cleansing swabs
- Pack of 12 vials, 12 injection syringes of 1 mL, 12 injection needles and 12 cleansing swabs

Not all pack sizes may be marketed.

Marketing Authorisation Holder:
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Hertfordshire EN11 9BU
United Kingdom

Manufacturer:
SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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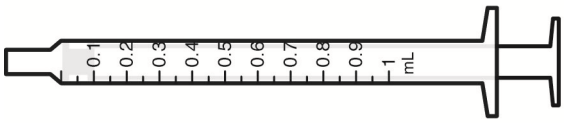
This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

HOW TO SELF INJECT INTRONA
Syringe with an unattached needle



The following instructions explain how to inject IntronA yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject IntronA. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of IntronA solution for injection;
- a syringe (for example 1 mL);
- a needle for the subcutaneous injection (for example 0.4 x 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of IntronA
Remove the cap from the vial. Clean the rubber stopper on the top of the vial containing the IntronA solution with a cleansing swab.
Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.
Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.
Hold the IntronA vial upright without touching the cleaned top of the vial with your hands.
Insert the needle into the vial containing the IntronA solution and inject air into the vial.
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the IntronA solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container.

Package leaflet: Information for the user

IntronA 10 million IU/mL solution for injection or infusion
Interferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IntronA is and what it is used for

IntronA (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases.

IntronA is used in adult patients to treat certain disorders that affect the blood, bone marrow, lymph glands, or skin and may extend into the body. Included are hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, and malignant melanoma.

IntronA is also used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

IntronA is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

2. What you need to know before you use IntronA

Do not use IntronA
- if you are allergic to interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medicines that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.
- if you are being treated with telbivudine (see section "Other medicines and IntronA").

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using IntronA
- if you are pregnant or planning to become pregnant (see section "Pregnancy and breast-feeding").
- if you are being treated for mental illness or had treatment in the past for any other nervous or mental disorder, including depression (such as feelings of sadness, dejection) or suicidal or homicidal behaviour (see section 4 "Possible side effects"). The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section "Do not use IntronA").
- if you have cirrhosis or other liver problems (other than hepatitis B or C).
- if you have psoriasis, it may get worse during treatment with IntronA.
- when receiving IntronA, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medicine seek medical help immediately.
- if you are also being treated for HIV (see section "Other medicines and IntronA").
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of IntronA with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs).

Be sure to tell your doctor if you are taking the Chinese herbal medicine Shosaikoto.

Other medicines and IntronA
IntronA will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medicines.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medicines you are taking, or have taken recently, even those not prescribed, as the dose of some medicines may have to be adjusted while you are treated with IntronA.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of IntronA and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with IntronA and

ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

If you take telbivudine with a pegylated interferon alfa-2a or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, the combination of IntronA with telbivudine is contraindicated.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

IntronA with food and drink and alcohol
While being treated with IntronA, your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed IntronA in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you or your partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking IntronA. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Driving and using machines
Do not drive or use machines if you become drowsy, tired, or confused from using this medicine.

IntronA contains less than 1 mmol sodium (23 mg) per 1 mL, i.e., essentially "sodium-free".

3. How to use IntronA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor has prescribed IntronA specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of IntronA according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting IntronA yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/m^2 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Hairy Cell Leukaemia: 2 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic Myelogenous Leukaemia: 4-5 million IU/m^2 daily injected subcutaneously (under the skin).

Multiple myeloma: 3 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Follicular lymphoma: Adjunctively with chemotherapy, 5 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Carcinoid tumour: 5 million IU, 3 times a week (every other day) injected subcutaneously (under the skin).

Malignant melanoma, induction therapy: 20 million IU/m^2, intravenously, given daily for 5 days a week for a 4 week period. Maintenance treatment: 10 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Your doctor may prescribe a different dose of IntronA alone or in combination with other medicines (e.g., cytarabine, ribavirin). If you are prescribed IntronA in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of IntronA is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
IntronA is usually intended for subcutaneous use. This means that IntronA is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see section “HOW TO SELF INJECT INTRONA” at the end of the leaflet).

Intravenous infusion:
The infusion must be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

No other medicinal product can be infused concomitantly with IntronA.

One dose of IntronA is given on each scheduled day. IntronA is given either daily (5 or 7 times a week), or three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use IntronA exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take IntronA for as long as prescribed.

If you use more IntronA than you should
Contact your doctor or healthcare professional as soon as possible.

If you forget to use IntronA
If you are self-administering treatment, or if you are the caregiver of a child taking IntronA in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this medicine every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Psychiatric and central nervous system:
Some people get depressed when taking IntronA alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with IntronA and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with IntronA in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 10-12 years after completing treatment.

If any of the following side effects happen, stop taking IntronA and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to IntronA. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels. Moderate and usually reversible reduction in all three blood elements-white blood cells, red blood cells and platelets, has been reported.

At the beginning of treatment with IntronA, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Possible side effects listed below are grouped by frequency of occurrence:

Very common	(affects more than 1 user in 10)
Common	(affects 1 to 10 users in 100)
Uncommon	(affects 1 to 10 users in 1,000)
Rare	(affects 1 to 10 users in 10,000)
Very rare	(affects less than 1 user in 10,000)
Not known	(frequency cannot be estimated from the available data)

The following side effects have been reported:

Very commonly reported side effects:
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects:
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis (“pink eye”), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Uncommonly reported side effects:
bacterial infection and feeling of pins and needles.

Rarely reported side effects:
pneumonia.

Very rarely reported side effects:
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.

Not known side effects:
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.
Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, mania (excessive or unreasonable enthusiasm), bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement), congestive heart failure, pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), and pulmonary fibrosis (scarring of the lungs) have been reported with IntronA use.

Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with IntronA.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can also help provide more information on the safety of this medicine.

5. How to store IntronA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the medicine is not used during the seven-day period, it should be discarded.

Do not use this medicine if you notice changes in the appearance of IntronA.

Any unused medicine must be discarded after withdrawal of the dose.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IntronA contains

- The active substance is recombinant interferon alfa-2b. Each vial contains 10 million IU in 1 mL of solution.
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

What IntronA looks like and contents of the pack

IntronA is presented as a solution for injection or infusion.
The clear and colourless solution is contained in a glass vial.

IntronA is available in four different pack sizes:
- Pack of 1 vial
- Pack of 1 vial, 1 injection syringe of 2 mL, 1 injection needle and 1 cleansing swab
- Pack of 6 vials, 6 injection syringes of 2 mL, 6 injection needles and 6 cleansing swabs
- Pack of 12 vials, 12 injection syringes of 2 mL, 12 injection needles and 12 cleansing swabs

Not all pack sizes may be marketed.

Marketing Authorisation Holder:
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Hertfordshire EN11 9BU
United Kingdom

Manufacturer:
SP Labo N.V.
Industriepark 30
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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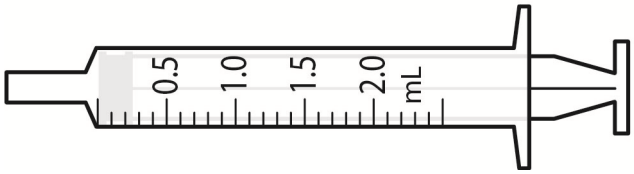
This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

HOW TO SELF INJECT INTRONA
Syringe with an unattached needle



The following instructions explain how to inject IntronA yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject IntronA. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of IntronA solution for injection;
- a syringe (for example 2 mL);
- a needle for the subcutaneous injection (for example 0.4 x 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of IntronA
Remove the cap from the vial. Clean the rubber stopper on the top of the vial containing the IntronA solution with a cleansing swab.
Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.
Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.
Hold the IntronA vial upright without touching the cleaned top of the vial with your hands.
Insert the needle into the vial containing the IntronA solution and inject air into the vial.
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the IntronA solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.
Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container.

Package leaflet: Information for the user

IntronA 18 million IU/3 mL solution for injection or infusion
Interferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IntronA is and what it is used for

IntronA (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases.

IntronA is used in adult patients to treat certain disorders that affect the blood, bone marrow, lymph glands, or skin and may extend into the body. Included are hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, and malignant melanoma.

IntronA is also used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

IntronA is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

2. What you need to know before you use IntronA

Do not use IntronA
- if you are allergic to interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medicines that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.
- if you are being treated with telbivudine (see section "Other medicines and IntronA").

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using IntronA
- if you are pregnant or planning to become pregnant (see section "Pregnancy and breast-feeding").
- if you are being treated for mental illness or had treatment in the past for any other nervous or mental disorder, including depression (such as feelings of sadness, dejection) or suicidal or homicidal behaviour (see section 4 "Possible side effects"). The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section "Do not use IntronA").
- if you have cirrhosis or other liver problems (other than hepatitis B or C).
- if you have psoriasis, it may get worse during treatment with IntronA.
- when receiving IntronA, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medicine seek medical help immediately.
- if you are also being treated for HIV (see section "Other medicines and IntronA").
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of IntronA with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs).

Be sure to tell your doctor if you are taking the Chinese herbal medicine Shosaikoto.

Other medicines and IntronA
IntronA will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medicines.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medicines you are taking, or have taken recently, even those not prescribed, as the dose of some medicines may have to be adjusted while you are treated with IntronA.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of IntronA and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with IntronA and

ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

If you take telbivudine with a pegylated interferon alfa-2a or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, the combination of IntronA with telbivudine is contraindicated.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

IntronA with food and drink and alcohol
While being treated with IntronA, your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed IntronA in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you or your partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking IntronA. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Driving and using machines
Do not drive or use machines if you become drowsy, tired, or confused from using this medicine.

IntronA contains less than 1 mmol sodium (23 mg) per 3 mL, i.e., essentially "sodium-free".

3. How to use IntronA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor has prescribed IntronA specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of IntronA according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting IntronA yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/m^2 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Hairy Cell Leukaemia: 2 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic Myelogenous Leukaemia: 4-5 million IU/m^2 daily injected subcutaneously (under the skin).

Multiple myeloma: 3 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Follicular lymphoma: Adjunctively with chemotherapy, 5 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Carcinoid tumour: 5 million IU, 3 times a week (every other day) injected subcutaneously (under the skin).

Malignant melanoma, induction therapy: 20 million IU/m^2, intravenously, given daily for 5 days a week for a 4 week period. Maintenance treatment: 10 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Your doctor may prescribe a different dose of IntronA alone or in combination with other medicines (e.g., cytarabine, ribavirin). If you are prescribed IntronA in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of IntronA is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
IntronA is usually intended for subcutaneous use. This means that IntronA is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see section “HOW TO SELF INJECT INTRONA” at the end of the leaflet).

Intravenous infusion:
The infusion must be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

No other medicinal product can be infused concomitantly with IntronA.

One dose of IntronA is given on each scheduled day. IntronA is given either daily (5 or 7 times a week), or three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use IntronA exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take IntronA for as long as prescribed.

If you use more IntronA than you should
Contact your doctor or healthcare professional as soon as possible.

If you forget to use IntronA
If you are self-administering treatment, or if you are the caregiver of a child taking IntronA in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this medicine every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Psychiatric and central nervous system:
Some people get depressed when taking IntronA alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with IntronA and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with IntronA in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 10-12 years after completing treatment.

If any of the following side effects happen, stop taking IntronA and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to IntronA. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels. Moderate and usually reversible reduction in all three blood elements-white blood cells, red blood cells and platelets, has been reported.

At the beginning of treatment with IntronA, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Possible side effects listed below are grouped by frequency of occurrence:

Very common	(affects more than 1 user in 10)
Common	(affects 1 to 10 users in 100)
Uncommon	(affects 1 to 10 users in 1,000)
Rare	(affects 1 to 10 users in 10,000)
Very rare	(affects less than 1 user in 10,000)
Not known	(frequency cannot be estimated from the available data)

The following side effects have been reported:

Very commonly reported side effects:
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects:
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis (“pink eye”), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Uncommonly reported side effects:
bacterial infection and feeling of pins and needles.

Rarely reported side effects:
pneumonia.

Very rarely reported side effects:
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.

Not known side effects:
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.
Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, mania (excessive or unreasonable enthusiasm), bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement), congestive heart failure, pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), and pulmonary fibrosis (scarring of the lungs) have been reported with IntronA use.

Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with IntronA.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can also help provide more information on the safety of this medicine.

5. How to store IntronA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the medicine is not used during the seven-day period, it should be discarded.

Once opened, the medicine may be stored for a maximum of 28 days at 2ºC – 8ºC.

Do not use this medicine if you notice changes in the appearance of IntronA.

6. Contents of the pack and other information

What IntronA contains

- The active substance is recombinant interferon alfa-2b Each vial contains 18 million IU in 3 mL of solution.
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.
- One mL of solution contains 6 million IU of interferon alfa-2b.

What IntronA looks like and contents of the pack

IntronA is presented as a solution for injection or infusion.
The clear and colourless solution is contained in a glass vial.

IntronA is available in nine different pack sizes:
- Pack of 1 vial
- Pack of 1 vial, 6 injection syringes of 1 mL, 6 injection needles and 12 cleansing swabs
- Pack of 1 vial, 6 injection syringes with attached needle and needle protection device of 1 mL and 12 cleansing swabs
- Pack of 2 vials
- Pack of 2 vials, 12 injection syringes of 1 mL, 12 injection needles and 24 cleansing swabs
- Pack of 2 vials, 12 injection syringes with attached needle and needle protection device of 1 mL and 24 cleansing swabs
- Pack of 12 vials
- Pack of 12 vials, 72 injection syringes of 1 mL, 72 injection needles and 144 cleansing swabs
- Pack of 12 vials, 72 injection syringes with attached needle and needle protection device of 1 mL and 144 cleansing swabs

Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer:
SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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MSD Belgium BVBA/SPRL
Tél/Tel: 0800 38 693 (+32(0)27766211)
dpoc_belux@merck.com

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This leaflet was last revised in.

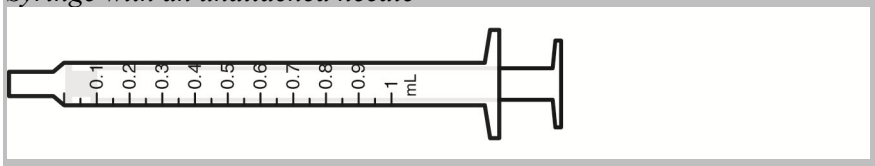
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

HOW TO SELF INJECT INTRONA

Syringe with an unattached needle



The following instructions explain how to inject IntronA yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject IntronA. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- a vial of IntronA solution for injection;
- a syringe (for example 1 mL);
- a needle for the subcutaneous injection (for example 0.4 x 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of IntronA

Remove the cap from the vial. If this is a multidose vial, you will only have to remove the cap when preparing the first dose. Clean the rubber stopper on the top of the vial containing the IntronA solution with a cleansing swab.

Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.

Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.

Hold the IntronA vial upright without touching the cleaned top of the vial with your hands.

Insert the needle into the vial containing the IntronA solution and inject air into the vial.

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the IntronA solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.

Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose.

Volume to be withdrawn according to the dose:

Volume (mL)	Corresponding dose (million IU) using IntronA 18 million IU/3 mL solution for injection or infusion
0.25	1.5
0.5	3
1	6
1.5	9
2	12
2.5	15
3	18

Replace the needle guard and place the syringe with the needle on a flat surface.

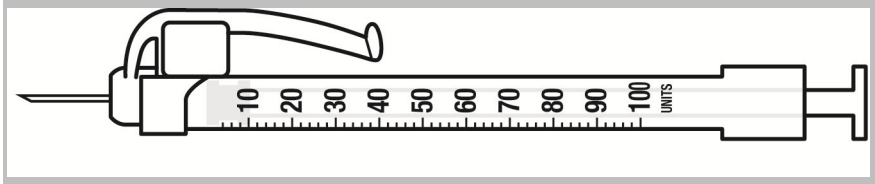
Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container. For multidose vials, be sure to return the vial to the refrigerator.

HOW TO SELF INJECT INTRONA

Syringe with an attached needle and a needle protection device



The following instructions explain how to inject IntronA yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject IntronA. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- a vial of IntronA solution for injection;
- a 1 mL syringe with an attached needle and a needle protection device (BD SafetyGlide syringe);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of IntronA

Remove the cap from the vial. If this is a multidose vial, you will only have to remove the cap when preparing the first dose. Clean the rubber stopper on the top of the vial containing the IntronA solution with a cleansing swab.

Remove the syringe from the wrapping. Rotate the needle protection device for bevel orientation or scale readability.

Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.

Hold the IntronA vial upright without touching the cleaned top of the vial with your hands.

Insert the needle into the vial containing the IntronA solution and inject air into the vial.

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the IntronA solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe (Diagram A).

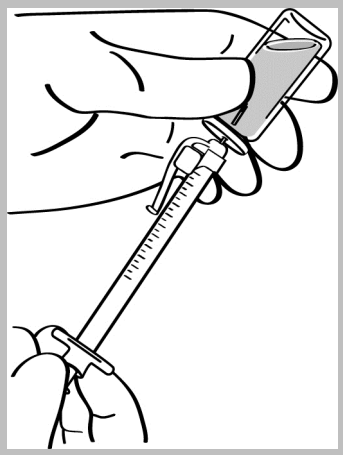


Diagram A

Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose.

Volume to be withdrawn according to the dose:

Volume (mL)	Corresponding dose (million IU) using IntronA 18 million IU/3 mL solution for injection or infusion
0.25	1.5
0.5	3
1	6
1.5	9
2	12
2.5	15
3	18

Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. For user convenience, the needle protection device can be rotated for ease of injection (Diagram B).

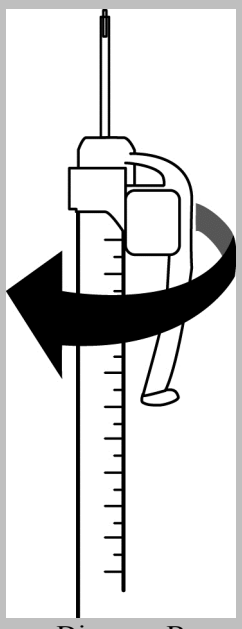


Diagram B

With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently (Diagram C).

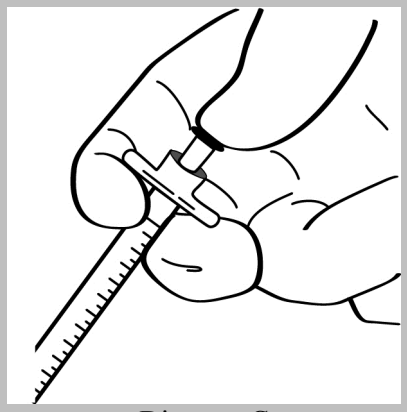


Diagram C

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial and injection materials intended for single use must be discarded. Activate Safety Mechanism of the syringe after removal from the injection site by moving the pushrod completely forward until the pushrod is fully extended and the needle tip is covered (Diagram D). Visually confirm the pushrod has fully advanced and the needle tip is covered. If unable to activate, discard immediately into an approved sharps collector. Dispose of the syringe with attached needle safely in a closed container. For multidose vials, be sure to return the vial to the refrigerator.

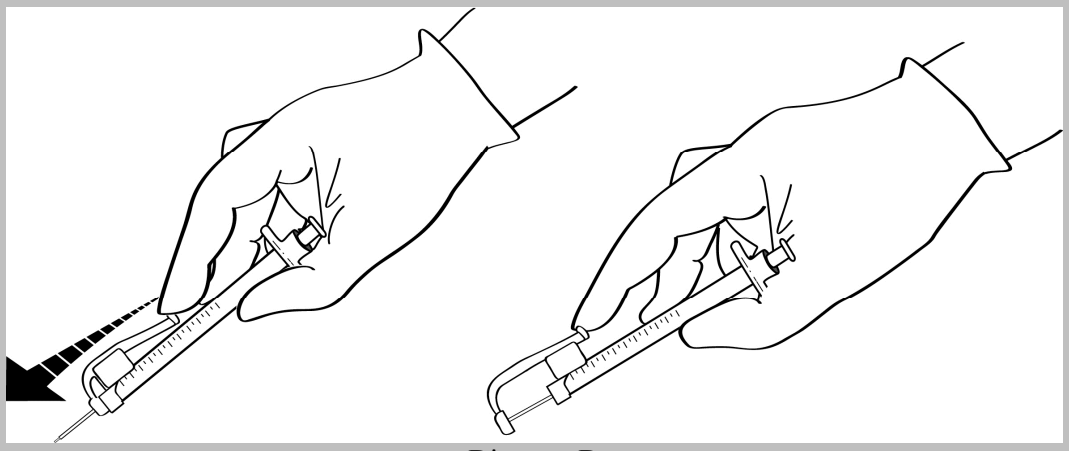


Diagram D

Authorized Representative:
BD, Laagstraat 57, B-9140
Temse, Belgium

Package leaflet: Information for the user

IntronA 25 million IU/2.5 mL solution for injection or infusion
Interferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IntronA is and what it is used for

IntronA (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases.

IntronA is used in adult patients to treat certain disorders that affect the blood, bone marrow, lymph glands, or skin and may extend into the body. Included are hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, and malignant melanoma.

IntronA is also used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

IntronA is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

2. What you need to know before you use IntronA

Do not use IntronA
- if you are allergic to interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medicines that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.
- if you are being treated with telbivudine (see section "Other medicines and IntronA").

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using IntronA
- if you are pregnant or planning to become pregnant (see section "Pregnancy and breast-feeding").
- if you are being treated for mental illness or had treatment in the past for any other nervous or mental disorder, including depression (such as feelings of sadness, dejection) or suicidal or homicidal behaviour (see section 4 "Possible side effects"). The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section "Do not use IntronA").
- if you have cirrhosis or other liver problems (other than hepatitis B or C).
- if you have psoriasis, it may get worse during treatment with IntronA.
- when receiving IntronA, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medicine seek medical help immediately.
- if you are also being treated for HIV (see section "Other medicines and IntronA").
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of IntronA with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs).

Be sure to tell your doctor if you are taking the Chinese herbal medicine Shosaikoto.

Other medicines and IntronA
IntronA will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medicines.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medicines you are taking, or have taken recently, even those not prescribed, as the dose of some medicines may have to be adjusted while you are treated with IntronA.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of IntronA and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with IntronA and

ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

If you take telbivudine with a pegylated interferon alfa-2a or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, the combination of IntronA with telbivudine is contraindicated.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

IntronA with food and drink and alcohol
While being treated with IntronA, your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed IntronA in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you or your partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking IntronA. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Driving and using machines
Do not drive or use machines if you become drowsy, tired, or confused from using this medicine.

IntronA contains less than 1 mmol sodium (23 mg) per 2.5 mL, i.e., essentially "sodium-free".

3. How to use IntronA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor has prescribed IntronA specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of IntronA according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting IntronA yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/m^2 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Hairy Cell Leukaemia: 2 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic Myelogenous Leukaemia: 4-5 million IU/m^2 daily injected subcutaneously (under the skin).

Multiple myeloma: 3 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Follicular lymphoma: Adjunctively with chemotherapy, 5 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Carcinoid tumour: 5 million IU, 3 times a week (every other day) injected subcutaneously (under the skin).

Malignant melanoma, induction therapy: 20 million IU/m^2, intravenously, given daily for 5 days a week for a 4 week period. Maintenance treatment: 10 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Your doctor may prescribe a different dose of IntronA alone or in combination with other medicines (e.g., cytarabine, ribavirin). If you are prescribed IntronA in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of IntronA is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
IntronA is usually intended for subcutaneous use. This means that IntronA is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see section “HOW TO SELF INJECT INTRONA” at the end of the leaflet).

Intravenous infusion:
The infusion must be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

No other medicinal product can be infused concomitantly with IntronA.

One dose of IntronA is given on each scheduled day. IntronA is given either daily (5 or 7 times a week), or three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use IntronA exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take IntronA for as long as prescribed.

If you use more IntronA than you should
Contact your doctor or healthcare professional as soon as possible.

If you forget to use IntronA
If you are self-administering treatment, or if you are the caregiver of a child taking IntronA in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this medicine every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Psychiatric and central nervous system:
Some people get depressed when taking IntronA alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with IntronA and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with IntronA in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 10-12 years after completing treatment.

If any of the following side effects happen, stop taking IntronA and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to IntronA. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels. Moderate and usually reversible reduction in all three blood elements-white blood cells, red blood cells and platelets, has been reported.

At the beginning of treatment with IntronA, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Possible side effects listed below are grouped by frequency of occurrence:

Very common	(affects more than 1 user in 10)
Common	(affects 1 to 10 users in 100)
Uncommon	(affects 1 to 10 users in 1,000)
Rare	(affects 1 to 10 users in 10,000)
Very rare	(affects less than 1 user in 10,000)
Not known	(frequency cannot be estimated from the available data)

The following side effects have been reported:

Very commonly reported side effects:
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects:
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis (“pink eye”), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Uncommonly reported side effects:
bacterial infection and feeling of pins and needles.

Rarely reported side effects:
pneumonia.

Very rarely reported side effects:
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.

Not known side effects:
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.
Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, mania (excessive or unreasonable enthusiasm), bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement), congestive heart failure, pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), and pulmonary fibrosis (scarring of the lungs) have been reported with IntronA use.

Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with IntronA.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can also help provide more information on the safety of this medicine.

5. How to store IntronA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the medicine is not used during the seven-day period, it should be discarded.

Once opened, the medicine may be stored for a maximum of 28 days at 2ºC – 8ºC.

Do not use this medicine if you notice changes in the appearance of IntronA.

6. Contents of the pack and other information

What IntronA contains

- The active substance is recombinant interferon alfa-2b Each vial contains 25 million IU in 2.5 mL of solution.
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.
- One mL of solution contains 10 million IU of interferon alfa-2b

What IntronA looks like and contents of the pack

IntronA is presented as a solution for injection or infusion.
The clear and colourless solution is contained in a glass vial.

IntronA is available in twelve different pack sizes:
- Pack of 1 vial
- Pack of 1 vial, 6 injection syringes of 1 mL, 6 injection needles and 12 cleansing swabs
- Pack of 1 vial, 6 injection syringes with attached needle and needle protection device of 1 mL and 12 cleansing swabs
- Pack of 1 vial, 6 injection syringes with attached needle of 1 mL and 12 cleansing swabs
- Pack of 2 vials
- Pack of 2 vials, 12 injection syringes of 1 mL, 12 injection needles and 24 cleansing swabs
- Pack of 2 vials, 12 injection syringes with attached needle and needle protection device of 1 mL and 24 cleansing swabs
- Pack of 2 vials, 12 injection syringes with attached needle of 1 mL and 24 cleansing swabs
- Pack of 12 vials
- Pack of 12 vials, 72 injection syringes of 1 mL, 72 injection needles and 144 cleansing swabs
- Pack of 12 vials, 72 injection syringes with attached needle and needle protection device of 1 mL and 144 cleansing swabs
- Pack of 12 vials, 72 injection syringes with attached needle of 1 mL and 144 cleansing swabs

Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer:
SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

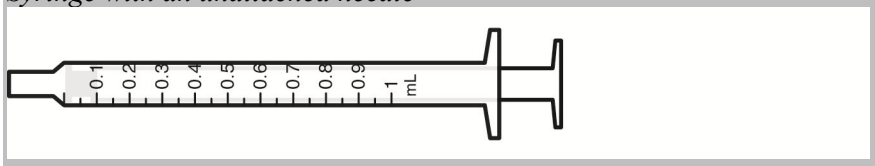
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

HOW TO SELF INJECT INTRONA

Syringe with an unattached needle



The following instructions explain how to inject IntronA yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject IntronA. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- a vial of IntronA solution for injection;
- a syringe (for example 1 mL);
- a needle for the subcutaneous injection (for example 0.4 x 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of IntronA

Remove the cap from the vial. If this is a multidose vial, you will only have to remove the cap when preparing the first dose. Clean the rubber stopper on the top of the vial containing the IntronA solution with a cleansing swab.

Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.

Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.

Hold the IntronA vial upright without touching the cleaned top of the vial with your hands.

Insert the needle into the vial containing the IntronA solution and inject air into the vial.

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the IntronA solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.

Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose.

Volume to be withdrawn according to the dose:

Volume (mL)	Corresponding dose (million IU) using IntronA 25 million IU/2.5 mL solution for injection or infusion
0.25	2.5
0.5	5
1	10
1.5	15
2	20
2.5	25

Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

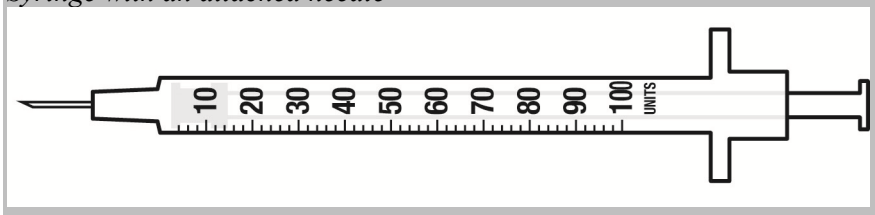
Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container. For multidose vials, be sure to return the vial to the refrigerator.

HOW TO SELF INJECT INTRONA

Syringe with an attached needle



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Preparation

Collect necessary items before you begin:

- a vial of IntronA solution for injection;
- a syringe with an attached needle for subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of IntronA

Remove the cap from the vial. If this is a multidose vial, you will only have to remove the cap when preparing the first dose. Clean the rubber stopper on the top of the vial containing the IntronA solution with a cleansing swab.

Remove the syringe from the wrapping. Ensure that needle with needle guard is firmly attached to the syringe by pushing while turning the needle guard.

Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.

Hold the IntronA vial upright without touching the cleaned top of the vial with your hands.

Insert the needle into the vial containing the IntronA solution and inject air into the vial.

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the IntronA solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.

Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose.

Volume to be withdrawn according to the dose:

Volume (mL)	Corresponding dose (million IU) using IntronA 25 million IU/2.5 mL solution for injection or infusion
0.25	2.5
0.5	5
1	10
1.5	15
2	20
2.5	25

Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

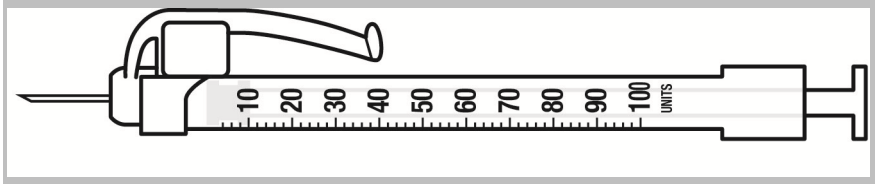
Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial and injection materials intended for single use must be discarded. Dispose of the syringe with attached needle safely in a closed container. For multidose vials, be sure to return the vial to the refrigerator.

HOW TO SELF INJECT INTRONA

Syringe with an attached needle and a needle protection device



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Preparation

Collect necessary items before you begin:

- a vial of IntronA solution for injection;
- a 1 mL syringe with an attached needle and a needle protection device (BD SafetyGlide syringe);
- a cleansing swab.

Wash your hands carefully.

Measuring the dose of IntronA

Remove the cap from the vial. If this is a multidose vial, you will only have to remove the cap when preparing the first dose. Clean the rubber stopper on the top of the vial containing the IntronA solution with a cleansing swab.

Remove the syringe from the wrapping. Rotate the needle protection device for bevel orientation or scale readability.

Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.

Hold the IntronA vial upright without touching the cleaned top of the vial with your hands.

Insert the needle into the vial containing the IntronA solution and inject air into the vial.

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the IntronA solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe (Diagram A).

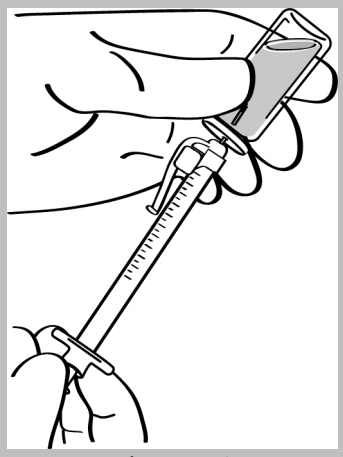

Diagram A

Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose.

Volume to be withdrawn according to the dose:

Volume (mL)	Corresponding dose (million IU) using IntronA 25 million IU/2.5 mL solution for injection or infusion
0.25	2.5
0.5	5
1	10
1.5	15
2	20
2.5	25

Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. For user convenience, the needle protection device can be rotated for ease of injection (Diagram B).

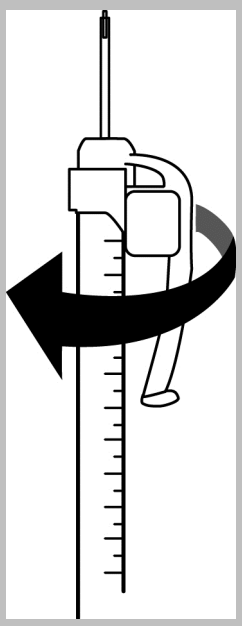

Diagram B

With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently (Diagram C).

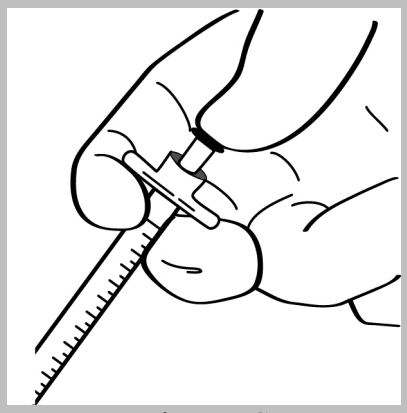

Diagram C

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial and injection materials intended for single use must be discarded. Activate Safety Mechanism of the syringe after removal from the injection site by moving the pushrod completely forward until the pushrod is fully extended and the needle tip is covered (Diagram D). Visually confirm the pushrod has fully advanced and the needle tip is covered. If unable to activate, discard immediately into an approved sharps collector. Dispose of the syringe with attached needle safely in a closed container. For multidose vials, be sure to return the vial to the refrigerator.

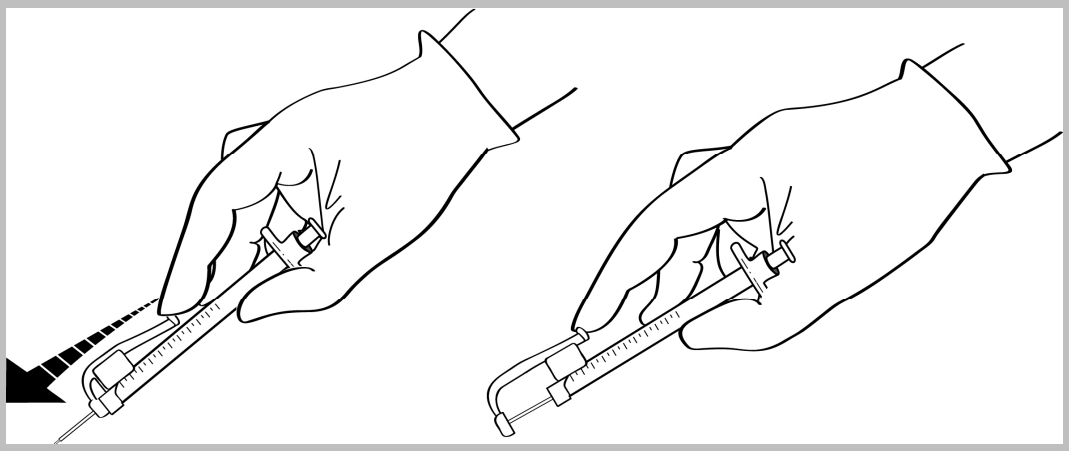

Diagram D

Authorized Representative:
BD, Laagstraat 57, B-9140
Temse, Belgium

Package leaflet: Information for the user

IntronA 18 million IU solution for injection in multidose pen
Interferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IntronA is and what it is used for

IntronA (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases.

IntronA is used in adult patients to treat certain disorders that affect the blood, bone marrow, lymph glands, or skin and may extend into the body. Included are hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, and malignant melanoma.

IntronA is also used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

IntronA is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

2. What you need to know before you use IntronA

Do not use IntronA
- if you are allergic to interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medicines that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.
- if you are being treated with telbivudine (see section "Other medicines and IntronA ").

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using IntronA
- if you are pregnant or planning to become pregnant (see section "Pregnancy and breast-feeding").
- if you are being treated for mental illness or had treatment in the past for any other nervous or mental disorder, including depression (such as feelings of sadness, dejection) or suicidal or homicidal behaviour (see section 4 "Possible side effects"). The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section "Do not use IntronA").
- if you have cirrhosis or other liver problems (other than hepatitis B or C).
- if you have psoriasis, it may get worse during treatment with IntronA.
- when receiving IntronA, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medicine seek medical help immediately.
- if you are also being treated for HIV (see section "Other medicines and IntronA").
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of IntronA with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs).

Be sure to tell your doctor if you are taking the Chinese herbal medicine Shosaikoto.

Other medicines and IntronA
IntronA will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medicines.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medicines you are taking, or have taken recently, even those not prescribed, as the dose of some medicines may have to be adjusted while you are treated with IntronA.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of IntronA and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with IntronA and

ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

If you take telbivudine with a pegylated interferon alfa-2a or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, the combination of IntronA with telbivudine is contraindicated.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

IntronA with food and drink and alcohol
While being treated with IntronA, your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed IntronA in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you or your partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking IntronA. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Driving and using machines
Do not drive or use machines if you become drowsy, tired, or confused from using this medicine.

IntronA contains less than 1 mmol sodium (23 mg) per 1.2 mL, i.e., essentially "sodium-free".

3. How to use IntronA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor has prescribed IntronA specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of IntronA according to your individual needs. The dosage will vary according to the disease being treated. The pen is designed to deliver its contents of 18 million IU in doses ranging from 1.5 to 6 million IU. The pen will deliver a maximum of 12 doses of 1.5 million IU over a period not to exceed 4 weeks.

If you are injecting IntronA yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/m^2 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Hairy Cell Leukaemia: 2 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic Myelogenous Leukaemia: 4-5 million IU/m^2 daily injected subcutaneously (under the skin).

Multiple myeloma: 3 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Follicular lymphoma: Adjunctively with chemotherapy, 5 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Carcinoid tumour: 5 million IU, 3 times a week (every other day) injected subcutaneously (under the skin).

Malignant melanoma, induction therapy: 20 million IU/m^2, intravenously, given daily for 5 days a week for a 4 week period. Maintenance treatment: 10 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Your doctor may prescribe a different dose of IntronA alone or in combination with other medicines (e.g., cytarabine, ribavirin). If you are prescribed IntronA in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of IntronA is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
IntronA is usually intended for subcutaneous use. This means that IntronA is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see section “HOW TO SELF INJECT INTRONA” at the end of the leaflet).

One dose of IntronA is given on each scheduled day. IntronA is given either daily (5 or 7 times a week), or three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use IntronA exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take IntronA for as long as prescribed.

If you use more IntronA than you should
Contact your doctor or healthcare professional as soon as possible.

If you forget to use IntronA
If you are self-administering treatment, or if you are the caregiver of a child taking IntronA in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this medicine every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Psychiatric and central nervous system:
Some people get depressed when taking IntronA alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with IntronA and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with IntronA in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 10-12 years after completing treatment.

If any of the following side effects happen, stop taking IntronA and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to IntronA. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels. Moderate and usually reversible reduction in all three blood elements-white blood cells, red blood cells and platelets, has been reported.

At the beginning of treatment with IntronA, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Possible side effects listed below are grouped by frequency of occurrence:

Very common	(affects more than 1 user in 10)
Common	(affects 1 to 10 users in 100)
Uncommon	(affects 1 to 10 users in 1,000)
Rare	(affects 1 to 10 users in 10,000)
Very rare	(affects less than 1 user in 10,000)
Not known	(frequency cannot be estimated from the available data)

The following side effects have been reported:

Very commonly reported side effects:
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects:
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Uncommonly reported side effects:
bacterial infection and feeling of pins and needles.

Rarely reported side effects:
pneumonia.

Very rarely reported side effects:
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.

Not known side effects:
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing),

bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.
Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, mania (excessive or unreasonable enthusiasm), bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement), congestive heart failure, pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), and pulmonary fibrosis (scarring of the lungs) have been reported with IntronA use.

Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with IntronA.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can also help provide more information on the safety of this medicine.

5. How to store IntronA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Each pen is intended for a maximum four-week use period and must then be discarded. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week period to cover accidental delays in returning the pen to the refrigerator.

Do not use this medicine if you notice changes in the appearance of IntronA.

Depending upon your dose, you may have extra needles and swabs left in the pack. Please discard these appropriately and safely.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IntronA contains

- The active substance is recombinant interferon alfa-2b. Each pen contains 18 million IU.
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

What IntronA looks like and contents of the pack

IntronA is presented as a solution for injection in a multidose pen.

The clear and colourless solution is contained in a glass cartridge.

IntronA is available in three different pack sizes:
- Pack of 1 pen, 12 injection needles and 12 cleansing swabs
- Pack of 2 pens, 24 injection needles and 24 cleansing swabs
- Pack of 8 pens, 96 injection needles and 96 cleansing swabs

Not all pack sizes may be marketed.

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Manufacturer:
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This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

HOW TO SELF INJECT INTRONA

The following instructions explain how to inject IntronA yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject IntronA. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- the IntronA multidose pen;
- a needle for subcutaneous injection (provided in the packaging);
- a cleansing swab (provided in the packaging).

Wash your hands carefully. Use the injection needles provided in the packaging only for IntronA. Use a new injection needle for each dose. Be sure the solution is at room temperature (up to 25°C) at the time of injection.

Diagrams A and B show you all the different parts of the pen and the injection needle. The most important parts to note are as follows:

- The push button scale tells you what dose has been set.
- The colour coding strip brown and the push button are at the bottom of the pen as it is held cap up.
- The pen can only be fully capped when the triangle on the cap scale is aligned with the dosage indicator on the barrel.

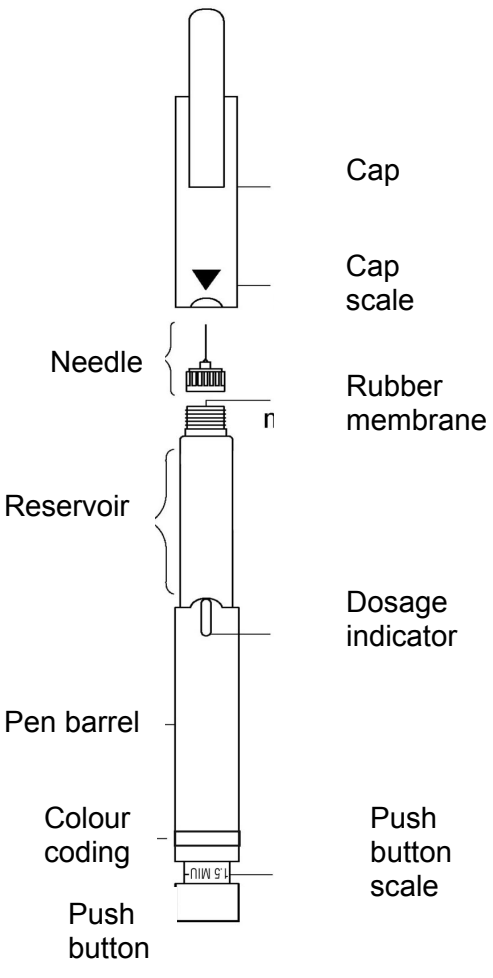

Diagram A

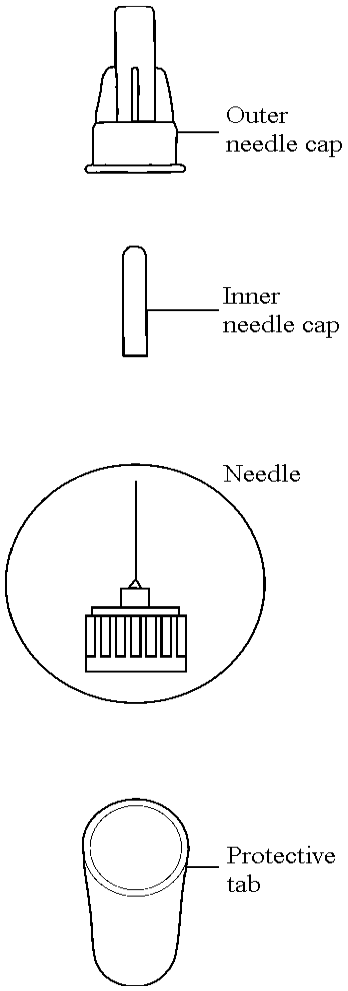

Diagram B

Measuring the dose of IntronA

Take the pen out of the refrigerator about one-half hour before administering the dose so that the solution in the pen is at room temperature when it is injected.

When you are ready to give your injection prepare your pen as follows:

Check that IntronA solution for injection is clear and colourless in appearance prior to use. If it does not have a clear uniform appearance or if it contains any particles, do not use.

Pull off the cap of the pen and disinfect the rubber membrane (see Diagram C) with one cleansing swab.

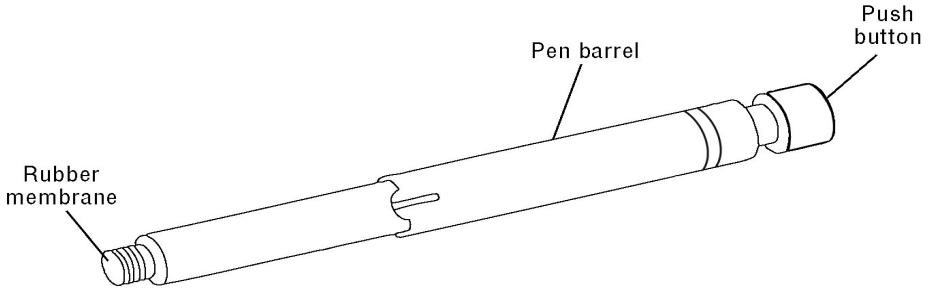

Diagram C

Remove the protective tab from the injection needle. Note that the rear portion of the injection needle is revealed once the protective tab is removed (see Diagram D).

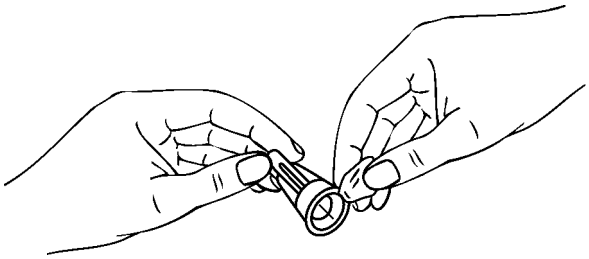

Diagram D

Gently push the injection needle onto the pen as shown in Diagram E. (Notice that the rear portion of the injection needle will pierce through the rubber membrane that you disinfected previously). Now screw the injection needle onto the pen securely by turning it in a clockwise direction (see Diagram F).

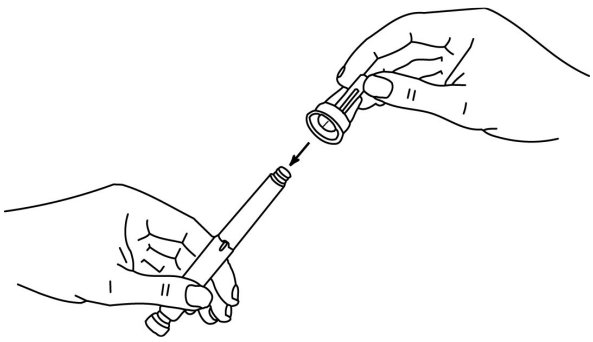

Diagram E

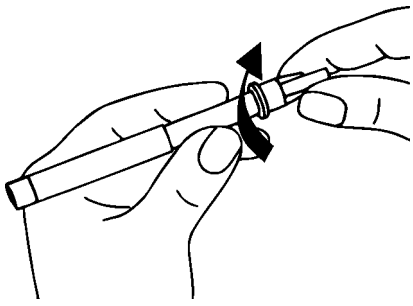

Diagram F

First, pull off the outer injection needle cap (Diagram G). Then, pull off the inner injection needle cap carefully, bearing in mind that the injection needle will now be exposed (Diagram H). Keep the outer injection needle cap for later use.

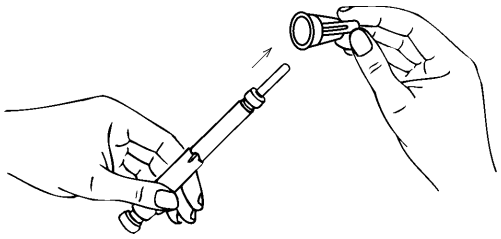

Diagram G

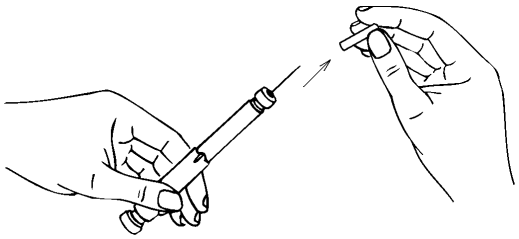

Diagram H

The pen is now ready to use. Since a small amount of air may collect in the injection needle and reservoir during storage, the next step is to remove any air bubbles. This is called performing the Air-Shot.

Hold the pen with the injection needle point upwards.

Tap the reservoir with your finger so that any air bubbles rise to the top of the reservoir, just below the injection needle (Diagram I).

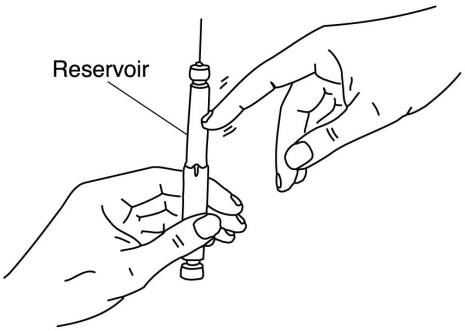

Diagram I

Hold the pen by the barrel and turn the reservoir in the direction as indicated by the arrow in Diagram J (clockwise) until you feel it click.

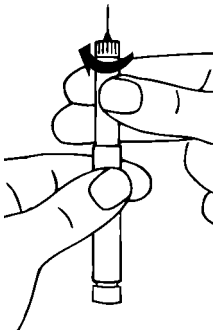

Diagram J

Keeping the pen pointing upwards, press the push button up fully and see if a drop of solution appears at the injection needle tip (Notice the drop at the tip of injection needle in Diagram K below).

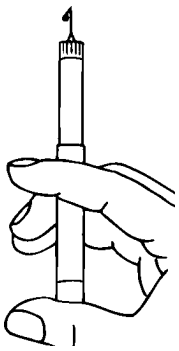

Diagram K

If no drop appears, use a different pen, and return the faulty pen to your provider.

Note: some air may remain in the pen, but this is not important as you have removed the air from the injection needle and the dose will be accurate.

Replace the pen cap with the ‘triangle’ opposite the dosage indicator as seen in Diagram L.

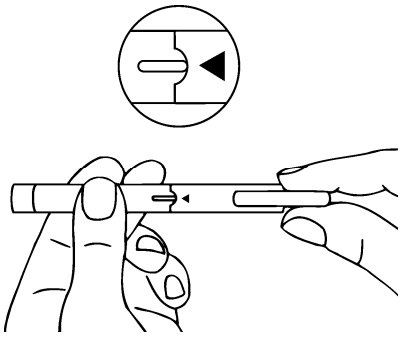

Diagram L

The pen is now ready to set the dose. For the next step hold the pen in the middle of the barrel. This will allow the push button to move freely, ensuring that the correct dose is set.

To set the required dose, hold the pen horizontally by the barrel with one hand. With the other hand, turn the cap in a clockwise direction indicated by the arrow in Diagram M. You will observe the push button rising, indicating the dose set. To set the correct dose, turn the cap as many times as indicated as follows:

Number of "turns" and "clicks"	Corresponding doses (million IU) using IntronA, solution for injection, multidose pen 18 million IU/pen
1 full turn (5 clicks)	1.5
6 clicks	1.8
7 clicks	2.1
8 clicks	2.4
9 clicks	2.7
2 full turns (10 clicks)	3
11 clicks	3.3
12 clicks	3.6
13 clicks	3.9
14 clicks	4.2
3 full turns (15 clicks)	4.5
16 clicks	4.8
17 clicks	5.1
18 clicks	5.4
19 clicks	5.7
4 full turns (20 clicks)*	6

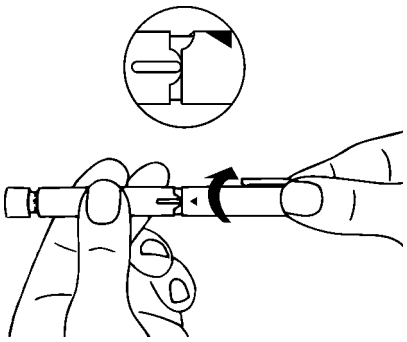

Diagram M

*4 full turns correspond to the maximum dose to be administered in one injection. The pen is designed to deliver its contents of 18 million IU in doses ranging from 1.5 to 6 million IU. The pen will deliver a maximum of 12 doses of 1.5 million IU over a period not to exceed 4 weeks.

The push button scale will show you the dose set (see Diagram N below). For doses corresponding to full turns, the scale should line up with the correct dose marking. For doses corresponding to clicks intermediate between full turns, the scale should line up between the two appropriate full-turn dose markings. At that point check that you have the correct dose.

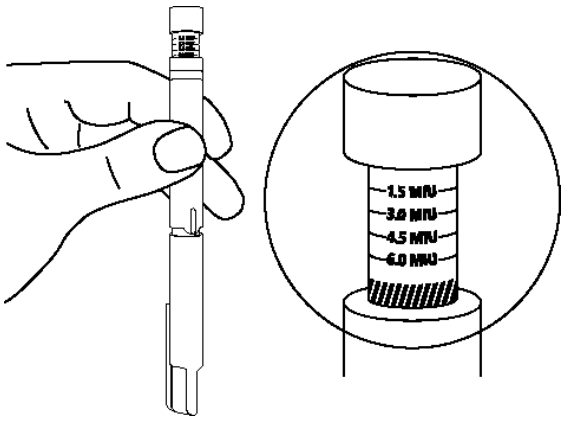

Diagram N

After each complete turn make sure that the triangle is opposite the dosage indicator (see Diagram O). If you have set a wrong dose, simply turn the cap back (anti-clockwise) as far as you can until the push button is fully home and start again. Once the correct dose is set you are ready to give the injection.

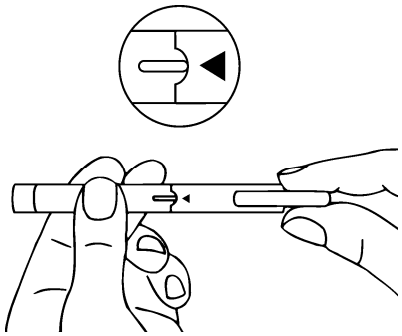

Diagram O

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection. Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry.
With one hand, pinch a fold of loose skin. With your other hand, pick up the pen and hold it as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°.

Then press the push button down fully (see Diagram P).

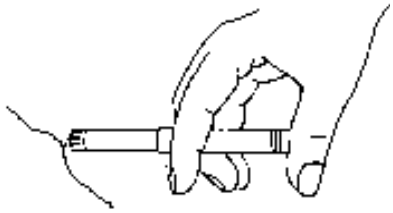

Diagram P

Keeping the push button down, leave the injection needle in place for a few seconds to allow the solution to distribute under the skin, then remove.

Carefully replace the outer injection needle cap (see Diagram Q).

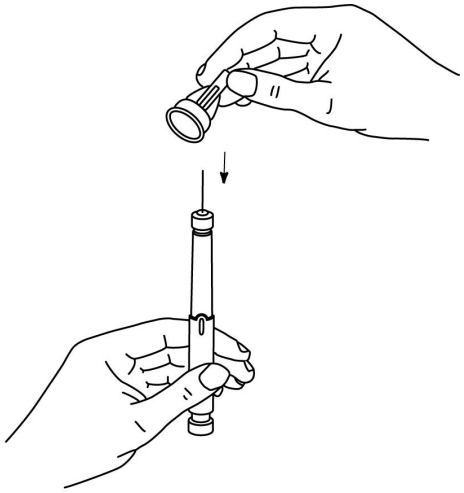

Diagram Q

Completely unscrew the injection needle assembly using an anti-clockwise turning motion as shown in Diagram R. Then carefully lift it off the pen and discard the capped injection needle (see Diagram S).

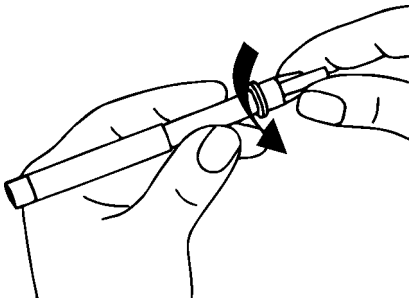

Diagram R

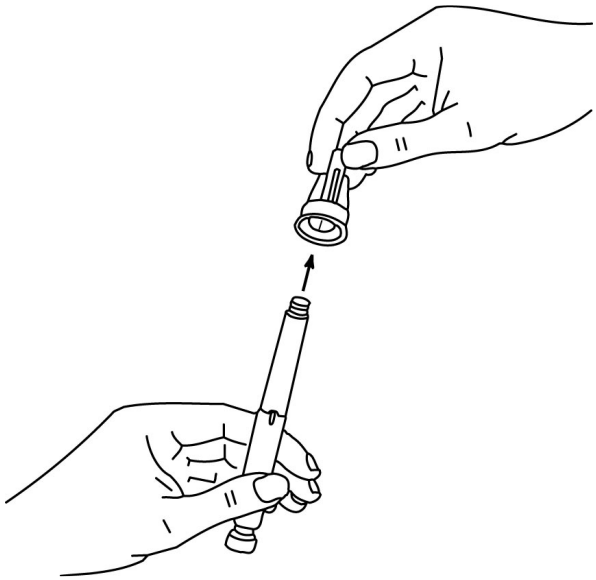

Diagram S

Replace the pen cap with the triangle once again opposite the dosage indicator as shown in Diagram T. Then return the pen to the refrigerator.

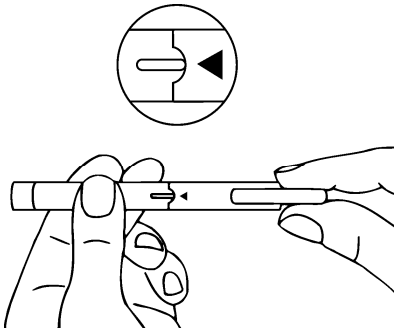

Diagram T

Package leaflet: Information for the user

IntronA 30 million IU solution for injection in multidose pen
Interferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IntronA is and what it is used for

IntronA (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases.

IntronA is used in adult patients to treat certain disorders that affect the blood, bone marrow, lymph glands, or skin and may extend into the body. Included are hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, and malignant melanoma.

IntronA is also used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

IntronA is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

2. What you need to know before you use IntronA

Do not use IntronA
- if you are allergic to interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medicines that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.
- if you are being treated with telbivudine (see section "Other medicines and IntronA").

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using IntronA
- if you are pregnant or planning to become pregnant (see section "Pregnancy and breast-feeding").
- if you are being treated for mental illness or had treatment in the past for any other nervous or mental disorder, including depression (such as feelings of sadness, dejection) or suicidal or homicidal behaviour (see section 4 "Possible side effects"). The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section "Do not use IntronA").
- if you have cirrhosis or other liver problems (other than hepatitis B or C).
- if you have psoriasis, it may get worse during treatment with IntronA.
- when receiving IntronA, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medicine seek medical help immediately.
- if you are also being treated for HIV (see section "Other medicines and IntronA").
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of IntronA with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs).

Be sure to tell your doctor if you are taking the Chinese herbal medicine Shosaikoto.

Other medicines and IntronA
IntronA will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medicines.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medicines you are taking, or have taken recently, even those not prescribed, as the dose of some medicines may have to be adjusted while you are treated with IntronA.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of IntronA and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with IntronA and

ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

If you take telbivudine with a pegylated interferon alfa-2a or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, the combination of IntronA with telbivudine is contraindicated.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

IntronA with food and drink and alcohol
While being treated with IntronA, your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed IntronA in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you or your partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking IntronA. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Driving and using machines
Do not drive or use machines if you become drowsy, tired, or confused from using this medicine.

IntronA contains less than 1 mmol sodium (23 mg) per 1.2 mL, i.e., essentially "sodium-free".

3. How to use IntronA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor has prescribed IntronA specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of IntronA according to your individual needs. The dosage will vary according to the disease being treated. The pen is designed to deliver its contents of 30 million IU in doses ranging from 2.5 to 10 million IU. The pen will deliver a maximum of 12 doses of 2.5 million IU over a period not to exceed 4 weeks.

If you are injecting IntronA yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/m^2 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Hairy Cell Leukaemia: 2 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic Myelogenous Leukaemia: 4-5 million IU/m^2 daily injected subcutaneously (under the skin).

Multiple myeloma: 3 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Follicular lymphoma: Adjunctively with chemotherapy, 5 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Carcinoid tumour: 5 million IU, 3 times a week (every other day) injected subcutaneously (under the skin).

Malignant melanoma, induction therapy: 20 million IU/m^2, intravenously, given daily for 5 days a week for a 4 week period. Maintenance treatment: 10 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Your doctor may prescribe a different dose of IntronA alone or in combination with other medicines (e.g., cytarabine, ribavirin). If you are prescribed IntronA in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of IntronA is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
IntronA is usually intended for subcutaneous use. This means that IntronA is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see section “HOW TO SELF INJECT INTRONA” at the end of the leaflet).

One dose of IntronA is given on each scheduled day. IntronA is given either daily (5 or 7 times a week), or three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use IntronA exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take IntronA for as long as prescribed.

If you use more IntronA than you should
Contact your doctor or healthcare professional as soon as possible.

If you forget to use IntronA
If you are self-administering treatment, or if you are the caregiver of a child taking IntronA in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this medicine every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Psychiatric and central nervous system:
Some people get depressed when taking IntronA alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with IntronA and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with IntronA in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 10-12 years after completing treatment.

If any of the following side effects happen, stop taking IntronA and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to IntronA. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels. Moderate and usually reversible reduction in all three blood elements-white blood cells, red blood cells and platelets, has been reported.

At the beginning of treatment with IntronA, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Possible side effects listed below are grouped by frequency of occurrence:

Very common	(affects more than 1 user in 10)
Common	(affects 1 to 10 users in 100)
Uncommon	(affects 1 to 10 users in 1,000)
Rare	(affects 1 to 10 users in 10,000)
Very rare	(affects less than 1 user in 10,000)
Not known	(frequency cannot be estimated from the available data)

The following side effects have been reported:

Very commonly reported side effects:
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects:
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Uncommonly reported side effects:
bacterial infection and feeling of pins and needles.

Rarely reported side effects:
pneumonia.

Very rarely reported side effects:
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.

Not known side effects:
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing),

bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.
Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, mania (excessive or unreasonable enthusiasm), bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement), congestive heart failure, pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), and pulmonary fibrosis (scarring of the lungs) have been reported with IntronA use.

Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with IntronA.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can also help provide more information on the safety of this medicine.

5. How to store IntronA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Each pen is intended for a maximum four-week use period and must then be discarded. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week period to cover accidental delays in returning the pen to the refrigerator.

Do not use this medicine if you notice changes in the appearance of IntronA.

Depending upon your dose, you may have extra needles and swabs left in the pack. Please discard these appropriately and safely.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IntronA contains

- The active substance is recombinant interferon alfa-2b. Each pen contains 30 million IU.
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

What IntronA looks like and contents of the pack

IntronA is presented as a solution for injection in a multidose pen.

The clear and colourless solution is contained in a glass cartridge.

IntronA is available in three different pack sizes:
- Pack of 1 pen, 12 injection needles and 12 cleansing swabs
- Pack of 2 pens, 24 injection needles and 24 cleansing swabs
- Pack of 8 pens, 96 injection needles and 96 cleansing swabs

Not all pack sizes may be marketed.

Marketing Authorisation Holder:
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United Kingdom

Manufacturer:
SP Labo N.V.
Industriepark 30
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

HOW TO SELF INJECT INTRONA

The following instructions explain how to inject IntronA yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject IntronA. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- the IntronA multidose pen;
- a needle for subcutaneous injection (provided in the packaging);
- a cleansing swab (provided in the packaging).

Wash your hands carefully. Use the injection needles provided in the packaging only for IntronA. Use a new injection needle for each dose. Be sure the solution is at room temperature (up to 25°C) at the time of injection.

Diagrams A and B show you all the different parts of the pen and the injection needle. The most important parts to note are as follows:

- The push button scale tells you what dose has been set.
- The colour coding strip blue and the push button are at the bottom of the pen as it is held cap up.
- The pen can only be fully capped when the triangle on the cap scale is aligned with the dosage indicator on the barrel.

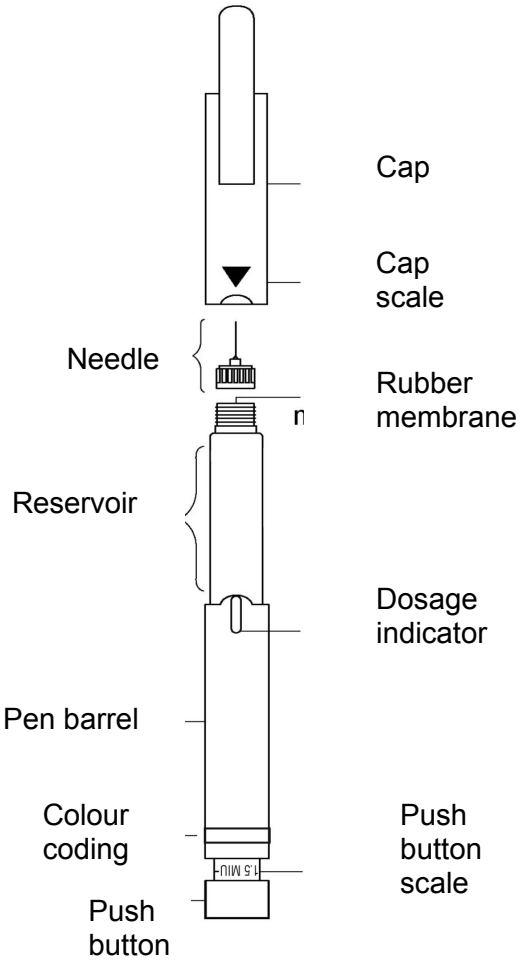

Diagram A

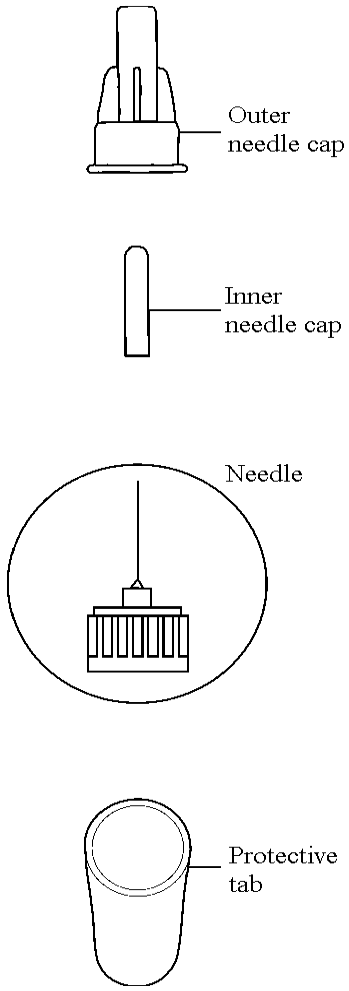

Diagram B

Measuring the dose of IntronA

Take the pen out of the refrigerator about one-half hour before administering the dose so that the solution in the pen is at room temperature when it is injected.

When you are ready to give your injection prepare your pen as follows:

Check that IntronA solution for injection is clear and colourless in appearance prior to use. If it does not have a clear uniform appearance or if it contains any particles, do not use.

Pull off the cap of the pen and disinfect the rubber membrane (see Diagram C) with one cleansing swab.

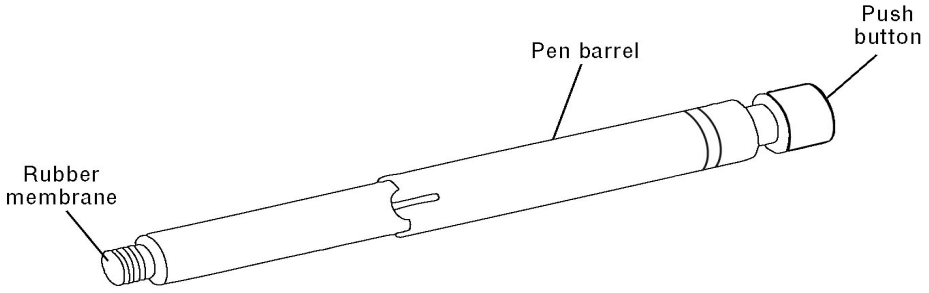

Diagram C

Remove the protective tab from the injection needle. Note that the rear portion of the injection needle is revealed once the protective tab is removed (see Diagram D).

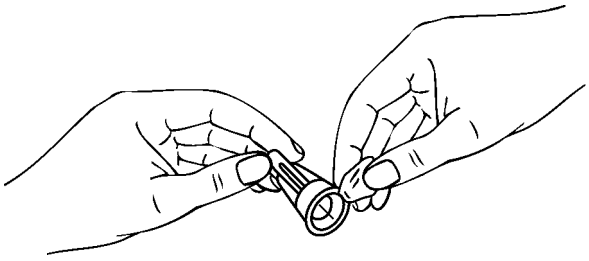

Diagram D

Gently push the injection needle onto the pen as shown in Diagram E. (Notice that the rear portion of the injection needle will pierce through the rubber membrane that you disinfected previously). Now screw the injection needle onto the pen securely by turning it in a clockwise direction (see Diagram F).

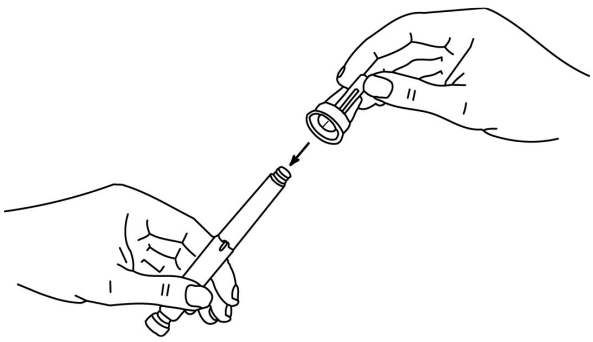

Diagram E

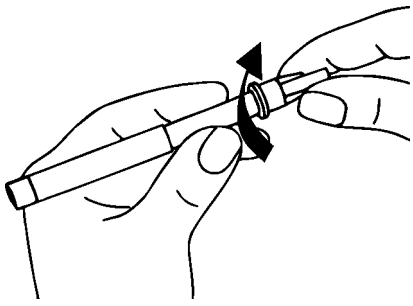

Diagram F

First, pull off the outer injection needle cap (Diagram G). Then, pull off the inner injection needle cap carefully, bearing in mind that the injection needle will now be exposed (Diagram H). Keep the outer injection needle cap for later use.

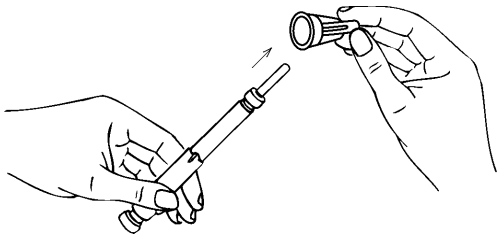

Diagram G

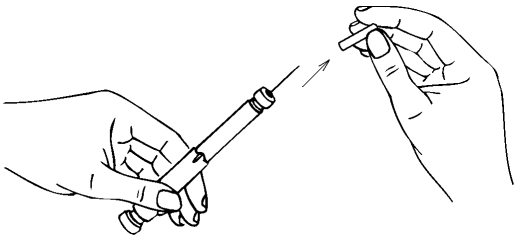

Diagram H

The pen is now ready to use. Since a small amount of air may collect in the injection needle and reservoir during storage, the next step is to remove any air bubbles. This is called performing the Air-Shot.

Hold the pen with the injection needle point upwards.

Tap the reservoir with your finger so that any air bubbles rise to the top of the reservoir, just below the injection needle (Diagram I).

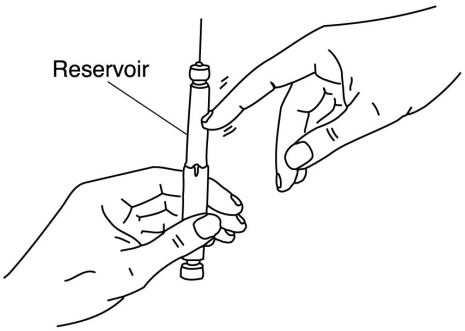

Diagram I

Hold the pen by the barrel and turn the reservoir in the direction as indicated by the arrow in Diagram J (clockwise) until you feel it click.

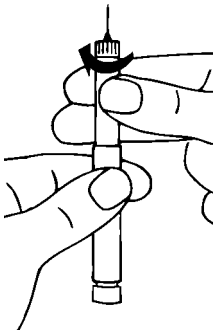

Diagram J

Keeping the pen pointing upwards, press the push button up fully and see if a drop of solution appears at the injection needle tip (Notice the drop at the tip of injection needle in Diagram K below).

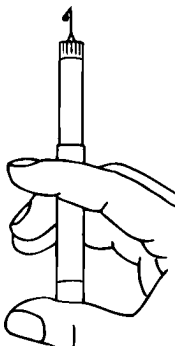

Diagram K

If no drop appears, use a different pen, and return the faulty pen to your provider.

Note: some air may remain in the pen, but this is not important as you have removed the air from the injection needle and the dose will be accurate.

Replace the pen cap with the ‘triangle’ opposite the dosage indicator as seen in Diagram L.

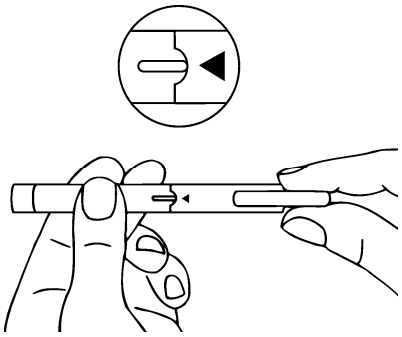

Diagram L

The pen is now ready to set the dose. For the next step hold the pen in the middle of the barrel. This will allow the push button to move freely, ensuring that the correct dose is set.

To set the required dose, hold the pen horizontally by the barrel with one hand. With the other hand, turn the cap in a clockwise direction indicated by the arrow in Diagram M. You will observe the push button rising, indicating the dose set. To set the correct dose, turn the cap as many times as indicated as follows:

Number of “turns” and “clicks”	Corresponding doses (million IU) using IntronA, solution for injection, multidose pen 30 million IU/pen:
1 full turn (5 clicks)	2.5
6 clicks	3
7 clicks	3.5
8 clicks	4
9 clicks	4.5
2 full turns (10 clicks)	5
11 clicks	5.5
12 clicks	6
13 clicks	6.5
14 clicks	7
3 full turns (15 clicks)	7.5
16 clicks	8
17 clicks	8.5
18 clicks	9
19 clicks	9.5
4 full turns (20 clicks)*	10

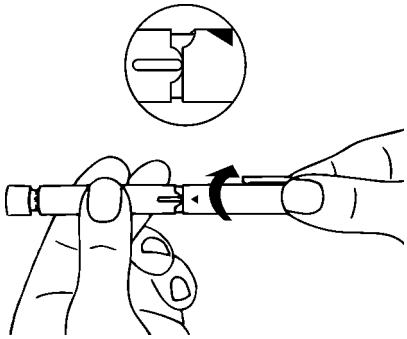

Diagram M

* 4 full turns correspond to the maximum dose to be administered in one injection. The pen is designed to deliver its contents of 30 million IU in doses ranging from 2.5 to 10 million IU. The pen will deliver a maximum of 12 doses of 2.5 million IU over a period not to exceed 4 weeks.

The push button scale will show you the dose set (see Diagram N below). For doses corresponding to full turns, the scale should line up with the correct dose marking. For doses corresponding to clicks intermediate between full turns, the scale should line up between the two appropriate full-turn dose markings. At that point check that you have the correct dose.

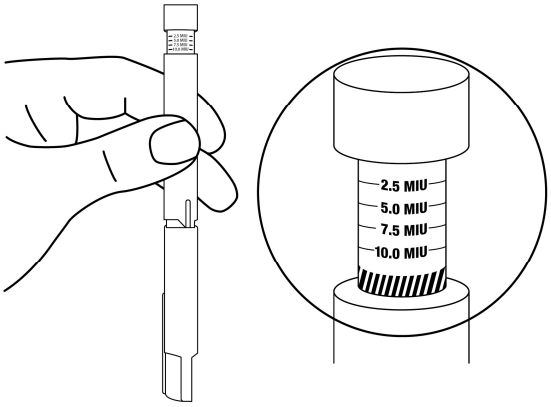

Diagram N

After each complete turn make sure that the triangle is opposite the dosage indicator (see Diagram O). If you have set a wrong dose, simply turn the cap back (anti-clockwise) as far as you can until the push button is fully home and start again. Once the correct dose is set you are ready to give the injection.

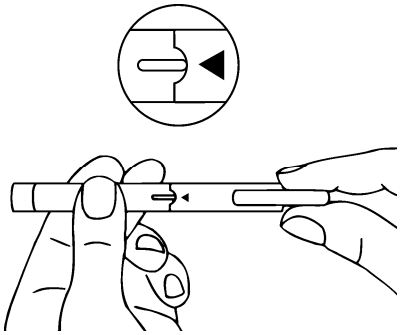

Diagram O

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection. Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry.
With one hand, pinch a fold of loose skin. With your other hand, pick up the pen and hold it as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°.

Then press the push button down fully (see Diagram P).

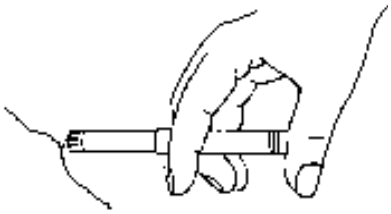

Diagram P

Keeping the push button down, leave the injection needle in place for a few seconds to allow the solution to distribute under the skin, then remove.

Carefully replace the outer injection needle cap (see Diagram Q).

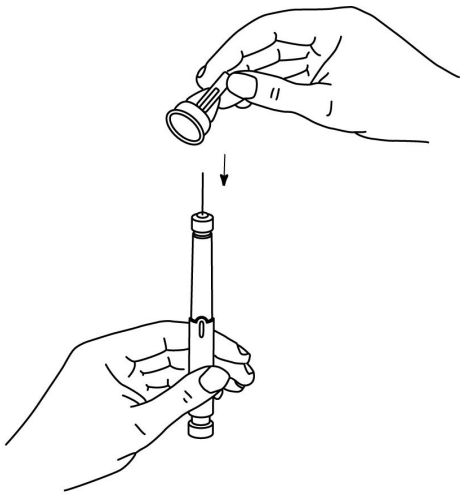

Diagram Q

Completely unscrew the injection needle assembly using an anti-clockwise turning motion as shown in Diagram R. Then carefully lift it off the pen and discard the capped injection needle (see Diagram S).

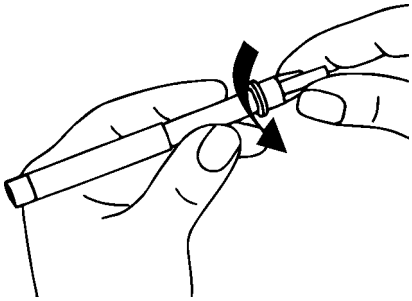

Diagram R

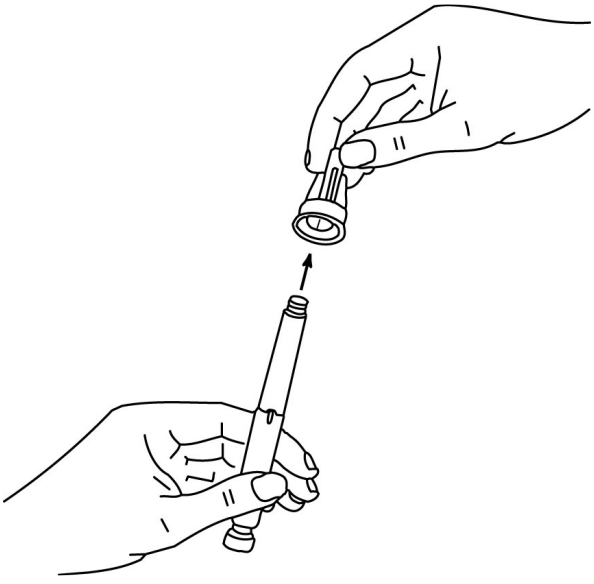

Diagram S

Replace the pen cap with the triangle once again opposite the dosage indicator as shown in Diagram T. Then return the pen to the refrigerator.

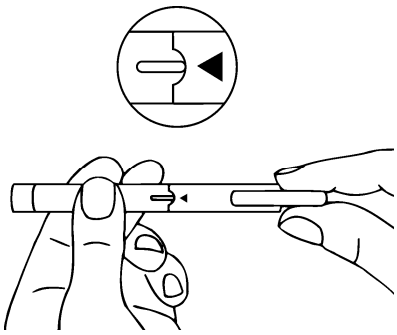

Diagram T

Package leaflet: Information for the user

IntronA 60 million IU solution for injection in multidose pen
Interferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IntronA is and what it is used for

IntronA (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases.

IntronA is used in adult patients to treat certain disorders that affect the blood, bone marrow, lymph glands, or skin and may extend into the body. Included are hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, and malignant melanoma.

IntronA is also used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

IntronA is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

2. What you need to know before you use IntronA

Do not use IntronA
- if you are allergic to interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medicines that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.
- if you are being treated with telbivudine (see section "Other medicines and IntronA").

Children and adolescents:
- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using IntronA
- if you are pregnant or planning to become pregnant (see section "Pregnancy and breast-feeding").
- if you are being treated for mental illness or had treatment in the past for any other nervous or mental disorder, including depression (such as feelings of sadness, dejection) or suicidal or homicidal behaviour (see section 4 "Possible side effects"). The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section "Do not use IntronA").
- if you have cirrhosis or other liver problems (other than hepatitis B or C).
- if you have psoriasis, it may get worse during treatment with IntronA.
- when receiving IntronA, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medicine seek medical help immediately.
- if you are also being treated for HIV (see section "Other medicines and IntronA").
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of IntronA with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs).

Be sure to tell your doctor if you are taking the Chinese herbal medicine Shosaikoto.

Other medicines and IntronA
IntronA will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medicines.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medicines you are taking, or have taken recently, even those not prescribed, as the dose of some medicines may have to be adjusted while you are treated with IntronA.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of IntronA and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with IntronA and

ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

If you take telbivudine with a pegylated interferon alfa-2a or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, the combination of IntronA with telbivudine is contraindicated.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

IntronA with food and drink and alcohol
While being treated with IntronA, your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.
If you are prescribed IntronA in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you or your partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking IntronA. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Driving and using machines
Do not drive or use machines if you become drowsy, tired, or confused from using this medicine.

IntronA contains less than 1 mmol sodium (23 mg) per 1.2 mL, i.e., essentially "sodium-free".

3. How to use IntronA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor has prescribed IntronA specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of IntronA according to your individual needs. The dosage will vary according to the disease being treated. The pen is designed to deliver its contents of 60 million IU in doses ranging from 5 to 20 million IU. The pen will deliver a maximum of 12 doses of 5 million IU over a period not to exceed 4 weeks.

If you are injecting IntronA yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/m^2 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Hairy Cell Leukaemia: 2 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic Myelogenous Leukaemia: 4-5 million IU/m^2 daily injected subcutaneously (under the skin).

Multiple myeloma: 3 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Follicular lymphoma: Adjunctively with chemotherapy, 5 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Carcinoid tumour: 5 million IU, 3 times a week (every other day) injected subcutaneously (under the skin).

Malignant melanoma, induction therapy: 20 million IU/m^2, intravenously, given daily for 5 days a week for a 4 week period. Maintenance treatment: 10 million IU/m^2, 3 times a week (every other day) injected subcutaneously (under the skin).

Your doctor may prescribe a different dose of IntronA alone or in combination with other medicines (e.g., cytarabine, ribavirin). If you are prescribed IntronA in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of IntronA is too strong or too weak, talk to your doctor or pharmacist.

Subcutaneous use:
IntronA is usually intended for subcutaneous use. This means that IntronA is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see section “HOW TO SELF INJECT INTRONA” at the end of the leaflet).

One dose of IntronA is given on each scheduled day. IntronA is given either daily (5 or 7 times a week), or three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use IntronA exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take IntronA for as long as prescribed.

If you use more IntronA than you should
Contact your doctor or healthcare professional as soon as possible.

If you forget to use IntronA
If you are self-administering treatment, or if you are the caregiver of a child taking IntronA in combination with ribavirin, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this medicine every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Psychiatric and central nervous system:
Some people get depressed when taking IntronA alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with IntronA and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with IntronA in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 10-12 years after completing treatment.

If any of the following side effects happen, stop taking IntronA and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to IntronA. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

Check with your doctor immediately if any of the following side effects occur:
- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels. Moderate and usually reversible reduction in all three blood elements-white blood cells, red blood cells and platelets, has been reported.

At the beginning of treatment with IntronA, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Possible side effects listed below are grouped by frequency of occurrence:

Very common	(affects more than 1 user in 10)
Common	(affects 1 to 10 users in 100)
Uncommon	(affects 1 to 10 users in 1,000)
Rare	(affects 1 to 10 users in 10,000)
Very rare	(affects less than 1 user in 10,000)
Not known	(frequency cannot be estimated from the available data)

The following side effects have been reported:

Very commonly reported side effects:
pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhoea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, changes in laboratory blood values including decreased white blood cell count. Some children have had a decrease in their rate of growth (height and weight).

Commonly reported side effects:
thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, arthritis.

Uncommonly reported side effects:
bacterial infection and feeling of pins and needles.

Rarely reported side effects:
pneumonia.

Very rarely reported side effects:
low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms.

Not known side effects:
Periodontal (affecting gums) and dental disorders, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing),

bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.
Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, mania (excessive or unreasonable enthusiasm), bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement), congestive heart failure, pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), and pulmonary fibrosis (scarring of the lungs) have been reported with IntronA use.

Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with IntronA.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can also help provide more information on the safety of this medicine.

5. How to store IntronA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Each pen is intended for a maximum four-week use period and must then be discarded. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the four-week period to cover accidental delays in returning the pen to the refrigerator.

Do not use this medicine if you notice changes in the appearance of IntronA.

Depending upon your dose, you may have extra needles and swabs left in the pack. Please discard these appropriately and safely.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IntronA contains

- The active substance is recombinant interferon alfa-2b. Each pen contains 60 million IU.
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

What IntronA looks like and contents of the pack

IntronA is presented as a solution for injection in a multidose pen.

The clear and colourless solution is contained in a glass cartridge.

IntronA is available in three different pack sizes:
- Pack of 1 pen, 12 injection needles and 12 cleansing swabs
- Pack of 2 pens, 24 injection needles and 24 cleansing swabs
- Pack of 8 pens, 96 injection needles and 96 cleansing swabs

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

HOW TO SELF INJECT INTRONA

The following instructions explain how to inject IntronA yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject IntronA. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- the IntronA multidose pen;
- a needle for subcutaneous injection (provided in the packaging);
- a cleansing swab (provided in the packaging).

Wash your hands carefully. Use the injection needles provided in the packaging only for IntronA. Use a new injection needle for each dose. Be sure the solution is at room temperature (up to 25°C) at the time of injection.

Diagrams A and B show you all the different parts of the pen and the injection needle. The most important parts to note are as follows:

- The push button scale tells you what dose has been set.
- The colour coding strip pink and the push button are at the bottom of the pen as it is held cap up.
- The pen can only be fully capped when the triangle on the cap scale is aligned with the dosage indicator on the barrel.

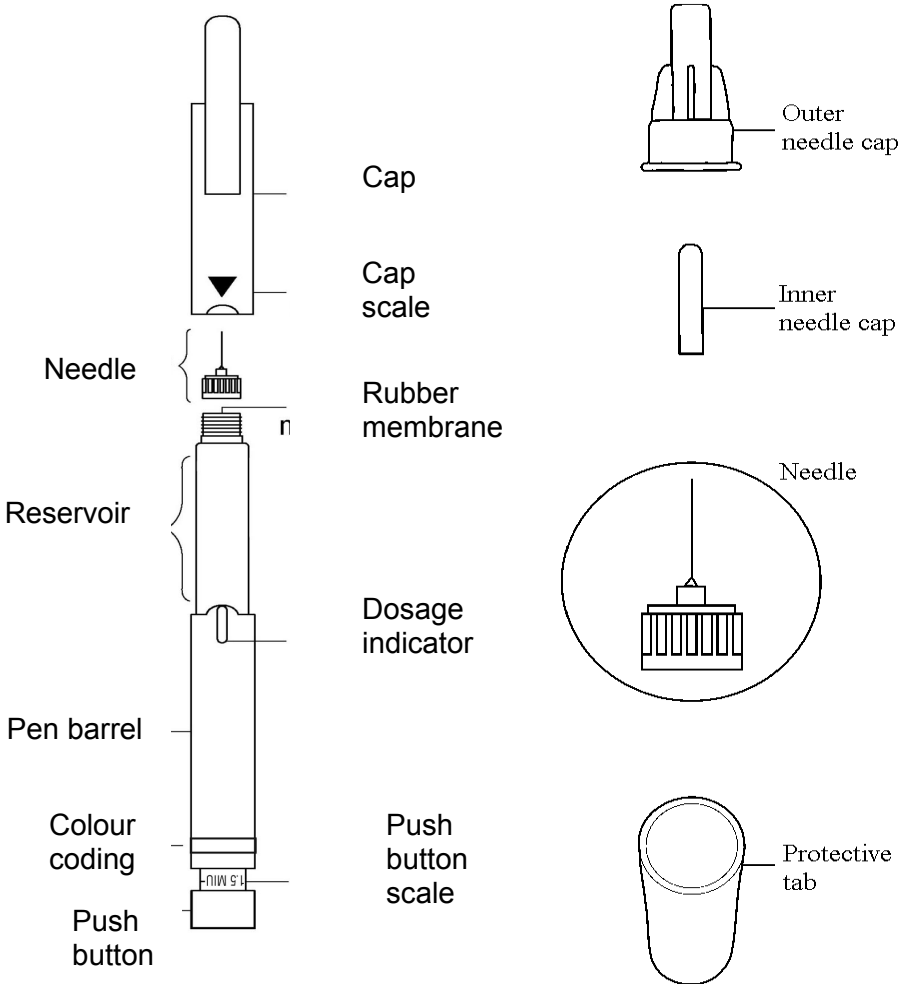

Diagram A

Diagram B

Measuring the dose of IntronA

Take the pen out of the refrigerator about one-half hour before administering the dose so that the solution in the pen is at room temperature when it is injected.

When you are ready to give your injection prepare your pen as follows:

Check that IntronA solution for injection is clear and colourless in appearance prior to use. If it does not have a clear uniform appearance or if it contains any particles, do not use.

Pull off the cap of the pen and disinfect the rubber membrane (see Diagram C) with one cleansing swab.

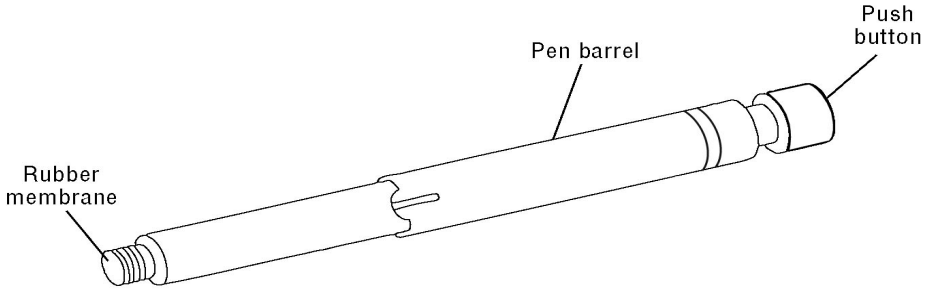

Diagram C

Remove the protective tab from the injection needle. Note that the rear portion of the injection needle is revealed once the protective tab is removed (see Diagram D).

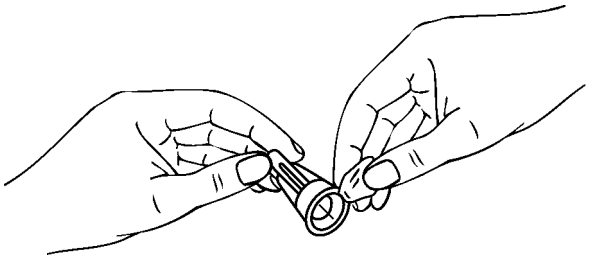

Diagram D

Gently push the injection needle onto the pen as shown in Diagram E. (Notice that the rear portion of the injection needle will pierce through the rubber membrane that you disinfected previously). Now screw the injection needle onto the pen securely by turning it in a clockwise direction (see Diagram F).

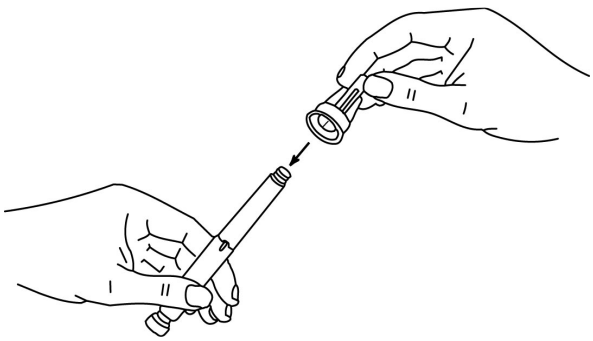

Diagram E

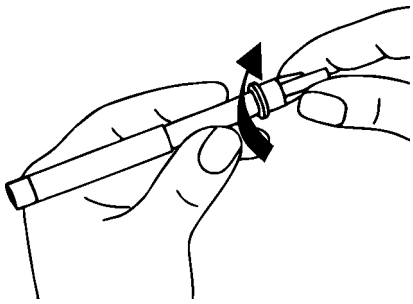

Diagram F

First, pull off the outer injection needle cap (Diagram G). Then, pull off the inner injection needle cap carefully, bearing in mind that the injection needle will now be exposed (Diagram H). Keep the outer injection needle cap for later use.

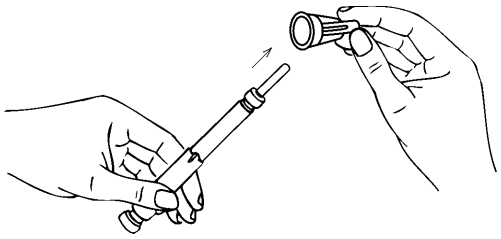

Diagram G

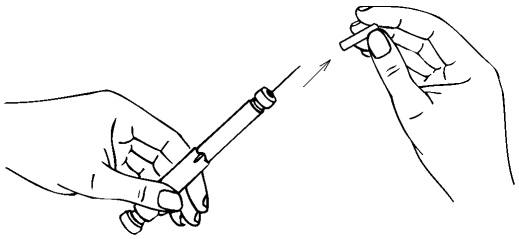

Diagram H

The pen is now ready to use. Since a small amount of air may collect in the injection needle and reservoir during storage, the next step is to remove any air bubbles. This is called performing the Air-Shot.

Hold the pen with the injection needle point upwards.

Tap the reservoir with your finger so that any air bubbles rise to the top of the reservoir, just below the injection needle (Diagram I).

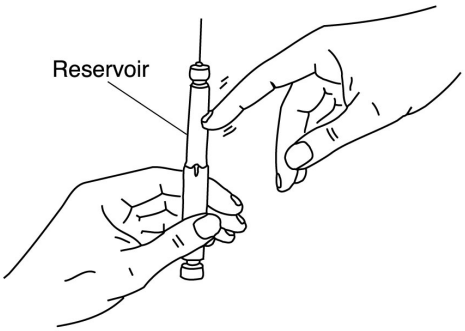

Diagram I

Hold the pen by the barrel and turn the reservoir in the direction as indicated by the arrow in Diagram J (clockwise) until you feel it click.

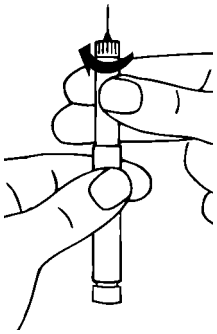

Diagram J

Keeping the pen pointing upwards, press the push button up fully and see if a drop of solution appears at the injection needle tip (Notice the drop at the tip of injection needle in Diagram K below).

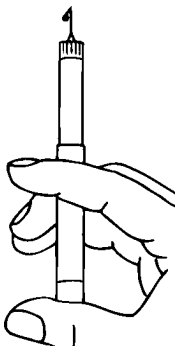

Diagram K

If no drop appears, use a different pen, and return the faulty pen to your provider.

Note: some air may remain in the pen, but this is not important as you have removed the air from the injection needle and the dose will be accurate.

Replace the pen cap with the ‘triangle’ opposite the dosage indicator as seen in Diagram L.

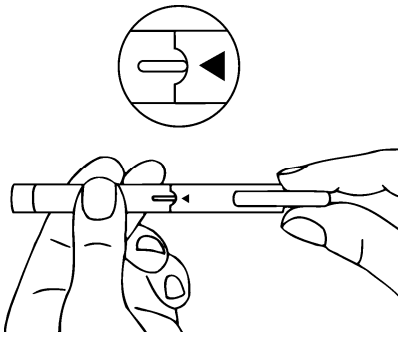

Diagram L

The pen is now ready to set the dose. For the next step hold the pen in the middle of the barrel. This will allow the push button to move freely, ensuring that the correct dose is set.

To set the required dose, hold the pen horizontally by the barrel with one hand. With the other hand, turn the cap in a clockwise direction indicated by the arrow in Diagram M. You will observe the push button rising, indicating the dose set. To set the correct dose, turn the cap as many times as indicated as follows:

Number of "turns" and "clicks"	Corresponding doses (million IU) using IntronA, solution for injection, multidose pen 60 million IU/pen:
1 full turn (5 clicks)	5
6 clicks	6
7 clicks	7
8 clicks	8
9 clicks	9
2 full turns (10 clicks)	10
11 clicks	11
12 clicks	12
13 clicks	13
14 clicks	14
3 full turns (15 clicks)	15
16 clicks	16
17 clicks	17
18 clicks	18
19 clicks	19
4 full turns (20 clicks)*	20

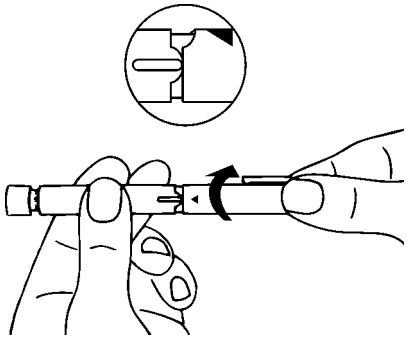

Diagram M

*4 full turns correspond to the maximum dose to be administered in one injection. The pen is designed to deliver its contents of 60 million IU in doses ranging from 5 to 20 million IU. The pen will deliver a maximum of 12 doses of 5 million IU over a period not to exceed 4 weeks.

The push button scale will show you the dose set (see Diagram N below). For doses corresponding to full turns, the scale should line up with the correct dose marking. For doses corresponding to clicks intermediate between full turns, the scale should line up between the two appropriate full-turn dose markings. At that point check that you have the correct dose.

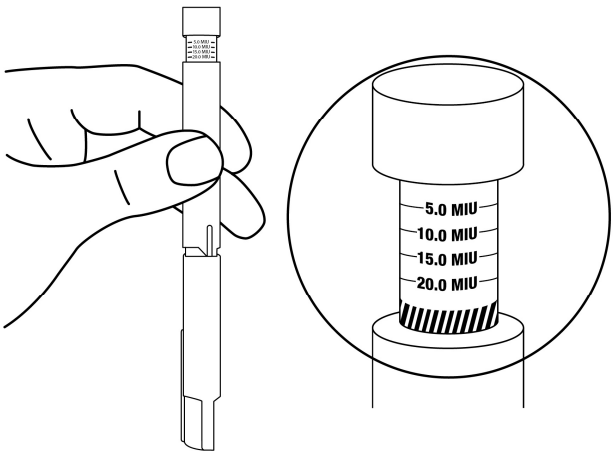

Diagram N

After each complete turn make sure that the triangle is opposite the dosage indicator (see Diagram O). If you have set a wrong dose, simply turn the cap back (anti-clockwise) as far as you can until the push button is fully home and start again. Once the correct dose is set you are ready to give the injection.

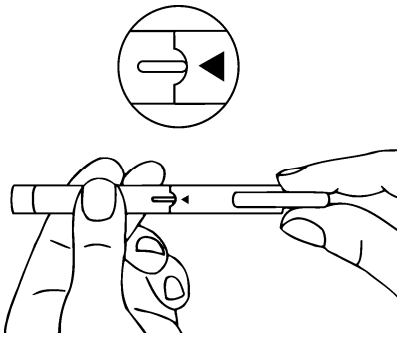

Diagram O

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection. Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry.
With one hand, pinch a fold of loose skin. With your other hand, pick up the pen and hold it as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°.

Then press the push button down fully (see Diagram P).

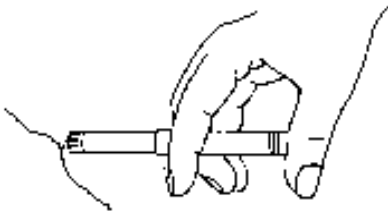

Diagram P

Keeping the push button down, leave the injection needle in place for a few seconds to allow the solution to distribute under the skin, then remove.

Carefully replace the outer injection needle cap (see Diagram Q).

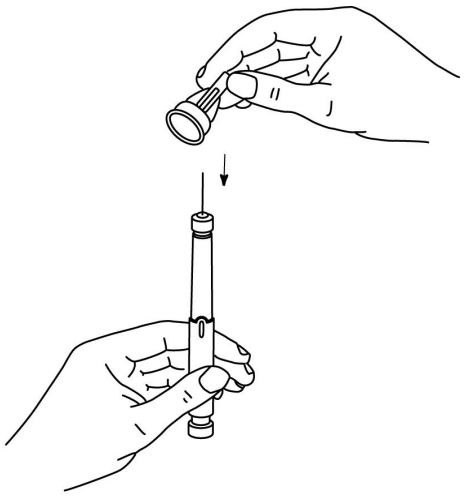

Diagram Q

Completely unscrew the injection needle assembly using an anti-clockwise turning motion as shown in Diagram R. Then carefully lift it off the pen and discard the capped injection needle (see Diagram S).

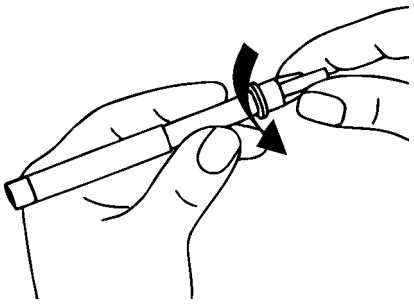

Diagram R

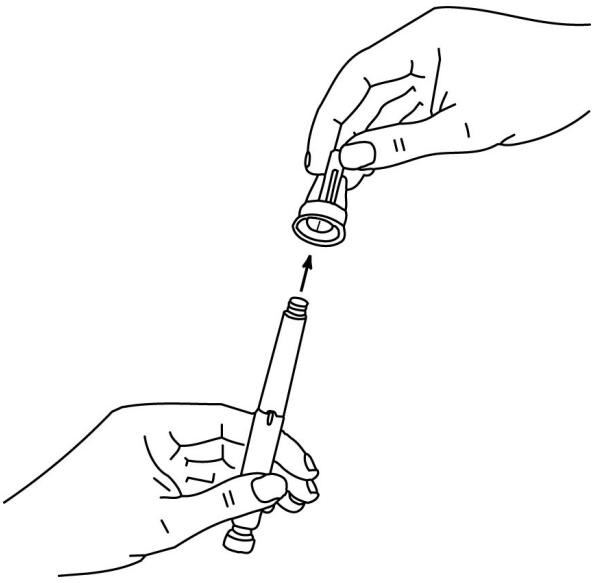

Diagram S

Replace the pen cap with the triangle once again opposite the dosage indicator as shown in Diagram T. Then return the pen to the refrigerator.

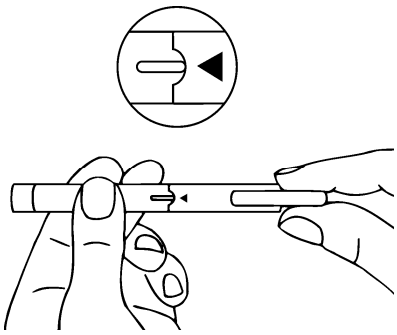

Diagram T