# LEUSTATIN® Injection
# cladribine
## PRODUCT INFORMATION

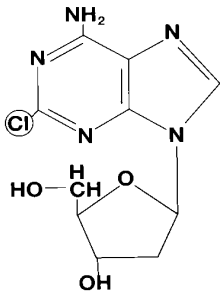
### NAME OF THE MEDICINE

LEUSTATIN (cladribine) Injection is a synthetic antineoplastic agent for continuous intravenous infusion.

### DESCRIPTION

LEUSTATIN injection is a clear, colourless, sterile, preservative-free, isotonic solution. LEUSTATIN, cladribine, injection is available in single-use vials containing 10 mg (1mg/mL) of cladribine, a chlorinated purine nucleoside analogue. Each millilitre of LEUSTATIN Injection contains 1 mg of the active ingredient, cladribine, and 9 mg (0.15 mEq) of sodium chloride as an inactive ingredient. The solution has a pH range of 5.5 to 8.0. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH.

The chemical name for cladribine is 2-chloro-6-amino-9-(2-deoxy-β-D-erythropento-furanosyl) purine and the structure is represented below:




cladribine MW 285.7

### PHARMACOLOGY

Cellular Resistance and Sensitivity

The selective toxicity of cladribine towards certain normal and malignant lymphocyte and monocyte populations is based on the high ratio of deoxycytidine kinase (which phosphorylates it) to deoxynucleotidase (which dephosphorylates it). In these cells, cladribine, a purine nucleoside analogue, passively crosses the cell membrane. It is phosphorylated by deoxycytidine kinase to 2-chloro-2′-deoxy-β-D-adenosine monophosphate (2-CdAMP). Since cladribine is resistant to deamination by adenosine deaminase and there is little deoxynucleotide deaminase in lymphocytes and monocytes, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2′-deoxy-β-D-adenosine triphosphate (2-CdATP). It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by cladribine as toxic deoxynucleotides accumulate intracellularly.

Cells continuing high concentrations of deoxynucleotides are unable to properly repair single-strand DNA breaks. The broken ends of DNA activate the enzyme poly (ADP-ribose) synthetase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is evidence, also, that 2-CdATP is incorporated into the DNA of dividing cells, resulting in impairment of DNA synthesis. Thus cladribine can be distinguished from other chemotherapeutic agents affecting purine metabolism in that it is cytotoxic to both actively dividing and quiescent lymphocytes and monocytes, inhibiting both DNA synthesis and repair. In a clinical investigation, 17 patients with Hairy Cell Leukaemia (HCL) and normal renal function were treated for 7 days with the recommended treatment regimen of LEUSTATIN (0.09 mg/kg/day) by continuous intravenous infusion. A mean steady-state serum concentration of ~7 ng/mL was observed with a systemic clearance of ~600 mL/h/kg. Accumulation of 2-chloro-2′-deoxy-β-D-adenosine over the seven-day treatment period was not noted. In Hairy Cell Leukaemia patients, there does not appear to be a relationship between serum concentrations of cladribine and ultimate clinical outcome.

In another study, 8 patients with haematologic malignancies received a two (2) hour infusion of LEUSTATIN (0.094 mg/kg). The mean end-of-infusion plasma cladribine concentration was 58±23 ng/mL. For 5 of these patients, the disappearance of cladribine could be described by either a biphasic or triphasic decline. For these patients with normal renal function, the mean terminal half-life was 5.4 hours. Mean values for clearance and steady-state volume of distribution were 933±403 mL/h/kg and 4.32±2.69 L/kg, respectively.

In patients with chronic B-cell lymphocytic leukaemia (CLL) there was considerable variability in cladribine kinetics after two hour intravenous infusions of 0.14mg/kg/day for 5 days. In one study (n=13), the mean volume of distribution was 53.6 ±23.7L/m2, mean clearance 25.9±7.8L/h/m2 and mean terminal plasma elimination half-life, 9.9±4.6h, on day 5. In another study (n=11adults) mean plasma elimination half-life was 16.4±7.1h and mean elimination half-life of intracellular cladribine nucleotides 33.1±18.3h, on day 5.

Cladribine is bound approximately 20% to plasma proteins.

There is variability in the metabolism and route of excretion of cladribine in Man. In a study of 12 healthy male volunteers, given an intravenous infusion of cladribine 22-45mg, 47% of the dose was excreted unchanged and 50% as metabolites in the urine. In 25 patients (16 male) with advanced solid tumours receiving cladribine 3.5-10.5mg/m2/day for 5 days as a 2 hour intravenous infusion the urinary recovery of unchanged drug was 32% in the first 24 hours. Renal excretion accounted for only 18% of the elimination of cladribine over a 5 day intravenous infusion of 3.5-8.1mg/m2/day in four patients aged 40-78 years with chronic lymphocytic leukaemia.

In a study of a small number of rats where radio labelled cladribine was administered, essentially all of the recoverable radioactivity was found in the urine. The effect of renal and hepatic impairment on the elimination of cladribine has not been investigated in humans.

**CLINICAL TRIALS**

In an open, single arm, multicentre study conducted in UK, 34 patients with previously treated Chronic Lymphocytic Leukaemia received up to 6 courses of LEUSTATIN. Each course consisted of 5 consecutive days of treatment at 0.12mg/kg/day, as a 2 hour daily i.v. infusion and courses were repeated at monthly intervals. Twenty-six patients were Binet Stage B or C with the remainder stage A but showing signs of progressive disease. Response, evaluated according to National Cancer Institute criteria was Complete Response (CR) 20.5%, partial response (PR) (56%). Two of seven CR patients relapsed after 64 and 65 weeks, eight of nineteen PR patients had a median duration of remission of 39 weeks before relapse.

Two single-center open studies of LEUSTATIN have been conducted in patients with Hairy Cell Leukaemia with evidence of active disease requiring therapy. In the study conducted at Centre A (Study A), 89 patients were treated with a single course of LEUSTATIN given by continuous infusion for 7 days at a dose of 0.09 mg/kg/day. In the study conducted at Center B (Study B), 35 patients were treated

with a 7-day continuous infusion of LEUSTATIN Injection at a comparable dose of 4 mg/m$^2$/day. Responses were assessed using criteria consistent with accepted medical practice. Among patients evaluable for efficacy (N=103), the complete response rates were 62% and 70% for Study A and Study B, respectively, yielding a combined complete response rate of 64%. Overall response rates (ie Complete plus Partial Responses) were 88% and 85% in Study A and Study B, respectively, for a combined overall response rate of 87%.

**RESPONSE RATES TO LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKAEMIA (EVALUABLE PATIENTS)**

| | Study A (n=76) | Study B (n=27) | Combined Studies (N=103) |
|---|---|---|---|
| Complete Response | 62% | 70% | 64% |
| Overall Response (Complete + Partial) | 88% | 85% | 87% |

In these studies, 53% of the patients had received some prior therapy for Hairy Cell Leukaemia including splenectomy, interferon and/or deoxycorformycin. Complete responses to LEUSTATIN were seen in 73% of patients without any prior treatment compared with 56% of previously treated patients. The overall response rate for patients without any prior treatment was 94% compared with 82% for previously treated patients. The complete and overall response rates in non-splenectomized patients were 71% and 93%, respectively, compared to a complete response rate of 49% and an overall response rate of 76% in previously splenectomized patients. For patients previously treated with interferon, the complete response and overall response rates were 57% and 80% respectively.

Response to LEUSTATIN was similar for those initially responsive to interferon and those refractory to or intolerant of interferon therapy.

**RESPONSE RATES TO LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKAEMIA PREVIOUSLY TREATED/UNTREATED PATIENTS**

| | Untreated | Previously Treated* |
|---|---|---|
| Complete Response | 73% | 56% |
| Overall Response (Complete + Partial) | 94% | 82% |

* prior therapies included splenectomy, interferon and/or deoxycoformycin

After a reversible decline, normalisation of peripheral blood counts (Haemoglobin ≥120 g/L, Platelets ≥100 x $10^9$/L, Absolute Neutrophil Count (ANC) ≥1.5 x $10^9$/L) was achieved by 91% of evaluable patients. In patients achieving a complete response or partial response, the median times to normalisation of peripheral counts were 52 days (Range: 14 to 297) and 70 days (Range: 27 - 267), respectively. The mean Platelet Count normalised by Day 12, the mean ANC normalised by Week 5 and the mean Haemoglobin normalised by Week 8. With normalisation of Platelet count and

Haemoglobin, requirements for platelet and RBC transfusions were abolished after Months 1 and 2, respectively, in responding patients. Corresponding to normalisation of ANC, a trend toward a reduced incidence of infection was seen after the third month, when compared to the months immediately preceding LEUSTATIN therapy.

**LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKAEMIA**
**TIME TO NORMALISATION OF PERIPHERAL BLOOD COUNTS**

| Parameter | Time to Normalisation of Mean Count* |
|---|---|
| Platelet Count | Day 12 |
| Absolute Neutrophil Count | Week 5 |
| Haemoglobin | Week 8 |

*Day 1 - First day of infusion

The median time to complete response (ie absence of hairy cells in bone marrow and peripheral blood together with normalisation of peripheral blood parameters), measured from treatment start, was approximately 4 months. Since bone marrow aspiration and biopsy were frequently not performed at the time of peripheral blood normalisation, the median time to complete response may actually be shorter than that which was recorded. At the time of the data cut-off, the median duration of complete response was approximately 5 months and ranged up to 25 months. No relapses have been observed among patients achieving a complete response.

## INDICATIONS

LEUSTATIN is indicated for the treatment of patients with Hairy Cell Leukaemia.

It is also indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia in whom treatment with alkylating agents has failed.

## CONTRAINDICATIONS

LEUSTATIN is contraindicated in those patients who are hypersensitive to this drug or any of its components.

LEUSTATIN is contraindicated during pregnancy and lactation.

## PRECAUTIONS

### General

LEUSTATIN Injection is a potent antineoplastic agent with potentially toxic side effects. It should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

Patients undergoing therapy should be closely observed for signs of haematologic and non-haematologic toxicity (see **Laboratory Tests**). Patients who are or become Coombs positive should be monitored carefully for potential haemolysis.

CLL
The weight of evidence suggests that a patient whose disease has progressed while treated with fludarabine is unlikely to respond to treatment with LEUSTATIN injection, and therefore, use in such patients is not recommended.

***Progressive Multifocal Leukoencephalopathy (PML)***
*Cases of Progressive Multifocal Leukoencephalopathy (PML) including fatal ones have been reported following the use of LEUSTATIN. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded (see* ***ADVERSE EFFECTS****).*

**Neurotoxicity**
Serious neurological toxicity (including irreversible paraparesis and quadraparesis) has been reported in patients who received LEUSTATIN Injection by continuous infusion at high doses (4 to 9 times the recommended dose for hairy cell leukaemia) (see **Overdose**). Neurological toxicity appears to be dose-dependent. Severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

**Bone Marrow Suppression**
Suppression of bone marrow function, including neutropenia, anaemia and thrombocytopenia should be anticipated. This is usually reversible and appears to be dose dependent, *although prolonged lymphopenia up to 5 years following treatment has been reported*. Proceed carefully in patients with severe bone marrow impairment of any aetiology since further suppression of bone marrow function should be anticipated.

Due to the prolonged immunosuppression associated with the use of nucleoside analogues like LEUSTATIN, secondary malignancies are a potential risk. Primary haematological malignancies are also a risk factor for secondary malignancies.

**HCL:** During the first two weeks after treatment initiation, mean platelet count, absolute neutrophil count (ANC) and haemoglobin concentration declined, and then subsequently increased with normalisation of mean counts by day 15, week 5 and week 8, respectively. The myelosuppressive effects of LEUSTATIN Injection were most notable during the first month following treatment. In the first month, the incidence of severe neutropenia was 70%. Careful haematologic monitoring, especially during the first 4 to 8 weeks after treatment with LEUSTATIN Injection is recommended.

HCL (data based on a subset of 124 patients enrolled in K90-091): Myelosuppression was frequently observed during the first month after starting treatment. Neutropenia (ANC $<0.5 \times 10^9$/L) was noted in 69% of patients, compared with 25% in whom it was present initially. Severe anaemia (Haemoglobin <85 g/L) developed in 41% of patients, compared with 12% initially and thrombocytopenia (Platelets $<20 \times 10^9$/L) developed in 14% of patients compared with 5% in whom it was noted initially.

Treatment with LEUSTATIN Injection is associated with prolonged depression of CD4 lymphocyte counts and transient suppression of CD8 lymphocyte counts. [In a follow-up of 78 of the 124 patients enrolled in the clinical trials, prior to treatment the CD4 count was $0.766 \times 10^9$/L. The mean CD4 count nadir, which occurred 4 to 6 months following treatment was $0.272 \times 10^9$/L. Fifteen months after treatment the mean CD4 count remained below $0.50 \times 10^9$/L. Although CD8 counts decreased initially, increasing counts were observed by 9 months.] The clinical significance of the prolonged CD4 lymphopenia is unclear.

Prolonged bone marrow hypocellularity (<35%) was observed. It is not known whether the hypocellularity is the result of disease related marrow fibrosis or LEUSTATIN Injection toxicity.

**CLL:** During the first 2 cycles of LEUSTATIN Injection therapy, haemoglobin concentration, platelet count and absolute neutrophil count declined to a nadir usually observed in cycle 2. Careful haematologic monitoring is recommended throughout administration of LEUSTATIN Injection treatment.

**CLL (Scripps study data based on a subset of 124 patients enrolled in L91-999)**: Patients with CLL treated with LEUSTATIN Injection were more severely myelosuppressed prior to therapy than HCL patients. Increased myelosuppression was observed during Cycle 1 and Cycle 2 of therapy, reaching a nadir during cycle 2. The percentage of patients having a haemoglobin level below 85 g/L was 16.9% at

baseline, 37.9% in Cycle 1 and 46.1% in Cycle 2. The percentage of patients with platelet counts below 20 x $10^9$/L was 4.0% at baseline, 20.2% during Cycle 1 and 22.5% during Cycle 2. Absolute neutrophil count was below 0.5 x $10^9$/L in 18.5% of patients at baseline, 56.5% in Cycle 1, 61.8% in Cycle 2, 59.3% in Cycle 3 and 55.9% in Cycle 4. Marked blood chemistry abnormalities noted during the study were pre-existing or were isolated abnormalities which resolved, or were associated with death due to the underlying disease.

**Fever/Infection**
Serious (e.g., respiratory infection, pneumonia and viral skin infections), including fatal infections (e.g., sepsis) were reported (see **ADVERSE REACTIONS**).

Patients with active infections should be treated for these underlying conditions prior to receiving LEUSTATIN injection therapy.

Patients should be monitored closely for infections. Those presenting with herpes infections should be treated with acyclovir.

**HCL:** In clinical trials, fever was associated with the use of LEUSTATIN Injection in approximately 72% (89/124) of patients. Most febrile episodes occurred during the first month and were not associated with documented infection. In the first month, the incidence of infection was 31%.

**HCL (data based on a subset of 124 patients enrolled in K90-091)**: Fever was a frequently observed adverse event during the first month on study. [During the first month, 12% of patients experienced severe fever (ie greater than or equal to $40^0$C.] [Of the 124 patients studied, 11 were noted to have a documented infection in the month prior to treatment.] 31% febrile patients had a documented infection: [13.7% of patients had bacterial infections, 6.5% had viral and 6.5% had fungal infections. Seventy percent (70%) of these patients were treated empirically with antibiotics.]

Serious, including fatal, infections (e.g. septicaemia, pneumonia) were reported in 7% of all patients. [During the second month, the overall rate of documented infection was 8%; these infections were mild to moderate and no severe systemic infections were seen. After the third month, the monthly incidence of infection was either less than or equal to that of the months immediately preceding LEUSTATIN Injection therapy.]

[Of the 124 hairy cell leukaemia patients entered in the two trials, there were 6 deaths following treatment; one death was due to infection, two to underlying cardiac disease and two to persistent hairy cell leukaemia with infectious complications. One patient died of progressive disease after receiving additional treatment with another chemotherapeutic agent.]

**CLL:** Pyrexia was reported in 23.6% of CLL patients during Cycle 1 of LEUSTATIN Injection therapy, and in less than 3% of patients during subsequent cycles. Forty of 123 patients (32.5%) reported at least one infection during cycle 1. Approximately 70% of patients had at least one infection during the overall study period of 6 years, including treatment and follow-up.

**CLL (Scripps study data based in a subset of 124 patients enrolled in L91-999)**: During Cycle 1 23.6% of patients experienced pyrexia, and 32.5% experienced at least one documented infection. Infections that occurred in 5% or more of the patients during Cycle 1 were: respiratory infection/inflammation (8.9%), pneumonia (7.3%), bacterial infection (5.6%) and viral skin infections (5.7%). In Cycles 2 through 9, 71.3% of the patients had at least one infection. Infections that occurred in 10% or more of patients were: pneumonia (28.7%), bacterial infection (21.8%), viral skin infection (20.8%), upper respiratory infection (12.9%), other intestinal infection/inflammation (12.9%), oral candidiasis (11.9%), urinary tract infection (11.9%) and other skin infections (11.9%). Overall, 72.4% of the patients had at least one infection during LEUSTATIN Injection therapy. Of these, 32.6% had been administered concomitant immunosuppressive therapy (prednisone).

Since the majority of fevers occurred in neutropenic patients, patients should be closely monitored during the first month of treatment and empiric antibiotics should be initiated as clinically indicated.

Febrile events should be investigated with appropriate clinical diagnostic tests. Practitioners should carefully evaluate the risks and benefits of administering this drug to patients with active infections. Since fever may be accompanied by increased fluid loss, patients should be kept well hydrated (see **ADVERSE EFFECTS**).

**Tumour Lysis Syndrome**
Hyperuricemia may occur as a result of rapid lysis of tumour cells, particularly in patients with large tumour burdens. Since cell lysis may begin as early as the first week of treatment caution should be exercised in those patients at risk of developing this complication. Rare cases of tumour lysis syndrome have been reported in patients with LEUSTATIN with other haematological malignancies. Allopurinol and adequate hydration should be considered for patients with initially high WBC to alleviate potential tumour lysis syndrome side effects of therapy.

**Renal and Hepatic Dysfunction**
Acute renal insufficiency has developed in some patients receiving high doses of LEUSTATIN injection (see OVERDOSE). As there are inadequate data on dosing of patients with renal or hepatic insufficiency, caution is advised when administering the drug to such patients. As with other potent chemotherapeutic agents, monitoring of renal and hepatic function should be performed as clinically indicated, especially in patients with underlying kidney or liver dysfunction. Physicians should consider delaying or discontinuing LEUSTATIN if renal toxicity occurs.

**Laboratory Tests**: During and following treatment, the patient's haematologic profile should be monitored regularly to determine the degree of haematopoietic suppression. In the clinical studies, following reversible declines in all cell counts, the mean Platelet Count reached 100 x $10^9$/L by Day 12, the mean Absolute Neutrophil Count reached 1.5 x $10^9$/L by Week 5 and the mean Haemoglobin reached 120 g/L by Week 8. After peripheral counts have normalised, bone marrow aspiration and biopsy should be performed to confirm response to treatment with LEUSTATIN. Febrile events should be investigated with appropriate laboratory and radiologic studies. Periodic assessment of renal function and hepatic function are recommended.

**Interactions with other medicines**
There are no known drug interactions with LEUSTATIN. Caution should be exercised if LEUSTATIN is administered following or in conjunction with other drugs known to cause myelosuppression or immunosuppression.

Due to increased risk of infection in the setting of immunosuppression with chemotherapy including LEUSTATIN, it is not recommended to administer live attenuated vaccines to patients receiving LEUSTATIN injection.

**Carcinogenicity**
No animal carcinogenicity studies with cladribine have been conducted. However, given that the drug causes DNA damage, the carcinogenic potential of cladribine cannot be excluded.

**Genotoxicity**
As expected for compounds in this class, cladribine has been shown to cause DNA damage. In mammalian cells in culture cladribine has been shown to cause an imbalance of intracellular deoxyribonucleotide triphosphate pools. This imbalance is thought to result in the inhibition of DNA synthesis and repair, yielding DNA strand breaks and subsequently cell death. Cladribine caused chromosomal damage in Chinese Hamster Ovary (CHO) cells in vitro and in bone marrow cells (polychromatic erythrocytes) in vivo, and has been shown to inhibit DNA repair induced by gamma-radiation in lymphocyte cultures. Cladribine was not mutagenic in bacteria (Salmonella typhimurium and Escherischia Coli) or Chinese hamster ovary cells, and did not induce unscheduled DNA synthesis (excision DNA repair) in primary rat hepatocyte cultures.

**Effects on Fertility**
Cladribine causes suppression of rapidly proliferating cells including testicular cells, resulting in hypospermia and aspermia when administered intravenously or subcutaneously to mice and monkeys.

Cladribine doses up to 8 mg/kg (25.6 mg/m$^2$ SC had no effect on female fertility and reproductive performance in mice. The effect of cladribine on human fertility is unknown. Antineoplastic agents, such as cladribine, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on human gametogenesis.. Men being treated with LEUSTATIN injection should be advised not to father a child up to 6 months after the last LEUSTATIN dose.

**Use in Pregnancy (Category D)**
LEUSTATIN may cause foetal harm when administered to pregnant women as it is teratogenic in animals. Treatment of pregnant mice during the period of organogenesis was associated with a significant increase in foetal variations at the dose of 1.5 mg/kg/day intravenously, and increased resorptions, reduced litter size and increased foetal malformations at 3.0 mg/kg/day. No foetal effects were seen in mice at 0.5 mg/kg/day. Foetal malformations were also observed in rabbits receiving 3.0 mg/kg/day intravenously during organogenesis, but not in rabbits receiving 1.0 mg/kg/day. An increased incidence of motor abnormalities in the offspring was additionally observed in mice treated with cladribine at doses up to 3.0 mg/kg/day during pregnancy and through the lactation period, although no effect was noted on other aspects of postnatal development, including reproductive function.

LEUSTATIN is contraindicated in pregnancy (see CONTRAINDICATIONS). Women of childbearing potential must use effective contraception during treatment with LEUSTATIN and for 6 months after the last dose of LEUSTATIN. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the foetus. There are no adequate and well-controlled studies in pregnant women.

**Use in Lactation**
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cladribine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother. LEUSTATIN is contraindicated in breastfeeding women (see CONTRAINDICATIONS).

**Paediatric Use**
Safety and effectiveness in children has not been established. In a Phase I study involving patients 1-21 years old with relapsed acute leukaemia, LEUSTATIN was given by continuous intravenous infusion in doses ranging from 3 to 10.7 mg/m$^2$/day for 5 days (one-half to twice the dose recommended in Hairy Cell Leukaemia). In this study, the dose-limiting toxicity was severe myelosuppression with profound neutropenia and thrombocytepenia. At the highest dose (10.7 mg/m$^2$/day), 3 of 7 patients developed irreversible myelosuppression and fatal systemic bacterial or fungal infections. No unique toxicities were noted in this study.

**Effects on Ability to Drive and Use Machines**

Given the patient's underlying medical condition, caution should be exercised when a patient is performing activities requiring substantial physical well-being while using LEUSTATIN injection.

## ADVERSE EFFECTS

**Clinical Trials**

The clinical trials of cladribine were uncontrolled. Adverse events were assessed based on investigators opinions of relationship to cladribine, seriousness, severity, frequency, timing of cladribine administration and event, confounding factors and consistency with the pharmacology of cladribine. The events listed in this section are considered related to cladribine.

The CIOMS III frequency categories are:

| | |
|---|---|
| Very Common | ≥ 10% |
| Common | ≥ 1% and < 10% |
| Uncommon | ≥ 0.1% and < 1% |
| Rare | ≥ 0.01% and < 0.1% |

*HCL:*

| **Table 1: Adverse Drug Reactions in ≥ 1% of Patients Treated With LEUSTATIN in HCL Clinical Trials K90-091 and L91-048** |
|---|
| **Infections and infestations** |
| *Very common;* infection (unspecified) |
| **Blood and Lymphatic System Disorders** |
| *Very common*: neutropenia; thrombocytopenia; anaemia; purpura |
| *Common:*, febrile neutropenia |
| **Psychiatric Disorders** |
| *Common:* anxiety; insomnia |
| **Nervous System Disorders** |
| *Very common*: headache; dizziness |
| *Common:* insomnia; anxiety |
| **Cardiovascular Disorders** |
| *Common:* tachycardia; oedema; oedema peripheral; heart murmur; hypotension; thrombosis |
| **Respiratory, Thoracic and Mediastinal Disorders** |
| *Very common*: abnormal breath sounds; abnormal chest sounds; cough |
| *Common:* dyspnoea*; rales |
| **Gastrointestinal Disorders** |
| *Very common*: nausea; decreased appetite; constipation; vomiting; diarrhoea; |
| *Common:* Abdominal pain**; flatulence; |
| **Skin and Subcutaneous Tissue Disorders** |
| *Very common*: rash***; diaphoresis; pruritus |
| *Common:* ecchymosis; hyperhidrosis; petechiae |
| **Musculoskeletal, Connective Tissue, and Bone Disorders** |
| *Common:* arthralgia; myalgia; pain****; muscular weakness |
| **General Disorders and Administration Site Conditions** |
| *Very common*: pyrexia; fatigue; asthenia; chills ; administration site reaction***** |
| *Common:*; malaise |
| **Injury, Poisoning and Procedural Complications** |
| *Common:* contusion |

* Dyspnoea includes dyspnoea, dyspnoea exertional and wheezing
** Abdominal pain includes abdominal discomfort, abdominal pain, and abdominal pain (lower and upper)
*** Rash includes erythema, rash, and rash macular, macula-papular, papular, pruritic, pustular and erythematous
**** Pain includes pain and back pain, chest pain, arthritis pain, bone pain, and pain in extremity
***** Administration site reactions includes administration site reaction, Catheter site cellulitis, erythema, haemorrhage, and pain, infusion site reaction, erythema, edema, and pain)

***CLL:***

| **Table 2: Adverse Drug Reactions in ≥ 1% of Patients Treated With LEUSTATIN in CLL Clinical Trials L91-999 and L091-048** | |
|---|---|
| **Infections and Infestations** | |
| *Very common*: infection (unspecified) | |
| *Common:* bacteraemia ; cellulitis; localised infection; pneumonia | |
| **Blood and Lymphatic System Disorders** | |
| *Very common*: anaemia; thrombocytopenia (with bleeding or petechiae ); neutropenia | |
| **Nervous System Disorders** | |
| *Very common*: Headache | |
| *Common:* somnolence; dizziness; confusion | |
| **Cardiovascular Disorders** | |
| *Very common*: oedema | |
| *Common:* phlebitis; oedema peripheral ; hypotension; chest pain; atrial fibrillation | |
| **Respiratory, Thoracic and Mediastinal Disorders** | |

| |
|---|
| *Very common*: cough; |
| *Common:* abnormal breath sounds; abnormal chest sounds; dyspnoea*; rales; pneumonia; upper respiratory tract infection |
| **Gastrointestinal Disorders** |
| *Very common*: abdominal pain; nausea |
| *Common:* diarrhoea; vomiting ; constipation |
| **Skin and Subcutaneous Tissue Disorders** |
| *Common:* hyperhidrosis; purpura; rash** |
| **Musculoskeletal, Connective Tissue, and Bone Disorders** |
| *Common:* pain***; muscular weakness; back pain; neck stiffness |
| **General Disorders and Administration Site Conditions** |
| *Very common*:; fatigue; pyrexia; Administration site reaction**** |
| *Common:* asthenia; crepitations; localised oedema; chills; weight loss |

* Dyspnoea includes dyspnoea and dyspnoea extertional
** Rash includes rash (macula-papular, pruritic, pustular) and erythema
*** Pain includes pain, arthralgia, back, bone, musculoskeletal and pain in extremity
**** Administration site reactions includes administration site reaction, catheter site (erythema and infection) and infusion site (cellulitis, erythema, irritation, oedema, pain, infection and phlebitis)

**Post Marketing Experience**

The following additional adverse reactions have been reported since the drug became commercially available. These adverse reactions have been reported primarily in patients who received multiple courses of LEUSTATIN Injection:

**Infections and infestations:**
*Common:* septic shock
*Uncommon:* opportunistic infections have occurred in the acute phase of treatment; **Progressive multifocal leukoencephalopathy (not known).*

**Blood and lymphatic system disorders:**
*Common:* haemolytic anaemia (including autoimmune haemolytic anaemia)
*Uncommon:* bone marrow suppression with prolonged pancytopenia; aplastic anaemia; hypereosinophilia; myelodysplastic syndrome.

**Immune system disorders:**
*Common:* hypersensitivity

**Metabolism and nutrition disorders:**
*Uncommon:* Tumour lysis syndrome; metabolic acidosis

**Psychiatric disorders:**
*Common:* confusion (including disorientation)

**Hepatobiliary disorders:**
*Uncommon:* reversible, generally mild, increases in bilirubin; increases in transaminases; jaundice
**Nervous System disorders:**
*Uncommon:* depressed level of consciousness; neurological toxicity including peripheral sensory neuropathy, motor neuropathy (paralysis), polyneuropathy, paraparesis

**Eye disorders:**
*Common:* Conjunctivitis

**Cardiovascular disorders:**
*Uncommon:* thrombophlebitis

**Respiratory, thoracic and mediastinal disorders:**

*Common:* pulmonary interstitial infiltrates (including lung infiltration, interstitial lung disease, pneumonitis and pulmonary fibrosis)

**Skin and subcutaneous tissue disorders:**
*Common:* urticaria
*Uncommon:* Stevens-Johnson syndrome; toxic epidermal necrolysis; toxic skin eruption

**Renal and urinary disorders:**
*Common:* renal failure (including renal failure acute, renal impairment)

**DOSAGE AND ADMINISTRATION**

**Usual Dose:**

*HCL:* The recommended treatment for Hairy Cell Leukaemia is a single course of LEUSTATIN given by continuous infusion for 7 consecutive days at a dose of 0.09mg/kg/day. Clinical experience is limited to these specific recommendations; deviation (e.g. use of higher doses or a longer duration of treatment) is not advised. If the patient does not respond to the initial course of Leustatin Injection, it is unlikely that they will benefit from additional courses. Physicians should consider delaying or discontinuing the drug if neurotoxicity or renal toxicity occurs. (see **WARNINGS**)

*CLL:* In patients with CLL, the recommended treatment consists of a continuous infusion of LEUSTATIN injection for 2 hours on days 1 to 5 of a 28 day cycle at a dose of 0.12mg/kg/day (4.8 $mg/m^2$/day). It is recommended that LEUSTATIN injection be administered in responding patients up to a maximum of 6 monthly cycles and that non-responding patients receive no more than 2 cycles of treatment.

Specific risk factors predisposing to increased toxicity from LEUSTATIN have not been defined. However, in view of the known toxicities of agents of this class, it would be prudent to proceed carefully in those with renal insufficiency or severe bone marrow impairment of any aetiology. Patients should be monitored closely for haematologic and non-haematologic toxicity.

**Preparation and Administration of Intravenous Solutions:**

LEUSTATIN Injection must be diluted with the designated diluent prior to administration. Since the drug product does not contain any microbial preservative or bacteriostatic agent, **aseptic technique and proper environmental precautions must be observed in preparation of LEUSTATIN solutions**.

[Should the drug accidently be given extravenously, local tissue damage is unlikely. If extravasation occurs, the administration should be stopped immediately and restarted in another vein. Other recommended local measures include elevating the arm and applying an ice pack to reduce swelling.]

*HCL:* To prepare a single daily dose: LEUSTATIN Injection should be passed through a sterile 0.22µm disposable hydrophilic syringe filter prior to introduction into the infusion bag, prior to each daily infusion.

Add the calculated dose (0.09 mg/kg or 0.09 mL/kg) of LEUSTATIN through the sterile filter to an infusion bag containing 100 to 500 mL of 0.9% Sodium Chloride Injection, USP. Infuse continuously over 24 hours. Repeat daily for a total of 7 consecutive days.

| | Dose of LEUSTATIN | Recommended Diluent | Quantity of Diluent |
|---|---|---|---|
| 24-hour infusion method | 0.09 mg/kg | 0.9% Sodium Chloride Injection | 100 - 500 mL |

*CLL:* Preparation of a Single Daily Dose: LEUSTATIN injection should be passed through a sterile 0.22µm disposable hydrophilic syringe filter prior to introduction into the infusion bag, prior to each daily infusion.

Add the calculated dose (0.12 mg/kg or 4.8mg/$m^2$) of LEUSTATIN injection through the sterile filter to an infusion bag containing 100 ml or 500 ml of 0.9% Sodium Chloride USP. Infuse continuously over 2 hours. Repeat daily for a total of 5 consecutive days. The use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine.

Since limited compatibility data are available, adherence to the recommended diluents is advised. The use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine. LEUSTATIN has been shown to be compatible with VIAFLEX† Infusion Bags, Pharmacia Deltec MEDICATION CASSETTES‡, and Millipore MILLEX-GV disposable filters§. Solutions containing LEUSTATIN should not be mixed with other intravenous drugs or additives or infused simultaneously via a common intravenous line, since compatibility testing has not been performed.

Care must be taken to assure the sterility of prepared solutions. Once diluted, solutions of LEUSTATIN Injection should be administered promptly or stored in the refrigerator ($2^0$ to $8^0$C) for no more than 8 hours prior to start of administration. Vials of LEUSTATIN are for single-use only. Any unused portion should be discarded in an appropriate manner. (see **Handling and Disposal**)

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. A precipitate may occur during the exposure of LEUSTATIN to low temperatures; it may be resolubilised by allowing the solution to warm naturally to room temperature and by shaking vigorously. **DO NOT HEAT OR MICROWAVE**.

**Chemical Stability of Vials and Infusion Solutions**

When stored in refrigerated conditions between $2^0$ to $8^0$C ($36^0$ to $46^0$F) protected from light, unopened vials of LEUSTATIN Injection are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. DO NOT heat or microwave. Once thawed, the vial of LEUSTATIN Injection is stable until expiry if refrigerated. DO NOT refreeze. Once diluted, solutions containing LEUSTATIN Injection should be administered promptly or stored in the refrigerator ($2^0$ to $8^0$C) for no more than 8 hours prior to administration.

**Handling and Disposal:**

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken when handling, preparing, and administering LEUSTATIN. The use of disposable gloves and protective garments is recommended. If LEUSTATIN contacts the skin or mucous membranes, wash the involved surface immediately with copious amounts of water. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Refer to your Institution's guidelines and all applicable state/local regulations for disposal of cytotoxic waste.

**OVERDOSAGE**

In a Phase 1 study with 31 patients in which LEUSTATIN Injection was administered at high doses (4 to 9 times that recommended for hairy cell leukaemia) for 7-14 days in conjunction with cyclophosphamide and total body irradiation [as preparation for bone marrow transplantation], acute nephrotoxicity, delayed onset neurotoxicity, severe bone marrow suppression with neutropenia, anaemia and thrombocytopenia and gastrointestinal symptoms were reported.

Six patients (19%) developed manifestations of acute renal dysfunction/insufficiency (e.g. acidosis, anuria, elevated serum creatinine, etc.) within 7 to 13 days after starting treatment with LEUSTATIN Injection, [5 of the affected patients required dialysis. Renal insufficiency was reversible in 2 (of 4)

patients whose renal function had not recovered at the time of death. Several of these patients had also been treated with other medications having known nephrotoxic potential].

Eleven patients (35%) experienced delayed onset neurologic toxicity. In the majority, this was characterised by progressive irreversible motor weakness, of the upper and/or lower extremities (paraparesis/quadraparesis), noted 35 to 84 days after starting high dose therapy.

Axonal peripheral polyneuropathy was observed in a dose escalation study at the highest dose levels (approximately 4 times the recommended dose for hairy cell leukaemia) in patients not receiving cyclophosphamide or total body irradiation.

[Non-invasive neurological testing was consistent with demyelinating disease].

There is no known specific antidote. It is not known whether the drug can be removed by dialysis or hemofiltration. Treatment of overdosage consists of discontinuation of LEUSTATIN Injection, careful observation and appropriate supportive measures.

**PRESENTATION AND STORAGE CONDITIONS**

LEUSTATIN Injection is sold as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/mL) of cladribine in a clear glass, single-use vial. LEUSTATIN is also conveniently packaged in a carton containing 1 vial.

Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.

**NAME AND ADDRESS OF THE SPONSOR**

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**DATE OF INCLUSION ON THE ARTG**

12 February 1994

**DATE OF MOST RECENT AMENDMENT**

15 May 2018

Please note change(s) presented as *italicised text in Product Information