PRODUCT MONOGRAPH

[Pr]IDARUBICIN HYDROCHLORIDE INJECTION
Idarubicin Hydrochloride

Professed
1 mg/mL

[5 mL, 10 mL and 20 mL vials]

Antineoplastic Agent

Sterile Solution

Mylan Pharmaceuticals ULC
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Etobicoke, ON
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous injection	Solution for injection 1 mg/mL (5mL, 10mL, and 20mL vials)	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Idarubicin Hydrochloride Injection alone or in combination chemotherapy regimens involving other cytotoxic agents is indicated in:

- Acute non-lymphocytic leukemia (ANLL); in adults for remission induction as front-line therapy or for remission induction in relapsed or refractory patients.
- Acute lymphocytic leukemia (ALL) as second line treatment in adults and children.

Pediatrics: Idarubicin Hydrochloride Injection is indicated in acute lymphocytic leukemia (ALL) as second line treatment in children.

Geriatrics (> 65 years of age): Patients over 60 years of age who were undergoing induction therapy experienced congestive heart failure, serious arrhythmias, chest pain, myocardial infarction, and asymptomatic declines in LVEF more frequently than younger patients (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION**, **TOXICITY** and **ADVERSE REACTIONS**).

CONTRAINDICATIONS

- Patients who are hypersensitive to idarubicin or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Hypersensitivity to any other anthracyclines or anthracenediones such as Pharmorubicin PFS (epirubicin hydrochloride), daunorubicin hydrochloride, mitoxantrone or mitomycin C;
- Uncontrolled infections;
- Marked persistent myelosuppression induced by prior treatment with other antitumour agents or by radiotherapy;
- Severe hepatic impairment;
- Severe renal impairment;
- Severe myocardial insufficiency;
- Recent myocardial infarction;
- Severe arrhythmias;
- History of severe cardiac disease;
- Previous treatment with maximum cumulative doses of idarubicin, doxorubicin, daunorubicin, epirubicin and/or other anthracyclines and anthracenediones (see **WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Idarubicin Hydrochloride Injection is intended for use under the direction of physicians experienced in chemotherapy.

- **Myelosuppression (see Warnings and Precautions, Hematologic)**
- **Cardiotoxicity (see Warnings and Precautions, Cardiovascular)**

General

Therapy with Idarubicin Hydrochloride Injection requires close observation of the patient and laboratory monitoring. Idarubicin may induce hyperuricemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells ('tumour lysis syndrome'). Blood uric acid levels, potassium, calcium, phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumour lysis syndrome. Appropriate measures must be taken to control any systemic infection before beginning therapy.

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with idarubicin.

Extravasation of Idarubicin Hydrochloride Injection at the site of intravenous injection can cause severe local tissue necrosis. The risk of thrombophlebitis at the injection site may be minimized by following the recommended procedure for administration.

Carcinogenesis and Mutagenesis

Like most other cytotoxic agents, idarubicin has mutagenic properties.

Idarubicin was genotoxic in most of the in vitro or in vivo tests performed. Intravenous idarubicin was carcinogenic, toxic to the reproductive organs, and embryotoxic and teratogenic in rats.

Idarubicin can induce chromosomal damage in human spermatozoa. For this reason, males undergoing idarubicin treatment should use contraceptive measures.

Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines, including idarubicin. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents. These leukemias can have a 1- to 3-year latency period.

Cardiovascular

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (ie, delayed) events.

Early (i.e., Acute) Events. Early cardiotoxicity of idarubicin consists mainly of sinus tachycardia and/or ECG abnormalities, such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for the discontinuation of idarubicin treatment. However acute life-threatening arrhythmias have been occasionally observed during therapy. Subacute effects such as pericarditis/myocarditis have also been reported.

Late (i.e., Delayed) Events. Delayed cardiotoxicity usually develops late in the course of therapy or within 2 to 3 months after completion of treatment, but later events, several months to years after completion of treatment have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

Cumulative dose limits for i.v. or oral idarubicin have not been defined. **However, idarubicin-related cardiomyopathy was reported in 5% of patients who received cumulative i.v. doses of 150 to 290 mg/m^2.** Available data on patients treated with oral idarubicin total cumulative doses up to 400 mg/m^2 suggest a low probability of cardiotoxicity.

Cardiac function should be assessed before patients undergo treatment with idarubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of idarubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of drugs with the ability to suppress cardiac contractility or cardiotoxic drugs. Anthracyclines including idarubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored.

Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The reported half-life of trastuzumab is approximately 28 -38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with idarubicin may also occur at lower cumulative doses whether or not cardiac risk factors are present.

Cardiac toxicity of the type described for other anthracycline compounds, manifested by clinically evident CHF or by a decrease in LVEF may occur during therapy or several weeks after termination of therapy. Discontinuation of Idarubicin Hydrochloride Injection and treatment with vasodilators, diuretics, digitalis, sodium restriction and bed-rest are indicated.

In infants and children, there appears to be a greater susceptibility to anthracycline-induced cardiac toxicity, and a long-term periodic evaluation of cardiac function should be performed.

Extravasation and Vascular Effects

Extravasation of Idarubicin Hydrochloride Injection during intravenous administration can cause local pain, severe tissue lesions (vesication, severe cellulitis) and severe local tissue necrosis. Extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If signs or symptoms of extravasation occur, the injection or infusion should be immediately stopped (see **DOSAGE AND ADMINISTRATION**).

Phlebosclerosis may result from an injection into a small vessel or from previous injections into

the same vein. Following the recommended procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see **DOSAGE AND ADMINISTRATION**).

As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism, have been coincidentally reported with the use of idarubicin.

Gastrointestinal

Idarubicin is emetogenic. Mucositis (mainly stomatitis, less often esophagitis) generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Occasionally, episodes of serious gastrointestinal events (such as perforation or bleeding) have been observed in patients receiving oral idarubicin who had acute leukemia or a history of other pathologies or had received medications known to lead to gastrointestinal complications. In patients with active gastrointestinal disease with increased risk of bleeding and/or perforation, the physician must balance the benefit of oral idarubicin therapy against the risk.

Hematologic

Idarubicin hydrochloride injection is potent bone marrow suppressant. Myelosuppression primarily of leukocytes will therefore occur in all patients given a therapeutic dose of this agent. Hematologic profiles should be assessed before and during each cycle of therapy with idarubicin including differential white blood cell (WBC) counts. A dose-dependent reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of idarubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopenia and neutropenia are usually severe; thrombocytopenia and anemia may also occur. Neutrophil and platelet counts usually reach their nadir 10 to 14 days following administration; however cell counts generally return to normal levels during the third week. Clinical consequences of severe myelosuppression may be fever, infections, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death. Facilities with laboratory and supportive resources adequate to monitor drug tolerability and protect and maintain a patient compromised by drug toxicity should be available. It must be possible to treat rapidly and completely a severe hemorrhagic condition and/or a severe infection.

Hepatic/Biliary/Pancreatic

Idarubicin Hydrochloride Injection therapy should not be administered in patients with severe liver impairment or in patients with uncontrolled infections unless the benefit outweighs the risk.

Since hepatic function impairment can affect the disposition of idarubicin, liver function should be evaluated with conventional clinical laboratory tests (using serum bilirubin as indicator) prior to, and during, treatment. In a number of Phase III clinical trials, treatment was not given if bilirubin serum levels exceeded 2 mg/dL. With other anthracyclines, a 50% dose reduction is generally employed if bilirubin levels exceed 40 µmol/L (2.35 mg/dL).

Renal

Idarubicin Hydrochloride Injection therapy should not be administered in patients with severe renal impairment.

Since renal function impairment can affect the disposition of idarubicin, kidney function should be evaluated with conventional clinical laboratory tests (using serum creatinine as indicator) prior to, and during, treatment. In a number of Phase III clinical trials, treatment was not given if creatinine serum levels exceeded 2 mg/dL. With other anthracyclines, a 50% dose reduction is generally employed if creatinine levels exceed 200 µmol/L (2.25 mg/dL).

Immunosuppressant Effects / Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including idarubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving idarubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Special Populations

Pregnant Women:

The embryotoxic potential of idarubicin has been demonstrated in both in vitro and in vivo studies. However, there are no adequate and well-controlled studies in pregnant women. Therefore, women of child bearing potential should be prescribed effective contraceptive methods and counselled on the risks of pregnancy. Idarubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The patient should be informed of the potential hazard to the fetus if Idarubicin Hydrochloride Injection is to be used during pregnancy, or if the patient becomes pregnant during therapy.

Nursing Women:

It is not known whether idarubicin or its metabolites are excreted in human milk. Mothers should be advised not to breastfeed while undergoing chemotherapy with Idarubicin Hydrochloride Injection.

Monitoring and Laboratory Tests

Therapy with Idarubicin Hydrochloride Injection requires close observation of the patient and laboratory monitoring (see **WARNINGS AND PRECAUTIONS**, General)

Cardiac function should be assessed before patients undergo treatment with idarubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment (see **WARNINGS AND PRECAUTIONS**, Cardiovascular)

Liver and kidney functions should be evaluated with conventional clinical laboratory tests (using serum bilirubin and serum creatinine as indicators) prior to, and during, treatment (see **WARNINGS AND PRECAUTIONS**, Hepatic/Biliary/Pancreatic and **WARNINGS AND PRECAUTION** Renal).

Hematologic profiles should be assessed before and during each cycle of therapy with idarubicin including differential white blood cell (WBC) counts (see **WARNINGS AND PRECAUTIONS**, Hematologic).

ADVERSE REACTIONS

Cardiovascular:
sinus tachycardia, ECG abnormalities, tachyarrhythmias, atrio-ventricular and bundle branch block, asymptomatic reductions in LVEF, CHF, pericarditis, myocarditis

Hematologic:
leukopenia, neutropenia, anemia, thrombocytopenia, hemorrhage

Gastrointestinal:
anorexia, nausea/vomiting, dehydration, mucositis/stomatitis, esophagitis, abdominal pain or burning sensation, erosions/ulceration, gastrointestinal tract bleeding, diarrhea, colitis, including severe enterocolitis/neutropenic enterocolitis with perforation

Liver:
elevation of liver enzymes and bilirubin

Endocrine:
hot flashes

Skin:
alopecia, local toxicity (see **WARNINGS AND PRECAUTIONS**), rash/itch, skin changes, skin and nail hyperpigmentation, hypersensitivity of irradiated skin (‘radiation recall reaction’), urticaria, acral erythema

Vascular:
phlebitis, thrombophlebitis, thromboembolism

Urological:
red color to the urine for 1-2 days after administration

Other:
anaphylaxis, infection, sepsis/septicemia, secondary leukemias (acute myeloid leukemia and myelodysplastic syndrome), fever, shock, hyperuricemia

Severe and sometimes fatal infections have been associated with idarubicin alone or in combination with cytarabine. Acute toxicities such as nausea and vomiting, mucositis, diarrhea and liver dysfunction are comparable to those of daunorubicin.

Idarubicin appears to have a cardiac toxicity potential which is similar to that of daunorubicin. Overall, the incidence of serious cardiac events has been 2.0% out of 1204 patients receiving idarubicin via i.v. administration. If patients previously treated with anthracyclines are excluded, the overall incidence is 1.58%. When idarubicin was administered orally, the incidence of serious cardiac events (grade 3 only) was 3.2%.

DRUG INTERACTIONS

Drug-Drug Interactions

Idarubicin is a potent myelosuppressant and combination chemotherapy regimens that contain other agents with similar action (e.g. other anthracyclines, anthracenediones) may lead to additive toxicity, especially with regard to bone marrow/hematologic and gastrointestinal effects (see **WARNINGS AND PRECAUTIONS**). Combination chemotherapy regimens that contain other agents which may potentiate additive hematological toxicity may include alkylating agents (e.g. cyclophosphamide), antineoplastic agents (such as etoposide, cytarabine, fludarabine), and corticosteroids (e.g. dexamethasone). The use of idarubicin in combination chemotherapy with other potentially cardiotoxic drugs (e.g. cyclophosphamide, paclitaxel), as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers such as amlodipine, diltiazem or verapamil), requires monitoring of cardiac function throughout treatment. Changes in hepatic or renal function induced by concomitant therapies may affect idarubicin metabolism, pharmacokinetics, and therapeutic efficacy and/or toxicity.

An additive myelosuppressant effect may occur when radiotherapy is given concomitantly or within 2-3 weeks prior to treatment with idarubicin.

Interactions with other drugs have not been established.

Precipitation occurs with heparin. Prolonged contact with any solution of an alkaline pH will result in degradation of the drug.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

As with all parenteral products, intravenous solution should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration. Solution showing haziness, particulate matter, precipitate, discolouration or leakage should not be used and **discard unused portions**.

Dosing Considerations

- These dose schedules should take into account the hematological status of the patient and the dosage of the other cytotoxic drugs when used in combination.

- Hepatic or Renal Dysfunction. While no specific dose recommendation can be made based on the limited available data in patients with hepatic and/or renal impairment, dose reductions should be considered in patients with bilirubin and/or creatinine serum levels greater than 2.0 mg/dL (see **WARNINGS AND PRECAUTIONS**).

- The total dose of Idarubicin Hydrochloride Injection administered to a patient should take into account: prior or concomitant therapy with related compounds such as epirubicin and daunorubicin or anthracene derivatives and/or radiotherapy to the mediastinal area.

Recommended Dose and Dosage Adjustment

Intravenous

Acute Non-Lymphocytic Leukemia (ANLL)
In adults, for remission induction as front line therapy or for remission induction in relapsed or refractory patients, the following dose schedules are recommended:

(a) 12 mg/m^2 daily by intravenous injection for 3 days in combination with cytarabine, or
(b) 8 mg/m^2 daily by intravenous injection as a single agent for 5 days.

Acute Lymphocytic Leukemia (ALL)
As a second line treatment, the following dose schedules are recommended:

(a) in adults, 12 mg/m^2 daily by intravenous injection for 3 days as a single agent, or
(b) in children, 10 mg/m^2 daily by intravenous injection for 3 days as a single agent.

Administration

IV administration:

Idarubicin Hydrochloride Injection **must not** be administered by intramuscular or subcutaneous injection. Unless specific compatibility data are available, Idarubicin Hydrochloride Injection should not be mixed with other drugs. Precipitation occurs with heparin. Prolonged contact with any solution of an alkaline pH will result in degradation of the drug.

Idarubicin Hydrochloride Injection should be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride injection, USP 0.9%. The tubing should be attached to a Butterfly® needle or other suitable device and inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein and the dosage. However, the dosage should be administered over 5 to 10 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see **WARNINGS AND PRECAUTIONS**).

If it is known or suspected that subcutaneous extravasation has occurred, it is recommended that intermittent ice packs (1/2 hour immediately, then 1/2 hour 4 times per day for 3 days) be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained early if there is any sign of a local reaction such as pain, erythema, edema or vesication. If ulceration begins or there is severe persistent pain at the site of extravasation, early wide excision of the involved area should be considered.

OVERDOSAGE

Very high doses of Idarubicin Hydrochloride Injection may be expected to cause acute myocardial toxicity within 24 hours and severe myelosuppression within 1 or 2 weeks. Treatment should aim to support the patient during this period and should utilize such measures as blood transfusions and reverse-barrier nursing. Delayed cardiac failure has been seen with the anthracyclines up to several months after the overdose. Patients should be observed carefully and if signs of cardiac failure arise, should be treated along conventional lines.

For management of a suspected drug overdose, contact your regional Poison Control Centre

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Idarubicin, either as a single agent or in combination, has been shown to be a potent antileukemic agent capable of inducing complete remission in previously untreated and in relapsed and refractory acute non-lymphocytic leukemia (ANLL) including resistant patients, and in adult and pediatric relapsed patients with acute lymphoblastic leukemia (ALL).

Idarubicin is a DNA-intercalating analog of daunorubicin which has an inhibitory effect on nucleic acid synthesis and interacts with the enzyme topoisomerase II. The modification, in position 4 of the anthracycline structure, gives the compound a high lipophilicity which results in an increased rate of cellular uptake compared with other anthracyclines.

Idarubicin has been shown to have a higher potency than daunorubicin and to be an effective agent against murine leukemias and lymphomas. In vitro studies on human and murine anthracycline resistant cells have revealed a lower degree of cross resistance for idarubicin in comparison with doxorubicin and daunorubicin.

Pharmacokinetics

Seven pharmacokinetic studies were carried out in 49 patients. The plasma concentrations of idarubicin fit a 2 or 3 compartment open models.

Studies of cellular (nucleated blood and bone marrow cells) drug concentrations in leukemic patients have shown that peak cellular idarubicin concentrations are reached a few minutes after injection. Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than 100 times the plasma concentrations. Idarubicin disappearance rates in plasma and cells were comparable with a terminal half-life of about 15 hours. The terminal half-life of idarubicinol in cells was about 72 hours.

Absorption:

After oral administration to patients with normal renal and hepatic function, idarubicin is rapidly absorbed, with a peak time of 2-4 hours.

Distribution:

The absolute bioavailability of idarubicin given orally has been shown to range between 18 and 39%, whereas that calculated from the data on the active metabolite, idarubicinol, is somewhat higher (29-58%). The effective bioavailability, calculated on the basis of the pharmacological response, is approximately 35%. Protein binding was studied in vitro by equilibrium dialysis at concentrations of idarubicin and idarubicinol similar to the maximum plasma level obtained in the pharmacokinetic studies. The percent of idarubicin and idarubicinol bound to human plasma proteins at the concentration of 100 ng/mL plasma is on the average 97% and 94%, respectively.

Metabolism:

After intravenous administration to patient with normal and hepatic function, idarubicin is

extensively metabolized to an active metabolite, idarubicinol.

Excretion:

After intravenous administration to patients with normal renal and hepatic function, idarubicin is eliminated from systemic circulation with a terminal plasma half-life ranging between 11-25 hours. Active metabolite, idarubicinol, is more slowly eliminated with a plasma half-life ranging between 41-69 hours. The drug is eliminated by biliary and renal excretion, mostly in the form of active metabolite idarubicinol.

After oral administration to patients with normal renal and hepatic function, idarubicin is rapidly absorbed, with a peak time of 2-4 hours. It is rapidly eliminated from systemic circulation with a terminal plasma $t_{1/2}$ ranging between 10-35 hours and is extensively metabolized to an active metabolite, idarubicinol. Idarubicinol is more slowly eliminated with a plasma $t_{1/2}$ ranging between 33-60 hours.

STORAGE AND STABILITY

Idarubicin Hydrochloride Injection (idarubicin hydrochloride injection) should be stored at 2-8°C (36°F - 46°F), protect from light.

Incompatibility:
Unless specific compatibility data are available, Idarubicin Hydrochloride Injection should not be mixed with other drugs. Precipitation occurs with heparin. Prolonged contact with any solution of an alkaline pH will result in degradation of the drug.

SPECIAL HANDLING INSTRUCTIONS

Preparation and handling

1. Personnel should be trained in good techniques for reconstitution and handling. Pregnant staff should be excluded from working with this drug.
2. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II). The work surface should be protected by disposable, plastic-backed, absorbent paper.
3. Personnel preparing idarubicin solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks. If idarubicin contacts the skin or mucosa, the area should be washed with soap and water immediately.
4. Personnel regularly involved in the preparation and handling of antineoplastics should have blood examinations on a regular basis.

Disposal

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.

2. All needles, syringes, vials and other materials which have come in contact with Idarubicin Hydrochloride Injection should be segregated in plastic bags, sealed and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

3. If incineration is not available, Idarubicin Hydrochloride Injection may be detoxified by adding sodium hypochlorite solution (household bleach) to the vial, in sufficient quantity to decolourize the idarubicin, care being taken to vent the vial to avoid a pressure build-up of the chlorine gas which is generated. Dispose detoxified vials in a safe manner.

Needles, syringes, disposable and non-disposable equipment

Rinse equipment with an appropriate quantity of sodium hypochlorite solution. Discard the solution in the sewer system with running water and discard disposable equipment in a safe manner. Thoroughly wash non-disposable equipment in soap and water.

Spillage/Contamination

Wear gloves, mask, protective clothing. Treat spilled powder or liquid with dilute sodium hypochlorite (1% available chlorine) solution. Carefully absorb solution with gauze or towels again and place in polyethylene bag; seal, double bag and mark as hazardous waste. Dispose waste by incineration or by other methods approved for hazardous materials. Personnel involved in cleanup should wash with soap and water.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Injection

Idarubicin Hydrochloride Injection is a sterile solution for injection. It is a clear, red-orange, aqueous, preservative-free solution, free from visible particles containing 1 mg/mL idarubicin hydrochloride. The solution is filled in glass vials.

5 mL Vial - Each vial contains 5 mg of idarubicin hydrochloride USP, 125 mg of Glycerol, USP/BP.Ph. Eur., Water for injection USP q.s., and Hydrochloric Acid, USNF/BP/Ph.Eur q.s. (pH adjusting agent)

10 mL Vial - Each vial contains 10 mg of idarubicin hydrochloride USP, 250 mg of Glycerol, USP/BP/Ph. Eur., Water for injection USP q.s., and Hydrochloric Acid, USNF/BP/Ph.Eur q.s. (pH adjusting agent)

20 mL Vial - Each vial contains 20 mg of idarubicin hydrochloride USP, 500 mg of Glycerol,

USP/BP/Ph. Eur., Water for injection USP q.s., and Hydrochloric Acid, USNF/BP/Ph.Eur q.s. (pH adjusting agent)

Packaging

Idarubicin Hydrochloride Injection is available in 5 mL, 10 mL, and 20 mL vials.
The 5 mL, 10 mL, and 20 mL vials are packaged and supplied in a single vial carton.

5 mL Fill: 5mL/20mm USP & Ph. Eur Type I Flint moulded vial, 20 mm Grey Bromobutyl Omni flex plus coated stopper, 20 mm Light blue flip off Aluminum seal

10 mL Fill: 10mL/20mm USP & Ph. Eur Type I Flint moulded vial, 20 mm Grey Bromobutyl Omni flex plus coated stopper, 20 mm Light blue flip off Aluminum seal

20 mL Fill: 20mL /20mm USP & Ph. Eur Type I Flint moulded vial, 20 mm Grey Bromobutyl Omni flex plus coated stopper, 20 mm Light blue flip off Aluminum seal

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

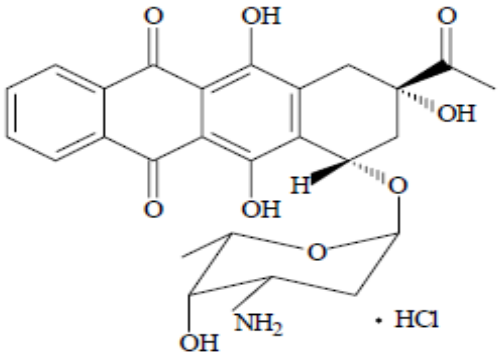
Drug Substance

Proper name: Idarubicin Hydrochloride

Chemical name: 5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-*h*exopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11- trihydroxyhydrochloride, (7*S*-*cis*)-.

Molecular formula and molecular mass: $C_{26}H_{27}NO_9$.HCl; 533.95 g/mol

Structural formula:



Physicochemical properties:

Idarubicin hydrochloride is a DNA intercalating analog of daunorubicin. The modification in position 4 of the aglycone, gives the compound a high lipophilicity.

It is a practically odourless red-orange powder. It is sparingly soluble in distilled water, slightly soluble in absolute ethanol and practically insoluble in non-polar organic solvents. Its melting point is 173-174°C.

CLINICAL TRIALS

Four prospective randomized studies have been conducted to compare the efficacy and safety of idarubicin (IDR) to that of daunorubicin (DNR), each in combination with cytarabine as induction therapy in previously untreated adult patients with acute non-lymphocytic leukemia (ANLL). These data are summarized in the following table:

	Induction[a] Regimen Dose in mg/m2- Daily x 3 Days		Complete Remission Rate, All Pts Randomized		Median Survival All Pts Randomized	
U.S. Studies	IDR	DNR	IDR	DNR	IDR	DNR
1. MSKCC* (Age ≤ 60 years)	12[b]	50[b]	48/60[+] (80%)	35/60 (58%)	19.7 months[+]	13.5 months
2. SEG** (Age ≥ 15 years)	12[c]	45[c]	75/105[+] (71%)	65/113 (58%)	297 days	277 days
3. U.S. Multicenter (Age ≥ 18 years) Italian study	13[c]	45[c]	68/101 (67%)	65/113 (58%)	12.9 months[+]	8.7 months
4. GIMEMA*** (Age ≥ 55 years)	12[c]	45[c]	50/124 (40%)	49/125 (39%)	87 days	169 days

*Memorial Sloan Kettering Cancer Center
**Southeastern Cancer Study Group
*** Gruppo Italiano Malattie Ematologiche Maligne dell' Adulto
[+]Overall $p < 0.05$, unadjusted for prognostic factors or multiple endpoints
[a] Patients who had persistent leukemia after the first induction course received a second course
[b] Cytarabine 25 mg/m^2 bolus IV followed by 200 mg/m^2 daily x 5 days by continuous infusion
[c] Cytarabine 100 mg/m^2 daily x 7 days by continuous infusion

There is no consensus regarding optional regimens to be used for consolidation; however, the following consolidation regimens were used in U.S. controlled trials. Patients received the same anthracycline for consolidation as was used for induction.

Studies 1 and 3 utilized 2 courses of consolidation therapy consisting of idarubicin 12 or 13 mg/m^2 daily for 2 days, respectively (or DNR 50 or 45 mg/m^2 daily for 2 days), and cytarabine, either 25 mg/m^2 by IV bolus followed by 200 mg/m^2 daily by continuous infusion for 4 days (Study 1), or 100 mg/m^2 daily for 5 days by continuous infusion (Study 3). A rest period of 4 to 6 weeks is recommended prior to initiation of consolidation and between the courses. Hematologic recovery is mandatory prior to initiation of each consolidation course.

Study 2 utilized 3 consolidation courses, administered at intervals of 21 days or upon hematologic recovery. Each course consisted of idarubicin 15 mg/m^2 IV for 1 dose (or DNR 50mg/m^2 IV for 1 dose), cytarabine 100 mg/m^2 every 12 hours for 10 doses and 6-thioguanine 100 mg/m^2 orally for 10 doses. If severe myelosuppression occurred, subsequent courses were given with 25% reduction in the doses of all drugs. In addition, this study included 4 courses of maintenance therapy (2 days of the same anthracycline as was used in induction and 5 days of cytarabine).

Toxicities and duration of aplasia were similar during induction on the 2 arms in the U.S. studies except for an increase in mucositis on the IDR arm in one study. During consolidation, duration of aplasia on the IDR arm was longer in all 3 studies and mucositis was more frequent in 2 studies. During consolidation, transfusion requirements were higher on the IDR arm in the 2 studies in which they were tabulated, and patients on the IDR arm in Study 3 spent more days on IV antibiotics (Study 3 used a higher dose of idarubicin).

The benefit of consolidation and maintenance therapy in prolonging the duration of remission and survival is not proven.

Intensive maintenance with idarubicin is not recommended in view of the considerable toxicity (including deaths in remission) experienced by patients during the maintenance phase of Study 2.

A higher induction death rate was noted in patients on the IDR arm in the Italian trial. Since this was not noted in patients of similar age in the U.S. trials, one may speculate that it was due to a difference in the level of supportive care.

DETAILED PHARMACOLOGY

The antitumour activity of idarubicin has been compared with that of daunorubicin against various murine leukemias. After intraperitoneal or intravenous treatment, idarubicin exhibited a comparable anti-leukemic activity and was more potent (approximately 5-6 fold) than the parent compound daunorubicin in the P388 and L1210 systems at the optimal doses. Conversely, in the EL-4 lymphoma model, idarubicin given intravenously, displayed a significantly better therapeutic effect than daunorubicin with a similar potency difference. The activity of idarubicin was also evaluated against disseminated (intravenously-transplanted) murine L1210, and Gross leukemias. Against advanced L1210 idarubicin was capable of significantly prolonging survival time whereas daunorubicin was inactive even at 10-fold higher doses. The effectiveness and the higher potency of idarubicin was also confirmed in the Gross leukemia model.

The antineoplastic efficacy of intravenous idarubicin has also been tested against a number of solid murine tumours. Idarubicin was only partially active against murine solid tumours. Specifically, idarubicin was as effective as daunorubicin on S180 and less active than doxorubicin against mammary carcinoma. In the Lewis lung carcinoma model, idarubicin showed antitumour activity greater than daunorubicin and comparable to doxorubicin, but at a toxic dose (33% of toxic deaths). Against the M5 reticulosarcoma model, idarubicin was inactive, as were daunorubicin and doxorubicin. In addition, idarubicin showed a lower activity than doxorubicin against a number of human solid tumours xenografted into nude mice. It is known however that solid murine tumours have only a relatively low level of predictiveness for clinical activity.

On the basis of the in vitro data which suggested incomplete cross-resistance between idarubicin and doxorubicin or daunorubicin, the in vivo activity of idarubicin was also tested against a

P388/DX leukemia subline. However, given in single intraperitoneal or intravenous doses, idarubicin was not significantly effective against this highly doxorubicin-resistant tumour.

In vivo, idarubicinol exhibited clear antitumour activity after intravenous and intraperitoneal treatment in mice bearing ascitic P388 or disseminated Gross leukemia, although its potency and activity were somewhat lower with respect to the parent drug.

Idarubicin was studied intravenously in mice and rats for other, possible, non-antitumoural activities. It was devoid of central nervous system activity (Irwin's behaviour test, body temperature, spontaneous motility, neuromuscular coordination) even at doses much higher than the LD_{50}.

The acute effect on the cardiovascular system in the rat is considered to be moderate, since a slight decrease in arterial pressure and in heart rate was seen only at doses equal to the LD_{50} which starts 1 hr after treatment. In another study, rats were observed for 36 days after a single intravenous injection of 1 mg/kg. Idarubicin did not alter arterial pressure, heart rate or duration of QRS complexes and only showed prolongation of Q - T interval on the last day.

By comparison, doxorubicin, given at an equitoxic dose of 5 mg/kg, did not alter the arterial pressure, but induced a progressive increase in the heart rate, a slight increase in the duration of the QRS complexes and a much more marked increase in the Q - T interval. Since the prolongation of the Q - T interval is a well-known aspect of anthracycline cardiotoxicity, the results of this study confirm that idarubicin is less cardiotoxic than doxorubicin.

In a series of in vivo and in vitro studies, idarubicin proved to be devoid of effects on the autonomic nervous system, as shown by the absence of interference with the mediators used. Intravenously in the rat, idarubicin induced a marked slowing of gastric emptying: this was already evident at the lowest dose tested, 0.625 mg/kg.

With regard to immunological activity, idarubicin had an inhibitory effect on antibody production (IgM and IgG) at 1/4 to 1/2 of the LD_{50} values, when administered concomitantly with, or after the antigen. This effect was similar to that of doxorubicin given at approximately equitoxic doses. However, unlike doxorubicin, idarubicin does not inhibit the production of antibodies when administered before the antigen. In the test of delayed hypersensitivity, idarubicin showed a slight inhibitory action, while daunorubicin was more active and doxorubicin proved to be inactive. Idarubicin delays skin graft rejection only if administered repeatedly.

In contrast with daunorubicin, idarubicin was found to be significantly more active on an immunogenic leukemia subline (L1210 Ha) than on a non-immunogenic subline (L1210 Cr), probably due to idarubicin interfering less with the antitumour resistance mechanism than daunorubicin.

TOXICOLOGY

In clinical oncology and in particular in the treatment of leukemia, which is and must be

particularly aggressive, the maximum tolerable doses are normally used, and are, therefore, of the order of magnitude of the LD_{10} values, expressed in mg/m^2. These values are useful only when degree of exposure as expressed by the area under the curve (AUC) is also taken into consideration.

In the mouse, the LD_{10} of idarubicin was equal to 12.35 mg/m^2. The mouse:man exposure ratio at the same doses is estimated at approximately 5:1 to 10:1. In addition, the metabolism of idarubicin as compared with the less toxic idarubicinol, is more extensive in man than in the mouse. Idarubicinol was shown to be considerably less toxic than idarubicin. These results offer a considerably wide margin of safety for clinical use of idarubicin. Studies in the mouse also indicate that idarubicin is less cardiotoxic than either daunorubicin or doxorubicin when evaluated at dose ratios which result in similar antileukemic efficacy for the 3 drugs.

Studies were carried out with idarubicin in the rat and dog under the same experimental conditions in parallel with doxorubicin. In the rat, idarubicin was approximately twice as toxic as doxorubicin and had a greater effect on the haematolymphopoietic system. At the same time, idarubicin had a more limited effect on the myocardial, renal, hepatic and testicular parenchymae. In the dog, idarubicin was slightly more toxic than doxorubicin due to greater hematological effect, whereas doxorubicin had a greater effect on the renal, hepatic, testicular and myocardial parenchymae. The cardiotoxicity of idarubicin, when compared to its relative toxicity and activity, proved to be lower than that of doxorubicin.

Teratology

Idarubicin is not teratogenic in the rabbit, even at toxic doses. However, it is teratogenic in the rat at doses of 0.1 - 0.2 mg/kg/day or 0.7 - 1.4 mg/m^2.

Carcinogenicity

Idarubicin was studied on female Sprague-Dawley rats treated with a single intravenous dose of 1.8 mg/kg in comparison with doxorubicin administered as an equitoxic dose of 5 mg/kg. Results indicate that idarubicin must be considered to be carcinogenic, a characteristic which it shares with most other antitumoural drugs.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

[Pr]IDArubicin Hydrochloride Injection
Professed
Sterile Solution

This leaflet is part III of a three-part "Product Monograph" published when Idarubicin Hydrochloride Injection was approved for sale in Canada and is designed specifically for Consumers.

This leaflet is a summary and will not tell you everything about Idarubicin Hydrochloride Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Idarubicin Hydrochloride Injection alone or in combination with other anticancer drugs are used in the treatment of:

- Acute non-lymphocytic leukemia (ANLL) as a first line in adult patients
- Acute lymphocytic leukemia (ALL) as a second line in adults and children.

What it does:

Idarubicin Hydrochloride Injection is cancer drug (chemotherapy drug) which works by killing rapidly dividing cells, such as cancer cells. This action can affect normal cells as well.

In people with leukemia, the bone marrow produces abnormal white blood cells. The abnormal white cells are cancer cells (leukemia cells).

When it should not be used:

Do not use the drugs if you:

- are allergic to idarubicin or any of the ingredients of the drug or its container (see **What the important non- medicinal ingredients are**),
- are allergic to other anthracyclines or anthracenediones such as epirubicin, daunorubicin, mitoxanthrone or mitomycin.
- have persistent low blood count (myelosuppression)
- have severe liver, renal or heart disease
- have recent heart attack
- have severe irregular heartbeat
- have history of severe cardiac disease
- have uncontrolled infections
- have been treated with a maximum cumulative dose of idarubicin, doxorubicin, daunorubicin, epirubicin or other anthracyclines or anthracenediones.

What the medicinal ingredient is:
Idarubicin hydrochloride is the active ingredient.

What the important non-medicinal ingredients are:
Glycerol USP/Ph.Eur.
Hydrochloric acid used to adjust pH
Water for Injection USP

What dosage forms it comes in:

Idarubicin Hydrochloride Injection 1mg/mL is a clear red-orange sterile solution to be given intravenously.

WARNINGS AND PRECAUTIONS

Idarubicin Hydrochloride Injection should be given under the supervision of a doctor experienced with the use of anticancer drugs.

Idarubicin Hydrochloride Injection should not be given to patients with the following conditions:

- **A low blood count (bone marrow suppression induced by previous drug therapy or radiotherapy);**
- **A heart disease and/or previous treatment with anthracyclines (cardiotoxic drugs)**

BEFORE you use Idarubicin Hydrochloride Injection talk to your doctor if you:

- Have low blood cell counts;
- Have heart beat disease, recent heart attack or irregular heartbeat;
- Have an infection;
- Have had radiotherapy to chest area;
- Are taking calcium channel blockers, such as amlodipine, diltiazem, verapamil;
- Are pregnant or planning to become pregnant
- Are breast-feeding or planning to breast-feed
- Have been previously treated with Idarubicin Hydrochloride Injection or other anti-cancer drugs, including anthracyclines (cardiotoxic drugs).

As Idarubicin Hydrochloride Injection may be harmful to an unborn child, women should be advised to avoid becoming pregnant. Effective contraceptive methods should be used.

Tell your doctor right away if you become pregnant during treatment. If you have been nursing, you should stop before starting treatment with Idarubicin Hydrochloride Injection. Ask your baby's doctor to recommend a formula that would be best for your baby.

IMPORTANT: PLEASE READ

As Idarubicin Hydrochloride Injection may cause fertility impairment and damage chromosomes in sperm, men undergoing treatment with Idarubicin Hydrochloride Injection, should use effective contraceptive methods.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you have or recently have taken any other medicines including medicines bought without prescription.

Drugs that may interact with Idarubicin Hydrochloride Injection include: cytarabine, other anthracyclines, anthracenediones and calcium channel blockers such amlodipine, diltiazem or verapamil.

Other drugs that may be used in therapy with Idarubicin Hydrochloride Injection may increase the chance of toxic effects include: cyclophosphamide, fludarabine, etoposide, paclitaxel.

Talk to your doctor before you receive a vaccine while treated with Idarubicin Hydrochloride Injection , as the combination may result in a serious infection in patients with a compromised immunity (ie patients taking oral corticosteroids, transplanted patients, elderly patients).

PROPER USE OF THIS MEDICATION

How is Idarubicin Hydrochloride Injection given?
You may receive Idarubicin Hydrochloride Injection through a vein in the arm ("intravenously" or "IV") by your doctor or nurse, usually in the hospital, outpatient department or clinic.

If you are getting many injections, for your convenience, your doctor may insert a catheter (thin tube) or port into a large vein in your body that is placed there as long as it is needed. Medicines get injected through the catheter or port rather than directly into a vein.

How much time does it take to get a treatment with Idarubicin Hydrochloride Injection?
It usually takes about 5-10 minutes to inject Idarubicin Hydrochloride Injection. However, you may get other medicines before or after Idarubicin Hydrochloride Injection, so your entire treatment may last an hour or longer.

How long will I need treatment?

Your doctor will determine the length of your treatment based on your treatment goals, the medicines you receive, and how your body responds to those medicines.

Your treatment cycle will depend on your medical condition and the other chemotherapy medicines you are getting. Idarubicin Hydrochloride Injection is usually given once a day for 3 consecutive days.

Overdose

If you think you are given more Idarubicin Hydrochloride Injection than you should, contact your doctor, nurse, or Poison Control Centre immediately.

Missed dose
If you miss your scheduled treatment with the drug, contact your doctor as soon as possible to schedule your next treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Idarubicin Hydrochloride Injection can have side effects.

Common side effects include:

- Hair loss, which is temporary and usually starts to grow back within 2 or 3 months after you have finished your treatments.
- Infection, as a result of low white blood cell count. The signs of infection include fever over 38°C (100°F), chills or sweating, sore throat or coughing, redness or swelling around a cut, wound or a catheter site, a burning feeling when you urinate, unusual vaginal itching or discharge.
- Nausea and vomiting
- Fatigue, or feeling tired
- Mouth sores
- Anemia, or low red blood cell count
- Red coloration of your urine for 1 to 2 days after administration during active therapy
- Diarrhea with dehydration and symptoms such as skin flushed, dry and pale, less urination
- Sensitivity of irradiated skin
- Hot flashes
- Skin and nail changes or colouration, tingling sensation
- Rash/itch/redness skin allergy

Rare side effects include:

- Severe adverse events such as local tissue damages due to leakage of Idarubicin Hydrochloride Injection from your vein into surrounding tissues with intravenous injection might be observed.
- Serious heart problems in a small percentage of patients
- Urticaria (hives)

IMPORTANT: PLEASE READ

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM		
Symptom /effect	**Talk with your doctor or pharmacist**	
	Only if severe	**In all cases**
• **Low white blood cell count** and symptoms such as increased infection, fever > 38°C, chills or sweating, sore throat, mouth sores, burning feeling when urinating, unusual vaginal itching or discharge		√
• **Anemia** (reduced red blood cell) and symptoms such as feeling weak, dizzy, shortness of breath		√
• **Injection site reactions** such as pain, sores, burning		√
• **Increased bleeding** with symptoms such as dark urines or dark/bloody stool, unexplained bruising		√
• **Cardiovascular problems** with symptoms such as irregular heartbeat, chest pain, swelling of the ankles, shortness of breath / cardiac problems		√
• **Bowel inflammation** (colitis) or, digestive tract bleeding and symptoms such as bloody stools, bloody vomit		√

This is not a complete list of side effects. For any unexpected effects while taking Idarubicin Hydrochloride Injection, contact your doctor or pharmacist.

HOW TO STORE IT

Idarubicin Hydrochloride Injection should be stored at 2-8°C (36°F - 46°F), protect from light.

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be found by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-800-575-1379.

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