PRODUCT MONOGRAPH

Pr

IDAMYCIN*,

idarubicin hydrochloride for injection, House Std.

5 mg and 10 mg vials

and

idarubicin hydrochloride capsules

5 mg, 10 mg and 25 mg

Pr

IDAMYCIN* PFS

idarubicin hydrochloride injection

1 mg/mL (5 mL, 10 mL and 20 mL vials)

Antineoplastic Agent

Pfizer Canada Inc.
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

*TM Pharmacia & Upjohn S.P.A
Pfizer Canada Inc., licensee

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IDAMYCIN*

idarubicin hydrochloride for injection, House Std.

idarubicin hydrochloride capsules

IDAMYCIN* PFS

idarubicin hydrochloride injection

PART I: HEALTH PROFESSIONAL INFORMATION

CAUTION: IDAMYCIN AND IDAMYCIN PFS ARE POTENT DRUGS AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPY DRUGS (SEE **WARNINGS AND PRECAUTIONS**). BLOOD COUNTS AND HEPATIC FUNCTION TESTS SHOULD BE PERFORMED REGULARLY. CARDIAC MONITORING IS ADVISED ESPECIALLY IN THOSE PATIENTS WHO HAVE RECEIVED MEDIASTINAL RADIOTHERAPY, PATIENTS WITH PRE-EXISTING CARDIAC DISEASE OR PREVIOUS THERAPY WITH ANTHRACYCLINES OR ANTHRACENES AT HIGH CUMULATIVE DOSES.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
parenteral	Lyophilised Sterile Powder, 5 mg and 10 mg vials (1mg/mL after reconstitution)	Lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*
parenteral	Solution for injection 1 mg/mL (5mL, 10mL, and 20mL vials)	*For a complete listing see Dosage Forms, Composition and Packaging section.*
oral	Capsules 5 mg , 10 mg, 25 mg	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Injection

IDAMYCIN (idarubicin hydrochloride for injection, house) and IDAMYCIN PFS (idarubicin hydrochloride injection) are 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.

Capsule

IDAMYCIN (idarubicin hydrochloride capsules) 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, whenever the intravenous route is not considered suitable.

IDAMYCIN (idarubicin hydrochloride capsules) may be used in combination chemotherapy regimens involving other cytotoxic agents.

Pediatrics: IDAMYCIN and IDAMYCIN PFS are 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 (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

IDAMYCIN AND IDAMYCIN PFS ARE INTENDED FOR USE UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN CHEMOTHERAPY.

IDAMYCIN AND IDAMYCIN PFS SHOULD NOT BE GIVEN TO PATIENTS WITH PRE-EXISTING BONE MARROW SUPPRESSION INDUCED BY PREVIOUS DRUG THERAPY OR RADIOTHERAPY UNLESS THE BENEFIT WARRANTS THE RISK.

PRE-EXISTING HEART DISEASE AND PREVIOUS THERAPY WITH ANTHRACYCLINES AT HIGH CUMULATIVE DOSES OR OTHER POTENTIALLY CARDIOTOXIC AGENTS ARE CO-FACTORS FOR INCREASED RISK OF IDARUBICIN-INDUCED CARDIAC TOXICITY AND THE BENEFIT TO RISK RATIO OF IDARUBICIN THERAPY IN SUCH PATIENTS SHOULD BE WEIGHED BEFORE STARTING TREATMENT WITH IDAMYCIN OR IMADYCIN PFS.

General

Therapy with IDAMYCIN or IDAMYCIN PFS 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 IDAMYCIN or IDAMYCIN PFS 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.

TOXICITY

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. 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 (ie, acute) or late (ie, delayed) events.

Early (ie, 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 (ie, 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. 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 IDAMYCIN or IDAMYCIN PFS and treatment with vasodilators, diuretics, digitalis, sodium restriction and bed-rest are indicated.

Extravasation and Vascular Effects

Extravasation of IDAMYCIN or IDAMYCIN PFS 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 emetiogenic. 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

Toxicity

IDAMYCIN and IDAMYCIN PFS are potent bone marrow suppressants. 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

IDAMYCIN or IDAMYCIN PFS 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

IDAMYCIN or IDAMYCIN PFS 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).

Special Populations

Pregnant Women:

The embryotoxic potential of idarubicin has been demonstrated in both in vitro and in vivo studies. However, there are no 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 IDAMYCIN or IDAMYCIN PFS is to be used during pregnancy, or if the patient becomes pregnant during therapy.

Nursing Women:

Mothers should be advised not to breastfeed while undergoing chemotherapy with IDAMYCIN or IDAMYCIN PFS.

Monitoring and Laboratory Tests

Therapy with IDAMYCIN or IDAMYCIN PFS requires close observation of the patient and laboratory monitoring (see **WARNINGS AND PRECAUTION**, 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 PRECAUTION**, 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 PRECAUTION**, 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 PRECAUTION**, Hematologic).

ADVERSE REACTIONS

Cardiovascular:
sinus tachycardia, ECG abnormalities, tachyarrhythmias, atrio-ventricular and bundle branch block, asymptomatic reductions in LEVF, 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, 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 (eg. 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 (eg. cyclophosphamide, paclitaxel), as well as the concomitant use of other cardioactive compounds (eg, calcium channel blockers such as amlodipine, diltiazem or verapamil), requires monitoring of cardiac function throughout treatment. Changes in hepatic 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 IDAMYCIN or IDAMYCIN PFS 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.

Capsule

Acute Non-Lymphocytic Leukemia (ANLL)
In adults, for remission induction as front-line therapy or for remission induction in relapsed or refractory patients whenever the intravenous route is not considered suitable, the following dose schedules are recommended:

(a) Monotherapy - 30 mg/m^2 daily for 3 consecutive days;
(b) Combination - 15-30 mg/m^2 daily for 3 consecutive days in combination with other antileukemic agents.

Administration

IV administration:

IDAMYCIN and IDAMYCIN PFS **must not** be administered by intramuscular or subcutaneous injection. Unless specific compatibility data are available, IDAMYCIN and IDAMYCIN PFS 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.

IDAMYCIN and IDAMYCIN PFS 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.

Oral administration:

The capsules should be swallowed whole with some water and should not be sucked, bitten, or chewed.

Reconstitution:

Parenteral Products:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
5mg	5mL Water for Injection USP	5mL	1mg/mL
10mg	10mL Water for Injection USP	10mL	1mg/mL

Preparation of the solution:
Caution in handling of the powder and preparation of the solution must be exercized as skin reaction associated with idarubicin may occur **(**see **SPECIAL HANDLING INSTRUCTIONS).**

IDAMYCIN 5 mg and 10 mg vials should be reconstituted with 5 mL and 10 mL respectively of Water for Injection USP to give a final concentration of 1 mg/mL of idarubicin hydrochloride. Diluents containing bacteriostatic agents are not recommended. The resulting solution is hypotonic and since the vial contents are under negative pressure, particular care should be taken when the needle is inserted to minimize aerosol formation during reconstitution. Inhalation of any aerosol produced during reconstitution must be avoided. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration at 2-8°C. The solution should be protected from exposure to direct light and any unused solution should be discarded.

OVERDOSAGE

Very high doses of IDAMYCIN or IDAMYCIN PFS 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.

With oral administration, the single-dose packaging is designed to minimize the risk of overdosage. While no data exist, should an overdose occur, gastric lavage should be carried out as soon as possible and the patient observed for possible gastrointestinal hemorrhage and severe mucosal damage.

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

IDAMYCIN PFS (idarubicin hydrochloride injection) should be stored at 2-8°C and protected from light.
IDAMYCIN (idarubicin hydrochloride capsules) should be stored at 15-30°C and protected from light.
IDAMYCIN (idarubicin hydrochloride for injection, house) should be stored at 15-30°C and protected from light.

Stability of the Reconstituted Solution:

Storage:
The reconstituted solution is stable for 24 hours at room temperature or for 48 hours under refrigeration. The solution should be protected from exposure to direct light and any unused solution should be discarded.

Incompatibility:
Unless specific compatibility data are available, IDAMYCIN and IDAMYCIN PFS 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 IDAMYCIN and IDAMYCIN PFS 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, IDAMYCIN and IDAMYCIN PFS 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
IDAMYCIN (idarubicin hydrochloride for injection, house) is a sterile, red-orange lyophilized powder.

5 mg Vial -Each vial contains 5 mg of idarubicin hydrochloride USP, and 50 mg of lactose NF.

10 mg Vial - Each vial contains 10 mg of idarubicin hydrochloride USP and 100 mg of lactose NF.

IDAMYCIN PFS (idarubicin hydrochloride injection) is a clear, red-orange, aqueous, preservative-free solution, free from visible particles containing 1 mg/mL idarubicin hydrochloride. The solution is filled in medical grade polypropylene vials.

5 mL Vial - Each vial contains 5 mg of idarubicin hydrochloride USP, 125 mg of Glycerol, USP/Ph.Eur., Water for injection USP q.s., hydrochloric acid NF q.s.

10 mL Vial - Each vial contains 10 mg of idarubicin hydrochloride USP, 250 mg of Glycerol, USP/Ph.Eur., Water for injection USP q.s., hydrochloric acid NF q.s.

20 mL Vial - Each vial contains 20 mg of idarubicin hydrochloride USP, 500 mg of Glycerol, USP/Ph.Eur., Water for injection USP q.s., hydrochloric acid NF q.s.

Capsule

5 mg Capsule -Each capsule contains 5 mg idarubicin hydrochloride USP, microcrystalline cellulose and glyceryl palmito-stearate.

Each capsule is composed of gelatin and contains as inactive ingredients red iron oxide, titanium dioxide and edible white ink.

10 mg Capsule -Each capsule contains 10 mg idarubicin hydrochloride USP, microcrystalline cellulose and glyceryl palmito-stearate.

Each capsule is composed of gelatin and contains as inactive ingredient titanium dioxide, red iron oxide and edible white ink.

25 mg Capsule - Each capsule contains 25 mg idarubicin hydrochloride USP, microcrystalline cellulose and glyceryl palmito-stearate.

Each capsule is composed of gelatin and contains as inactive ingredients titanium dioxide and edible red ink.

Packaging

IDAMYCIN (idarubicin hydrochloride for injection, house) is available in 5 mg and 10 mg vials. The 5 mg and 10 mg vials are packaged and supplied in a single vial carton.

IDAMYCIN PFS (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.

IDAMYCIN (idarubicin hydrochloride capsules) is available as:
5 mg hard gelatin capsules with a red body and cap, imprinted with idarubicin 5 in white ink on the cap.

10 mg hard gelatin capsules with a white body and red cap imprinted with idarubicin 10 in white ink on the cap.

25 mg hard gelatin capsules with a white body and cap imprinted with idarubicin 25 in red ink on the cap.

The 5 mg, 10 mg and 25 mg capsules are packaged and supplied in a single bottle carton containing one capsule.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

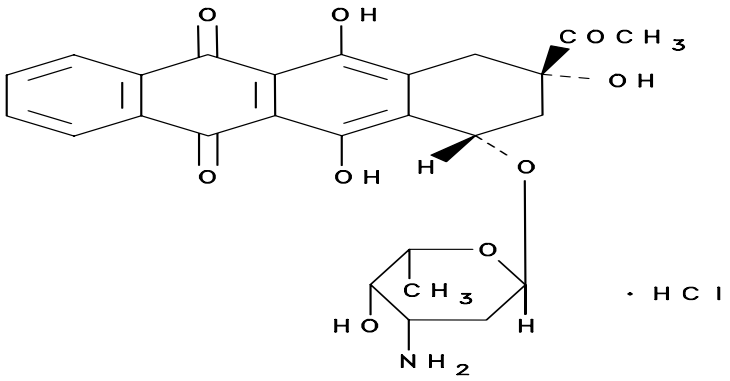
Drug Substance

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

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	
	IDR	DNR	IDR	DNR	IDR	DNR
U.S. Studies						
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)	13_c	45_c	68/101 (67%)	65/113 (58%)	12.9 months$^+$	8.7 months
Italian study						
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 hamatolymphopoietic 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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PART III: CONSUMER INFORMATION

IDAMYCIN
Idarubicin hydrochloride for injection, house
Idarubicin hydrochloride capsule

IDAMYCIN PFS
Idarubicin hydrochloride injection

This leaflet is part III of a three-part "Product Monograph" published when IDAMYCIN and IDAMYCIN PFS were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about IDAMYCIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

IDAMYCIN (idarubicin hydrochloride for Injection, house) and IDAMYCIN PFS (idarubicin hydrochloride injection) are chemotherapy agents used to treat two different types of leukemia (blood cancer):

- Acute non-lymphocytic leukemia (ANLL) in adults and
- Acute lymphocytic leukemia (ALL) in adults and children.

IDAMYCIN Capsule is used to treat one type of blood cancer:
- Acute non-lymphocytic leukemia (ANLL) in adults, whenever the intravenous route is not considered suitable.

IDAMYCIN (idarubicin hydrochloride capsules) may be used in combination with other chemotherapy agents.

What it does:

IDAMYCIN and IDAMYCIN PFS are chemotherapy drugs, often used in combination with other drugs to kill cancer cells. In people with Leukemia, the bone marrow produces abnormal white blood cells. The abnormal cells are leukemia cells (cancer cells). Most chemotherapy agents (including IDAMYCIN and IDAMYCIN PFS) work by killing rapidly dividing cells, such as cancer cells. This action can affect normal cells as well.

When it should not be used:

- If you are allergic to idarubicin or any of the ingredients of the drug or its container (see **What the important nonmedicinal ingredients are**),
- If you are allergic to other anthracyclines or anthracediones such as epirubicin, daunorubicin, mitoxanthrone or mitomycin.
- If you have:
    - Persistent low blood count (myelosuppression)
    - Severe liver, renal or heart disease
    - Recent heart attack
    - Severe irregular heartbeat
    - History of severe cardiac disease
    - Uncontrolled infections
- If you have been treated with a maximum 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:
IDAMYCIN PFS 1mg/mL (idarubicin hydrochloride injection):
Glycerol USP/Ph.Eur.
Hydrochloric acid
Water for Injection USP

IDAMYCIN (idarubicin hydrochloride for injection, house):
Lactose NF

IDAMYCIN (idarubicin hydrochloride capsules):
Glyceryl Palmito-stearate
Microcrystalline cellulose
Each capsule is composed of gelatin and contains as inactive ingredients red iron oxide, titanium dioxide and edible white ink or red ink.

What dosage forms it comes in:

IDAMYCIN PFS 1mg/mL (idarubicin hydrochloride injection) is a clear red-orange sterile solution to be given intravenously.

IDAMYCIN (idarubicin hydrochloride for injection, house) is a red-orange sterile powder to be given intravenously after reconstitution with sterile water for injection.

IDAMYCIN (idarubicin hydrochloride capsule)

WARNINGS AND PRECAUTIONS

BEFORE you use IDAMYCIN or IDAMYCIN PFS talk to your doctor if you have:
- Low blood cell counts;
- Heart disease, recent heart attack or irregular heartbeat;
- Infection;
- Had radiotherapy to chest area;
- If you are taking calcium channel blockers, such as amlodipine, diltiazem, verapamil;
- if you are taking any other medications **(see INTERACTIONS WITH THIS MEDICATION)** ;
- You are pregnant, breast-feeding or planning to become pregnant

As IDAMYCIN and IDAMYCIN PFS 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 IDAMYCIN or IDAMYCIN PFS. Ask your baby's doctor to recommend a formula that would be best for your baby.

As IDAMYCIN and IDAMYCIN PFS may cause fertility impairment and damage chromosomes in sperm. Men undergoing treatment with IDAMYCIN or IDAMYCIN PFS, should use effective contraceptive methods.

Will I be able to work?
Some people work full time, while others work part time or wait until their chemotherapy treatments are finished. It depends on the type of job you have and the side effects you experience.

What happens after treatment?
After you have completed all your chemotherapy treatments, your doctor will check you regularly to make sure the cancer has not returned.

INTERACTIONS WITH THIS MEDICATION

Drug that may interact with IDAMYCIN or IDAMYCIN PFS include: cytarabine, other anthracyclines, anthracenediones and calcium channel blockers such amlodipine, diltiazem or verapamil.

Other drugs that may be used in therapy with IDAMYCIN or IDAMYCIN PFS may increase the chance of toxic effects include: cyclophosphamide, fludarabine, etoposide, paclitaxel.

Previous or concomitant radiotherapy of chest area may also lead to additive toxicity especially with regard to blood cell count and cardiac effects. (see **WARNINGS AND PRECAUTIONS**).

PROPER USE OF THIS MEDICATION

How are* IDAMYCIN and IDAMYCIN PFS *given?
You may receive IDAMYCIN or IDAMYCIN PFS 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.

Is treatment with* IDAMYCIN or IDAMYCIN PFS *painful?
It is unusual to feel pain during the injection, however, if you do feel pain or burning, you should immediately tell your nurse or doctor.

How much time does it take to get a treatment with IDAMYCIN?
It usually takes about 5-10 minutes to inject IDAMYCIN or IDAMYCIN PFS. However, you may get other medicines before or after IDAMYCIN or IDAMYCIN PFS, 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. IDAMYCIN and IDAMYCIN PFS are usually given once a day for 3 consecutive days.

Your first treatment: what to expect
There will be tests
Before you get your first treatment, your doctor will probably order blood tests to check your blood count (white blood cells, red blood cells, and platelets), heart and liver function tests, X-rays or other tests. These "baseline" tests show your current condition, and will be compared to future test results.

You may get one or more medicines
Before your first treatment, you and your doctor will discuss all of the medicines you will receive during the treatment session. In addition to IDAMYCIN or IDAMYCIN PFS, you may get other intravenous (IV) medicines, such as a medicine to prevent nausea, and other chemotherapy medicines. You can also ask your doctor about possible side effects and what to do if you experience any of these side effects.

Receiving your treatment

Your nurse may insert a very thin plastic tube (IV) into your vein, which allows fluid to drip into your vein from a plastic bag. If you are getting a medicine to prevent nausea, you will probably take that medicine first. Then you will get the rest of your IV medicines - including IDAMYCIN or IDAMYCIN PFS- one at a time.

Capsules:

Handling instructions:
You should swallow the capsules whole with some water and should not suck, bit, or chew them.

Missed dose and overdose:
Please communicate with your doctor, should you miss a dose or take more than the dose prescribed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Hearing about all of the side effects from chemotherapy may seem overwhelming. But many people go through chemotherapy with very mild or few side effects.

Other people, who are more sensitive to chemotherapy, may have many side effects - but they can usually be controlled. Everyone reacts in a different way to chemotherapy.

Because IDAMYCIN and IDAMYCIN PFS are given with other chemotherapy medicines, it is sometimes hard to know which medicine is causing a particular side effect. If you are having a problem with side effects, call your doctor or nurse. They can suggest medicines or other ways to prevent or relieve your discomfort. Do not skip doses or make changes in your treatment on your own.

Why do side effects occur?

Chemotherapy medicines work by killing the fastest growing cells in the body, which include cancer cells and some normal cells. Normal cells that grow very rapidly are in your bone marrow, lining of the mouth, stomach, and hair follicles. These fast-growing cells can be affected by the chemotherapy medicines too, sometimes causing side effects such as low white blood cell count, low red blood cell count (anemia), nausea and vomiting, mouth sores, rash, itch and hair loss. These side effects usually disappear after treatment ends. Before your next cycle of chemotherapy, your white blood cell count normally increases and new cells grow back. After your chemotherapy is completely finished, your hair will begin to grow back.

SIDE EFFECTS YOU MAY EXPERIENCE WITH CHEMOTHERAPY

Hair loss

Hair loss is common in chemotherapy with IDAMYCIN and IDAMYCIN PFS. However, the hair loss is temporary, and your hair usually starts to grow back within 2 or 3 months after you've finished your treatments.

Infection

A week or two after a chemotherapy cycle, your white blood cell count may be low. This is the most dangerous time for getting an infection. White blood cells defend your body against infections. When there are very few white blood cells, there may not be enough to fight off an infection. It's important to know the signs of infection so that you can get treatment before the infection becomes serious. 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.

Your doctor may prescribe oral antibiotics to help prevent infection during chemotherapy. Your doctor may also give you a medicine to help increase the number of your white blood cells. If there is evidence of an infection, your doctor may need to admit you to the hospital for a short period of time to receive intravenous antibiotics.

If you have signs of an infection, call your doctor right away. Waiting too long (even a few hours) can lead to a serious illness.

The following tips can help you prevent infections.

- Wash your hands often. Use lotion afterwards to prevent your skin from becoming dry and cracked.
- Bathe or shower every 1 to 2 days.
- Be careful not to cut yourself when you use a knife, scissors, razor or other sharp objects.
- Stay away from people who are sick.
- Have someone else clean cat litter boxes, bird cages or fish tanks.
- Eat well-balanced meals.

Nausea and vomiting

The amount of nausea and vomiting varies widely from person to person. Some have mild nausea and vomiting, while others may have severe nausea and vomiting for a short time after treatment. Nausea and vomiting may start right after a chemotherapy treatment or several hours later. Your doctor can give you medicine to prevent nausea or reduce its severity. If you've been treated with a medicine for nausea, but still feel sick to your stomach or you vomit, tell your doctor. There are other medicines your doctor can give you that may work better for you. You can also try drinking clear fluids (water, diluted soft drinks, apple juice, and broth) or sucking on popsicles and ice chips. Here are some tips that may help reduce nausea.

- Eat small meals or snacks throughout the day instead of 2 or 3 large meals.
- Eat foods that are cold or at room temperature.
- Cut out foods that are fried, spicy, fatty or sweet.
- Stay away from odours that may bother you such as cooking smells, cigarette smoke, car exhaust or perfume.
- Sit upright in a chair after eating - don't lie flat for at least 2 hours.
- Wear loose-fitting clothes, especially around the waist.
- Suck on ice, mints or sour candy (but avoid sour candy if you have mouth sores).
- Eat something light a few hours before your chemotherapy treatment.

Fatigue

Feeling tired - or fatigued - is one of the most common side effects of chemotherapy. Many other factors such as stress, diet, sleeping patterns, and your age can also cause fatigue. For some, fatigue may start to improve 2 to 3 months after you complete your chemotherapy treatments. Here's how you can help reduce fatigue.

- Plan your activities. Allow rest between periods of activity.
- List all of the things you have to do, and number them in order of importance. Only do the things on your list

that must get done. Leave the other tasks for another day.
- Ask family and friends to help you with driving, housework or other tasks. For example, ask your friend to pick up a few things for you the next time she goes to the supermarket.
- Eat a well-balanced diet.
- Do light exercise regularly.

Anemia

Chemotherapy medicines affect the bone marrow, which is where red blood cells are formed. Red blood cells carry oxygen to the muscles and other tissues in your body. When there are too few red blood cells, your muscles, and other body tissues can't get enough oxygen to do their work, and you feel exhausted. If your red blood cell count drops very low, you may also feel weak or dizzy, or may have shortness of breath. These are all symptoms of anemia. If you have these symptoms, tell your doctor or nurse. Your doctor may give you medicine to treat anemia that is caused by chemotherapy. Do not start taking iron tablets on your own - they may not work for anemia caused by chemotherapy medicines and can make your nausea worse.

Mouth sores

Chemotherapy medicines may cause sores in your mouth and throat about a week or two after a chemotherapy treatment. It's important to keep your mouth clean during the time you're having chemotherapy because mouth sores can be a source of infection. Be sure to brush your teeth after each meal with a soft toothbrush. You should also see your dentist before you start chemotherapy to have your teeth cleaned and to take care of any dental work you might need. Mouth sores can be painful, but there are a few things you can do to relieve the pain and prevent further irritation.

- Talk to your doctor about medicines you can use to relieve painful mouth sores. There are anesthetic lozenges and sprays you can use to numb the sores before you eat.
- Eat your food cold or at room temperature. Eating warm or hot food can irritate your mouth sores.
- Cook your food until it's soft and tender.
- Eat soft, smooth foods such as applesauce, bananas, cooked cereals, scrambled eggs, yogurt, noodles, macaroni and cheese, mashed potatoes, cottage cheese, custards, puddings, milk shakes, and ice cream. You can also make foods smoother and easier to eat by pureeing them in a blender. Some people enjoy eating baby food as the pureed fruits are tasty, easy to store, and ready to eat.
- Cut out spicy or acidic foods (citrus fruits or tomatoes) or rough, coarse foods that can irritate mouth sores such as toast and raw vegetables.
- Use a straw to drink liquids. Rinse your mouth with water to remove pieces of food that may get stuck in the mouth sore.
- Avoid mouthwashes that contain alcohol, smoking cigarettes or drinking alcoholic beverages (beer, wine, and hard liquor).

Coloration of Urine

You can expect to see red coloration of your urine for 1 to 2 days after administration during active therapy.

At site of injection

Severe adverse events such as local tissue damages due to leakage of IDAMYCIN or IDAMYCIN PFS from your vein into surrounding tissues with intravenous injection might be observed. If you start to have pain, redness, or swelling where the intravenous injection is given tell your doctor or nurse right away.

Possible long-term cardiac risks after receiving IDAMYCIN or IDAMYCIN PFS

In a small number of patients, there may be serious side effects after treatment has ended including heart problems, which may include damage to the heart muscle or heart failure. Up to 3.5% of patients may have heart problems, either during treatment or many years later. Few patients treated with IDAMYCIN or IDAMYCIN PFS have had serious heart problems caused by their treatment.

You may also experience*:*

- Sensitivity of irradiated skin
- Urticaria (hives)
- Hot flashes
- Skin and nail changes or colouration, tingling sensation
- Rash/itch/redness skin allergy
- Diarrhea with dehydration and symptoms such as skin flushed, dry and pale, less urination

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, unusal vaginal itching or discharge		✓
• **Anemia** and symptoms such as feeling weak, dizzy, shortness of breath		✓
• **Injection site reactions** such as pain, sores, burning		✓
• **Reduced red blood cell important for blood clotting and increased bleeding** with symptoms such as dark urine or dark/bloody stool, unexplained bruising, colour change in the mouth mucosa		✓
• **Cardiovascular problems** with symptoms such as irregular heartbeat,chest pain, swelling of the ankle, 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 IDAMYCIN or IDAMYCIN PFS, contact your doctor or pharmacist.

HOW TO STORE IT

IDAMYCIN PFS (idarubicin hydrochloride injection) should be stored at 2-8°C and protected from light.
IDAMYCIN (idarubicin hydrochloride capsules) should be stored at 15-30°C and protected from light.
IDAMYCIN (idarubicin hydrochloride for injection, house) should be stored at 15-30°C and protected from light.

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, may be obtained by contacting the sponsor, Pfizer Canada Inc. at: 1-800-463-6001.

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