Drug Monograph

A - Drug Name

IDArubicin

COMMON TRADE NAME(S): Idamycin®

back to top

B - Mechanism of Action and Pharmacokinetics

Idarubicin is an analogue of daunorubicin. It is 5 to 6 times more potent than daunorubicin. The mechanism of action of anthracyclines is poorly understood. Cytotoxicity is generally attributed to intercalation of the drug into DNA and inhibition of DNA topoisomerase II activity resulting in double and single strand DNA breaks.

Absorption	Bioavailability	Oral: Rapid but erratic absorption, about 35% bioavailability.
Distribution	Bone marrow, extensive tissue uptake and plasma protein binding	
	Cross blood brain barrier?	yes
	PPB	97 %
Metabolism	Mainly in liver	
	Active metabolites	Idarubicinol
	Inactive metabolites	yes
Elimination	Eliminated by biliary and renal excretion, mostly as idarubicinol.	
	Feces	17% (IV) 8% (oral) over 5 days

Urine	16% (IV) 5% (oral) over 4 days
Half-life	15 hours; 72 hrs for idarubicinol

back to top

C - Indications and Status

Health Canada Approvals:

- Acute lymphocytic leukemia
- Acute non-lymphocytic leukemia

Refer to the product monograph for a full list and details of approved indications.

back to top

D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: Vesicant

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare, transient, or bundle branch block)	I
	Heart failure (2%) (severe)	D L
	Myocarditis (rare)	E
	Pericarditis (rare)	E
	Venous thromboembolism	E
Dermatological	Alopecia (75%) (usually partial)	E
	Nail disorder	E
	Radiation recall reaction (rare)	I
	Rash	E
	Urticaria	E
Gastrointestinal	Abdominal pain	E
	Anorexia	E

	Dehydration	E
	Diarrhea	E
	Dyspepsia	E
	GI hemorrhage	E
	GI perforation (rare)	E
	Mucositis (50%)	E
	Nausea, vomiting (80%)	I
	Typhlitis (rare)	E
Hematological	Hemorrhage	E
	Myelosuppression (nadir 7-14 days, recovery 21-24 days)	E
Hepatobiliary	↑ LFTs (transient, 20-30%)	E
Hypersensitivity	Anaphylaxis (rare)	I
Infection	Infection	E
	Sepsis	E
Injection site	Injection site reaction (flare reaction - histamine release)	I
	Phlebitis (chemical)	I
Metabolic / Endocrine	Hyperuricemia	I
Neoplastic	Leukemia (secondary)	L
Reproductive and breast disorders	Infertility	E
	Other (menopausal symptoms)	E
Urinary	Urine discoloration (red, for 1-2 days)	I
Vascular	Flushing (facial; with rapid injection)	I

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Myelosuppression and cardiotoxicity are the major dose-limiting side effects.

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (e.g., some leukemias and lymphomas), can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalinized, by addition of sodium bicarbonate to the IV fluids.

Acute life-threatening arrhythmias have been occasionally described during therapy. Cardiac toxicity is as described for other anthracyclines, manifested by congestive heart failure or by a decrease in left ventricular ejection fraction that may occur during or several weeks to years after therapy. There is no currently recommended maximum cumulative lifetime dose for idarubicin; however, cardiomyopathy was reported in 5% of patients who received cumulative idarubicin IV doses of 150 to 290 mg/m^2. Cumulative oral doses of < 400mg/m^2 have a low probability of cardiotoxicity. The risk of cardiotoxicity is increased with cardiac radiation, other cardiac abnormalities or prior exposure to anthracyclines, other cardiotoxic agents and trastuzumab; such patients should be carefully monitored.

The ***tissue necrosis*** that occurs with ***extravasation*** may happen days to weeks after the treatment. Patients must be observed for delayed reactions and prior injection sites carefully inspected. ***Local erythematous streaking along the vein and facial flushing*** may result from too rapid administration.

Idarubicin has the potential to enhance radiation injury to tissues. While often called ***radiation recall reactions***, the timing of the radiation may be before, concurrent with or even after the administration of idarubicin. Recurrent injury to a previously irradiated site may occur weeks to months following radiation.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline

Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Consider prophylaxis with allopurinol and hydration for patients at risk of tumour lysis.

Guidelines for dosing also include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

Adults:

Intravenous:

- q3w: 8 mg/m^2 IV daily x 5 days (ANLL)
- q3w: 12 mg/m^2 IV daily x 3 days (ANLL or ALL)

Dosage with Toxicity:

Dosage with changes in cardiac function:

- Discontinue at first sign of impaired cardiac function; investigate and treat appropriately.

Dosage with myelosuppression:

- Modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Hematologic and Non-Hematologic Toxicities."

Management of Infusion-related reactions with Anthracyclines:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms.	• Consider pre-medications and administering at a slower infusion rate.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital symptoms have been affected. • Consider desensitization if therapy is necessary.

Dosage with Hepatic Impairment:

Do not treat with severe hepatic impairment.

Bilirubin (µmol/L)	% usual dose
> 40-85	50%
>85	OMIT

Dosage with Renal Impairment:

Creatinine (µmol/L)	% usual dose
> 200	50%
Severe impairment	Discontinue

Dosage in the elderly:

There is an increased rate of adverse events in patients ≥ 60 years (cardiac).

Children:

- 8-10 mg/m^2/day IV x 3 days. Children may be more at risk of developing cardiac toxicity.

back to top

F - Administration Guidelines

Intravenous

- Slow push through sidearm of free flowing IV (5% Dextrose, Normal Saline, or 2/3-1/3); Give over 5-10 minutes.
- Direct IV push not recommended due to risk of extravasation
- Slow down injection rate if erythematous streaking or facial flushing occurs.
- Diluents containing bacteriostatic agents are not recommended.
- When admixed with heparin, precipitation may occur.

The oral dosage form has been discontinued by the manufacturer.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

back to top

G - Special Precautions

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Mutagenicity: Yes
- Genotoxicity: Yes
- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Documented in animals
  Idarubicin is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **6.5 months** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **3.5 months** after the last dose.
- Excretion into breast milk: Likely
  Breastfeeding is not recommended during treatment and for **14 days** after the last dose.
- Fertility effects: Probable

Other:

Idarubicin is **contraindicated** in patients with a history of allergic reactions to the drug, its excipients or other anthracyclines or anthracenediones, pre-existing myelosuppression, severe renal and liver impairment, uncontrolled infections, recent myocardial infarction, severe cardiac disease, severe arrhythmias, or prior maximal cumulative lifetime doses of anthracyclines or anthracenediones. Do not use live vaccines.

Cardiac toxicity is cumulative across members of the anthracycline (doxorubicin, epirubicin, daunorubicin, idarubicin) and anthracenedione (mitoxantrone) classes of drugs. Patients who have received these agents are at increased risk of toxicity, and should be carefully monitored. The cumulative doses are lower in patients who have received radiation to the mediastinal area or concomitant therapy with other cardiotoxic agents such as cyclophosphamide.

back to top

H - Interactions

No formal interaction studies have been performed to date. Since idarubicin is an anthracycline it may interact with radiation and drugs in a manner similar to doxorubicin. Please refer to the **Doxorubicin** monograph for details.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Other cardiotoxic drugs (ie. trastuzumab cyclophosphamide, paclitaxel)	↑ risk of cardiotoxicity	Additive cardiotoxic effects	Avoid. Monitor cardiac function if must use. Avoid use for ≥ 24 weeks after stopping trastuzumab.
Drugs that suppress cardiac contractility (ie. Verapamil)	May exacerbate cardiotoxicity		Caution; monitor cardiac function closely
Medications that may cause GI complications (ie. NSAIDS)	↑ risk of gastrointestinal perforation or bleeding (associated with oral idarubicin)		Caution

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Renal function tests	Baseline and regular
Liver function tests	Baseline and regular
CBC	Baseline and regular
Cardiac tests for all patients with cardiac risk factors, or patients at or above 150mg/m^2 IV cumulative dose	periodic
Clinical toxicity assessment for cardiac failure, infection, GI toxicity	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Cardiac function tests (Echo, RNA and/or MUGA scans), especially in patients with risk factors for cardiotoxicity	Baseline

back to top

K - References

Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA)

Idarubicin: Micromedex® Healthcare Series. Accessed March 5, 2009.

Prescribing information: idarubicin. Pfizer Labs (US), April 2022.

Product Monograph: idarubicin. Pfizer Canada, February 2009 and September 2022.

Summary of product characteristics: Idarubicin. Pfizer Ltd (UK), Sep 2022.

October 2023 Modified Indications and Pregnancy/lactation sections

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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back to top