

DRUG NAME: Idarubicin**SYNONYM(S):** Idarubicin Hydrochloride, IDR, 4-Demethoxydaunorubicin, 4-DMDR, IMI 30, SC 33428^{1,2}**COMMON TRADE NAME(S):** IDAMYCIN®, IDAMYCIN PFS®**CLASSIFICATION:** antitumour antibiotic*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Idarubicin (demethoxydaunorubicin)³ is a highly lipophilic molecule metabolized to the active metabolite idarubicinol.⁴ It is 5-6 times more potent than daunorubicin; its metabolite, idarubicinol, is as potent as the parent drug.⁴ Cytotoxic effect is primarily due to its ability to intercalate between DNA base pairs resulting in DNA strand breaks.^{1,3,5} This mechanism involves topoisomerase II, the enzyme that regulates the 3-dimensional structure of DNA.³ Idarubicin inhibits the topoisomerase II enzyme interfering with the replication of DNA and RNA transcription.^{1,3,5,6} In addition, anthracyclines readily bind to iron; this drug-iron complex undergoes reduction to generate free radicals leading to cell death.³ Idarubicin is cell cycle phase-specific and arrests growth in the G1 and G2 phase.⁷

PHARMACOKINETICS:

Oral Absorption	rapidly absorbed, peak 2–4 h ^{5,8}	
Distribution	peak effect in minutes (undetectable after 24 h); idarubicinol plasma levels detectable at 120 h ⁹	
	cross blood brain barrier?	yes
	volume of distribution	1700-1800 L/m ²
	plasma protein binding	not concentration dependent; idarubicin (97%), idarubicinol (94%)
Metabolism	2- or 3-compartment model with correlation between dose and pharmacokinetics; rapidly reduced to idarubicinol in plasma; displays extensive enterohepatic recycling ^{3,8}	
	active metabolite(s)	idarubicinol
	inactive metabolite(s)	none
Excretion	Idarubicin: slow, primarily in bile ⁵ (7-17%) ⁹ ; idarubicinol: primarily renal ⁵ . Urinary elimination may require ≥ 10 days after successive daily injections.	
	urine	idarubicin (2-7%), idarubicinol (8-10%)
	feces ^{9,10}	bile (17%)
	terminal half-life	idarubicin (11–25 h), idarubicinol (41–69 h)
	clearance ^{3,11}	500 mL/min/m ² ; correlated with creatinine clearance
Children	terminal half-life 2.5-22.4 h ¹ ; no difference in half-life between daily and weekly administration ⁵	

Adapted from standard reference⁴ unless specified otherwise.

USES:**Primary uses:**

- *Leukemia, acute myeloid
- *Leukemia, acute lymphocytic

Other uses:

- Breast cancer³
- Lymphoma, non-Hodgkin's³
- Multiple myeloma³
- Leukemia, acute promyelocytic¹²

*Health Canada approved indication

SPECIAL PRECAUTIONS:**Contraindications:**

- history of hypersensitivity to idarubicin, other anthracyclines or anthracenediones (i.e., epirubicin, daunorubicin, mitoxantrone, mitomycin C)⁴
- total bilirubin >86 µmol/L²

Caution:

- Existing or prior **cardiovascular disease**, including severe myocardial insufficiency, recent myocardial infarction, or severe arrhythmias may predispose the patient to cardiac toxicity. Other risk factors for cardiac toxicity include prior or concomitant radiation to the thoracic area, concomitant use of other cardiotoxic agents (e.g., trastuzumab) and previous therapy with anthracyclines/anthracenediones. Baseline ECG and either MUGA or ECHO is recommended. Observe maximum cumulative doses of anthracyclines/anthracenediones.⁴
- **Concomitant or prior radiation** within 2-3 weeks before idarubicin may predispose the patient to increased myelosuppression.⁴

Special populations: Patients over 60 years of age with preexisting cardiac disease or who are taking other cardiotoxic agents experience asymptomatic declines in LVEF more frequently than younger patients.^{4,13}

Carcinogenicity: Idarubicin may cause secondary leukemias, more commonly when given in combination with DNA-damaging antineoplastic agents. These leukemias have a 1 to 3 year latency period.⁴

Mutagenicity: Idarubicin is mutagenic and clastogenic in unspecified tests.⁴

Fertility: Idarubicin has been reported to be toxic to the reproductive organs and can induce chromosomal damage to human spermatozoa. Men are advised to use appropriate contraceptive methods during treatment to prevent pregnancy.⁴

Pregnancy: FDA Pregnancy Category D.^{1,14} There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).¹⁵

Breastfeeding is not recommended due to the potential secretion into breast milk.^{4,5,14} Parent drug and metabolite may require 10 days or longer to be eliminated from breast milk.¹⁴

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.^{12,16}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood and lymphatic system/febrile neutropenia	anemia (10%) ^{1,5,10}
	hemorrhage (63%) ^{5,13} ; does not occur unless thrombocytopenic ¹⁶
	leucopenia (>10%) ^{1,5,10} ; nadir 8-29 days ^{1,10}
	neutropenia (100%) ^{5,17} ; nadir 14-16 days ³
	thrombocytopenia (>10%) ^{5,10} ; nadir 10-15 days ¹
cardiac (see paragraph following Side Effects table)	arrhythmias (<10%) ^{1,5,17}
	atrioventricular and bundle-branch block
	bradycardia
	CHF (>10%); typically dose related ^{1,5,10}
	ECG abnormalities (>10%) ^{1,10}
	LVEF reduction (18%) ¹⁸
	myocarditis/ pericarditis
	tachycardia (>10%) ¹⁰
gastrointestinal	<i>emetogenic potential</i> : low-moderate ^{10,19}
	abdominal pain (51-64%, severe <5%) ^{5,13}
	anorexia ¹
	diarrhea (9-22%) ^{9,10}
	enterocolitis with perforation (<1%) ^{5,13}
	erosions/ulcerations
	esophagitis
	gastrointestinal tract bleeding (30%) ^{9,10}
	mucositis (50%, severe <5%) ^{5,13}
	nausea (22-52%, severe <5%) ^{1,5,13}
	vomiting (30-60%, severe <5%) ^{10,13}
	general disorders and administration site conditions
erythematous streaking from injection site (>10%) ^{1,10} ; occurs with rapid administration	
fatigue	
fever (26%) ^{5,13}	
tissue necrosis after extravasation (>10%) ^{1,10} ; rare when using central lines ¹⁶	
immune system	anaphylaxis ¹
infections and infestations	infection (95%) ^{5,13}
	sepsis
investigations	alkaline phosphatase, increased ¹ (<5%) ⁹
	aspartate aminotransferase, increased ¹ (<5%) ⁹
	creatinine, increased (severe <1%) ^{5,13} ; transient
	gamma-glutamyltransferase, increased ¹ (<5%) ⁹

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	hyperbilirubinemia ¹ (<5%) ⁹
	hyperuricemia ² (<1%) ^{1,10} ; see paragraph following Side Effects table
	lactate dehydrogenase, increased ¹
neoplasms	secondary leukemia AML or ALL, dose-related ²¹ ; may occur 1-3 years after treatment start ¹⁸
renal and urinary	urine discoloration, dark yellow to red (>10%) ^{1,2,4,10} occurs 1-2 days after administration ^{1,10}
respiratory, thoracic and mediastinal	pulmonary effects, allergy-related pulmonary symptoms(2%) ^{5,13}
	pulmonary effects, unspecified (39%) ^{5,13}
skin and subcutaneous tissue	alopecia (25-77%) ^{5,9,10}
	bullous erythema (25%) ^{1,5,13} ; affects palms and soles
	radiation recall reaction (>10%) ^{4,10,13}
	skin/nail hyperpigmentation
	skin rash (11%) ^{1,5}
	urticaria (>10%) ¹⁰
vascular	tumour lysis syndrome (<1%) ¹⁰ ; see paragraph following Side Effects table
	phlebitis/thrombophlebitis
	thromboembolism

Adapted from standard reference⁴ unless specified otherwise.

Hyperuricemia may result from cell lysis by idarubicin and may lead to electrolyte disturbances or acute renal failure.²² It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients²³:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.²⁴ It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminium hydroxide (AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.²⁵

Cardiotoxicity is thought to be due to free radical damage as myocardial tissue is susceptible to these highly reactive species.¹⁸ Anthracycline cardiotoxicity may present with early or late effects.^{4,26} The following information applies to all anthracyclines, anthracenediones and mitoxantrone.^{18,26,27}

Early cardiotoxic effects are not dose-related and may present from mild ECG changes to life-threatening arrhythmias.^{4,18,27} These events may occur during or immediately after a single dose of anthracycline treatment,^{18,27} but do not predict subsequent development of delayed cardiotoxicity and are not considered indications for suspension of therapy.^{4,18,27-30}

Late cardiotoxic effects, which are dose-related and clinically the most important type of cardiotoxic effect, present as reduced LVEF or symptomatic CHF, and typically occur weeks to years after completion of treatment.^{18,26-29} Abnormalities in LVEF are associated with all the anthracyclines and their derivatives.²⁶ LVEF changes are related to the total cumulative dose, are irreversible and refractory to medical therapy.^{18,31}

Prevention and treatment: Cardiac assessment should occur at baseline and throughout therapy. Monitor for symptomatic congestive heart failure (CHF) or reduced left ventricular ejection fraction (LVEF). Sensitive, non-invasive methods to measure LVEF include radionuclide angiography (RNA), MUGA, or echocardiogram.²⁶ Late cardiotoxic effects may be prevented by stopping treatment with the associated anthracycline once patients have reached the suggested maximum cumulative dose.^{18,31} Management of anthracycline cardiotoxicity includes discontinuation of the drug and initiating standard treatment of CHF.²⁶

Cardiotoxicity risk can be reduced but not eliminated with the use of alternative anthracyclines (i.e., epirubicin or liposomal doxorubicin) or by altering the frequency of administration (once a week vs. once every 3 weeks, or continuous infusion).²⁶ Cardioprotectant therapy with dexrazoxane may be considered for patients with cumulative doxorubicin-equivalent doses greater than 300 mg/m².^{27,32,33}

Cumulative doses should be calculated using the following table, taking into account all previous anthracyclines or anthracenediones received during the patient's lifetime.

AGENT	SUGGESTED CONVERSION FACTOR TO DOXORUBICIN DOSE ^{21,34,35*}	SUGGESTED MONITORING THRESHOLD ^{26,36-42**}
DAUNOrubicin	x 0.5-0.83	450 mg/m ²
DOXOrubicin	x 1	300 mg/m ²
epirubicin	x 0.5-0.67	600 mg/m ²
IDArubicin	x 2-5	150 mg/m ²
mitoXANTRONE	x 2.2-4	140 mg/m ²

* based on relative hematological toxicities²¹

** Treatment may continue beyond these doses in selected patients, if the clinician has considered the potential risks and benefits. The addition of dexrazoxane may be considered, and monitoring should be increased. Maximum tolerated doses are variable; some patients may tolerate doxorubicin equivalent doses exceeding 1000 mg/m² while other patients exhibit symptomatic CHF at doxorubicin equivalent doses less than 300 mg/m².

INTERACTIONS :

AGENT	EFFECT	MECHANISM	MANAGEMENT
trastuzumab ^{1,4}	increased risk of cardiac dysfunction	ventricular dysfunction and CHF enhanced with combination	modify therapy based on change in baseline ECG and MUGA or ECHO; wait 24 weeks after trastuzumab before starting idarubicin
vaccines, live (i.e., BCG, influenza, measles) ^{1,4,9,13}	increased risk of serious infection and diminished therapeutic effect of vaccine	decreased immune response allows live vaccine to produce infection	avoid vaccination with live vaccines during treatment; use live vaccine no sooner than 3 months post treatment
vaccines, inactivated ^{1,4,13}	risk of diminished therapeutic effect of vaccine	no information found	vaccinate prior to treatment or delay vaccination if possible

Induction or inhibition of P-glycoprotein (PGP) in the biliary tract may lead to increased or decreased excretion of idarubicin into the bile.^{1,11}

SUPPLY AND STORAGE:

Injection: Pfizer Canada Inc. supplies idarubicin as 5 mg and 10 mg vials of sterile lyophilized powder. Vials contain lactose. Store at room temperature. Protect from light.⁴

Pfizer Canada Inc. and Pharmaceutical Partners of Canada Inc. supply idarubicin as 5mg, 10 mg, and 20 mg single-use (preservative free) vials of aqueous solution in a concentration of 1 mg/mL. Refrigerate. Protect from light.^{2,4,43}

For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

Additional information: compatible with D5W and saline solutions.^{4,44}

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold, italics***

Subcutaneous	not used due to corrosive nature ^{4,5,10}
Intramuscular	not used due to corrosive nature ^{4,5,10}
<i>Direct intravenous</i>	over 3 -10 minutes ^{4,10} into tubing of running IV; see BC Cancer III-20 Policy Prevention and Management of Extravasation of Chemotherapy
Intermittent infusion	over 10-15 minutes into tubing of running IV of NS or D5W ^{2,10}
Intraperitoneal	has been used ^{2,4,10}
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	bladder instillation in 50 mL NS has been used ^{2,10,45}

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

<i>Intravenous:</i> ^{4,10,13}	Cycle Length:	
	3 weeks	<i>8 mg/m² IV once daily for 5 consecutive days starting on day 1</i>
	28 days	<i>12 mg/m² IV once daily for 3 consecutive days starting on day 1</i>

BC Cancer usual dose noted in ***bold, italics***

Cycle Length:

Concurrent radiation: no information found*Dosage in myelosuppression:* modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"*Dosage in renal failure:*^{2,10}

Creatinine clearance (mL/min)	Dose
≥50	100%
Children <50 Adults 10 - 50	75%
Adults <10	50%
<25	discontinue

Calculated creatinine clearance = $\frac{N \times (140 - \text{Age}) \times \text{weight in kg}}{\text{Serum Creatinine in } \mu\text{mol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

Bilirubin, total ($\mu\text{mol/L}$) ¹⁰		AST (IU/L) ¹³	Dose
40-86	or	60-180	50%
>86		-	omit

Dosage in dialysis: no supplemental doses required in hemodialysis or continuous ambulatory peritoneal dialysis^{5,10}**Children:**

Cycle Length:

Intravenous 3 weeks 10-12 mg/m² IV daily for 3 days starting on day 1^{1,4,10}**REFERENCES:**

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