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/m²
	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/m²; 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 reference [4] unless specified otherwise.

Developed: 1 May 2011
Revised: 1 March 2025

USES:

Primary uses:
*Leukemia, acute myeloid
*Leukemia, acute lymphocytic

Other uses:
Breast cancer [3]
Lymphoma, non-Hodgkin's [3]
Multiple myeloma [3]
Leukemia, acute promyelocytic [12]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity to idarubicin, other anthracyclines or anthracenediones (e.g., epirubicin, daunorubicin, mitoxantrone, mitomycin C) [4]
- total bilirubin >86 micromol/L [2]

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 can have a 1 to 3 year latency period. [14]

Mutagenicity: Idarubicin was genotoxic in most of the *in vitro* and *in vivo* tests performed. [14]

Fertility: Idarubicin has been reported to be toxic to the reproductive organs and can induce chromosomal damage to human spermatozoa. Fertility preservation should be considered by male and female patients of reproductive potential prior to treatment. [14]

Pregnancy: There are no controlled studies in pregnant women. However, idarubicin is genotoxic. Embryotoxic potential has been demonstrated in both *in vitro* and *in vivo* studies. In animal studies, idarubicin has been shown to be teratogenic in rats, but not rabbits. In female patients of reproductive potential, contraception is recommended during treatment and for at least 6.5 months after the last dose. In male patients with female partners of reproductive potential, contraception is recommended during treatment and for at least 3.4 months after the last dose. [14]

Breastfeeding is not recommended due to the potential secretion into breast milk. Parent drug and metabolite may require 10 days or longer to be eliminated from breast milk. [15] Lactating women should not breastfeed during treatment and for at least 14 days after the last dose. [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

Developed: 1 May 2011
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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	*emetogenic potential:* low to moderate [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	***extravasation hazard****:* vesicant [20]
	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]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	aspartate aminotransferase, increased [1] (<5%) [9]
	creatinine, increased (severe <1%) [5,13]; transient
	gamma-glutamyltransferase, increased [1] (<5%) [9]
	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 reference [4] 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 patients [23]:

- 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. Aluminum hydroxide (AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate. [25]

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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 radionucleotide 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/m^2. [27,32,33]

Cumulative doses should be calculated and account for all previous anthracyclines or anthracenediones received during the patient's lifetime. For further information on suggested conversion factors and monitoring thresholds for anthracyclines, see ***Dose Conversion for Anthracyclines Exposure*** in Appendix.

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 [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]

Developed: 1 May 2011
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SUPPLY AND STORAGE:

***Injection*:** Pfizer Canada ULC supplies idarubicin as 5 mg, 10 mg, and 20 mg ready-to-use single-use (preservative free) vials in a concentration of 1 mg/mL. Refrigerate. Protect from light. [14]

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. [4,34]

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]
Direct intravenous	over 3 -10 minutes [4,10] into tubing of running IV; see ***Systemic Therapy Policy III-20: 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 [2,10,35]

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***

	Cycle Length:	
Intravenous: [4,10,13]	3 weeks:	8 mg/m² IV once daily for 5 consecutive days starting on day 1
	28 days:	12 mg/m² IV once daily for 3 consecutive days starting on day 1
Concurrent radiation:	no information found	

Developed: 1 May 2011
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BC Cancer usual dose noted in ***bold, italics***

Dosage in myelosuppression:

Cycle Length: 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

$$\text{Calculated creatinine clearance} = \frac{\text{N* x (140 - Age) x weight in kg}}{\text{Serum Creatinine in µmol/L}}$$

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

Dosage in hepatic failure:

Bilirubin, total (micromol/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]

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Developed: 1 May 2011
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Developed: 1 May 2011
Revised: 1 March 2025