DRUG NAME: Idarubicin

SYNONYM(S): Idarubicin Hydrochloride, IDR, 4-Demethoxydaunorubicin, 4-DMDR, IMI 30, SC 33428\(^1\,^2\)

COMMON TRADE NAME(S): IDAMYCIN\textsuperscript{®}, IDAMYCIN PFS\textsuperscript{®}

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.\(^1\,^3\) 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.\(^1\,^3\,^5\) 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:

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Absorption</td>
<td>rapidly absorbed, peak 2–4 h(^5,^6)</td>
</tr>
<tr>
<td>Distribution</td>
<td>peak effect in minutes (undetectable after 24 h); idarubicinol plasma levels detectable at 120 h(^6)</td>
</tr>
<tr>
<td></td>
<td>cross blood brain barrier? yes</td>
</tr>
<tr>
<td></td>
<td>volume of distribution 1700-1800 L/m(^2)</td>
</tr>
<tr>
<td></td>
<td>plasma protein binding not concentration dependent; idarubicin (97%), idarubicinol (94%)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>2- or 3-compartment model with correlation between dose and pharmacokinetics; rapidly reduced to idarubicinol in plasma; displays extensive enterohepatic recycling(^3,^8)</td>
</tr>
<tr>
<td></td>
<td>active metabolite(s) idarubicinol</td>
</tr>
<tr>
<td></td>
<td>inactive metabolite(s) none</td>
</tr>
<tr>
<td>Excretion</td>
<td>Idarubicin: slow, primarily in bile(^5) (7-17%)(^5); idarubicinol: primarily renal(^5). Urinary elimination may require ≥ 10 days after successive daily injections.</td>
</tr>
<tr>
<td></td>
<td>urine idarubicin (2-7%), idarubicinol (8-10%)</td>
</tr>
<tr>
<td></td>
<td>feces(^9,^10) bile (17%)</td>
</tr>
<tr>
<td></td>
<td>terminal half-life idarubicin (11–25 h), idarubicinol (41–69 h)</td>
</tr>
<tr>
<td></td>
<td>clearance(^3,^11) 500 mL/min/m(^2); correlated with creatinine clearance</td>
</tr>
<tr>
<td>Children</td>
<td>terminal half-life 2.5-22.4 h(^1); no difference in half-life between daily and weekly administration(^5)</td>
</tr>
</tbody>
</table>

Adapted from standard reference\(^9\) unless specified otherwise.
USES:

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

Other uses:
Breast cancer
Lymphoma, non-Hodgkin’s
Multiple myeloma
Leukemia, acute promyelocytic

*SPECIAL PRECAUTIONS:

Contraindications:
• history of hypersensitivity to idarubicin, other anthracyclines or anthracenediones (i.e., epirubicin, daunorubicin, mitoxantrone, mitomycin C)
• total bilirubin >86 mcmol/L

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.
• Concomitant or prior radiation within 2-3 weeks before idarubicin may predispose the patient to increased myelosuppression.

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.

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.

Mutagenicity: Idarubicin is mutagenic and clastogenic in unspecified tests.

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.

Pregnancy: FDA Pregnancy Category D. 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).

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.

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.
<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT</th>
</tr>
</thead>
</table>
| blood and lymphatic system/febrile neutropenia | *anemia* (10%)<sup>1,3,10</sup>  
*hemorrhage* (63%)<sup>5,13</sup>; does not occur unless thrombocytopenic<sup>16</sup>  
*leucopenia* (>10%)<sup>1,3,10</sup>; nadir 8-29 days<sup>1,10</sup>  
*neutropenia* (100%)<sup>5,17</sup>; nadir 14-16 days<sup>3</sup>  
*thrombocytopenia* (>10%)<sup>5,16</sup>; nadir 10-15 days<sup>1</sup> |
| cardiac (see paragraph following Side Effects table) | arrhythmias (<10%)<sup>1,5,17</sup>  
atricentric and bundle-branch block  
bradycardia  
*CHF* (>10%); typically dose related<sup>1,5,10</sup>  
ECG abnormalities (>10%)<sup>1,10</sup>  
*LVEF reduction* (18%)<sup>18</sup>  
myocarditis/pericarditis  
tachycardia (>10%)<sup>10</sup> |
| gastrointestinal | *emetogenic potential*: low-moderate<sup>10,19</sup>  
*abdominal pain* (51-64%, severe <5%)<sup>5,13</sup>  
*anorexia*<sup>1</sup>  
*diarrhea* (9-22%)<sup>9,10</sup>  
enterocolitis with perforation (<1%)<sup>5,13</sup>  
erosions/ulcerations  
esophagitis  
gastrointestinal tract bleeding (30%)<sup>9,10</sup>  
mucositis (50%, severe <5%)<sup>5,13</sup>  
*nausea* (22-52%, severe <5%)<sup>1,5,13</sup>  
*vomiting* (30-60%, severe <5%)<sup>10,13</sup> |
| general disorders and administration site conditions | *extravasation hazard*: vesicant<sup>20</sup>  
erythematous streaking from injection site (>10%)<sup>1,10</sup>; occurs with rapid administration  
fatigue  
*fever* (26%)<sup>5,13</sup>  
tissue necrosis after extravasation (>10%)<sup>1,10</sup>; rare when using central lines<sup>18</sup> |
| immune system | anaphylaxis<sup>1</sup> |
| infections and infestations | *infection* (95%)<sup>5,13</sup>  
sepsis |
| investigations | alkaline phosphatase, increased<sup>1</sup> (<5%)<sup>9</sup>  
aspartate aminotransferase, increased<sup>1</sup> (<5%)<sup>9</sup>  
creatinine, increased (severe <1%)<sup>5,13</sup>; transient  
gamma-glutamyltransferase, increased<sup>1</sup> (<5%)<sup>9</sup> |
Idarubicin

**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%)\(^8,9,10\)
- 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\(^6\) 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\(^6\):

- 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 alkalized 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 alkalization 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 (AMPHOGET®) may be added orally if phosphate becomes elevated. If aluminium 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.\(^4,16,27\) 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.\(^7,18,27,30\)
**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. Abnormalities in LVEF are associated with all the anthracyclines and their derivatives. LVEF changes are related to the total cumulative dose, are irreversible and refractory to medical therapy.

**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. Late cardiotoxic effects may be prevented by stopping treatment with the associated anthracycline once patients have reached the suggested maximum cumulative dose. Management of anthracycline cardiotoxicity includes discontinuation of the drug and initiating standard treatment of CHF.

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). Cardioprotectant therapy with dexrazoxane may be considered for patients with cumulative doxorubicin-equivalent doses greater than 300 mg/m².

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

<table>
<thead>
<tr>
<th>AGENT</th>
<th>SUGGESTED CONVERSION FACTOR TO DOXORUBICIN DOSE</th>
<th>SUGGESTED MONITORING THRESHOLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAUNORubicin</td>
<td>x 0.5-0.83</td>
<td>450 mg/m²</td>
</tr>
<tr>
<td>DOXOrubicin</td>
<td>x 1</td>
<td>300 mg/m²</td>
</tr>
<tr>
<td>epirubicin</td>
<td>x 0.5-0.67</td>
<td>600 mg/m²</td>
</tr>
<tr>
<td>IDArubicin</td>
<td>x 2-5</td>
<td>150 mg/m²</td>
</tr>
<tr>
<td>mitoXANTRONE</td>
<td>x 2.2-4</td>
<td>140 mg/m²</td>
</tr>
</tbody>
</table>

* based on relative hematological toxicities

**INTERACTIONS:**

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

Induction or inhibition of P-glycoprotein (PGP) in the biliary tract may lead to increased or decreased excretion of idarubicin into the bile.
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:

<table>
<thead>
<tr>
<th>Method</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous</td>
<td>not used due to corrosive nature4,5,10</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>not used due to corrosive nature4,5,10</td>
</tr>
<tr>
<td><strong>Direct intravenous</strong></td>
<td>over 3 -10 minutes4,10 into tubing of running IV; see BC Cancer III-20 Policy <a href="#">Prevention and Management of Extravasation of Chemotherapy</a></td>
</tr>
<tr>
<td>Intermittent infusion</td>
<td>over 10-15 minutes into tubing of running IV of NS or D5W2,10</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>has been used2,4,10</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>no information found</td>
</tr>
<tr>
<td>Intrapleural</td>
<td>no information found</td>
</tr>
<tr>
<td>Intra-arterial</td>
<td>no information found</td>
</tr>
<tr>
<td>Intravesical</td>
<td>bladder instillation in 50 mL NS has been used2,10,45</td>
</tr>
</tbody>
</table>

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:**

<table>
<thead>
<tr>
<th>Cycle Length</th>
<th>Dosage</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 weeks</td>
<td>8 mg/m² IV once daily for 5 consecutive days starting on day 1</td>
<td>BC Cancer usual dose noted in <strong>bold, italics</strong></td>
</tr>
<tr>
<td>28 days</td>
<td>12 mg/m² IV once daily for 3 consecutive days starting on day 1</td>
<td></td>
</tr>
</tbody>
</table>

[BC Cancer Drug Manual®](#)  
Developed: 1 May 2011  
Revised: 1 July 2019
Idarubicin

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:**

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>100%</td>
</tr>
<tr>
<td>Children &lt;50</td>
<td>75%</td>
</tr>
<tr>
<td>Adults 10 - 50</td>
<td></td>
</tr>
<tr>
<td>Adults &lt;10</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;25</td>
<td>discontinue</td>
</tr>
</tbody>
</table>

Calculated creatinine clearance = \( N \times (140 - \text{Age}) \times \text{weight in kg} \)

Serum Creatinine in µmol/L

* For males \( N=1.23 \); for females \( N=1.04 \)

**Dosage in hepatic failure:**

<table>
<thead>
<tr>
<th>Bilirubin, total (µmol/L)</th>
<th>AST (IU/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-86</td>
<td>or 60-180</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;86</td>
<td>-</td>
<td>omit</td>
</tr>
</tbody>
</table>

**Dosage in dialysis:** no supplemental doses required in hemodialysis or continuous ambulatory peritoneal dialysis

**Children:**

**Intravenous** Cycle Length: 3 weeks 10-12 mg/m² IV daily for 3 days starting on day 1

**REFERENCES:**

17. Tom Nevill MD. Personal communication. Leukemia/BMT Program; 14 April 2011.