Drug Monograph

A - Drug Name

DAUNOrubicin

SYNONYM(S): Daunomycin; Rubidomycin

COMMON TRADE NAME(S): Cerubidine®

back to top

B - Mechanism of Action and Pharmacokinetics

Daunorubicin was originally isolated from Streptomyces caeruleorubidus and entered clinical trials in the early 1960's. It is an anthracycline antibiotic, which damages DNA by intercalation, metal ion chelation, or by generation of free radicals. Daunorubicin has also been shown to inhibit DNA polymerases and affect regulation of gene expression. Cytotoxic activity is cell cycle phase-nonspecific.

Absorption	Bioavailability	oral: no
Distribution	Rapid and wide distribution. Highest levels in liver, kidneys, lungs, spleen and heart. Crosses placenta.	
	Cross blood brain barrier?	No
	PPB	63%
Metabolism	Rapidly metabolized in the liver and other tissues, mainly by cytoplasmic aldo-keto reductases.	
	Active metabolites	Daunorubicinol (major metabolite)
	Inactive metabolites	yes

Elimination	Triphasic elimination of unchanged drug and metabolites. Hepatobiliary secretion in feces is predominant route of elimination (40%).	
	Urine	Slow elimination; 25% within the first 5 days
	Half-life	daunorubicin 18.5 h (terminal), daunorubicinol 26.7 h (terminal)

back to top

C - Indications and Status

Health Canada Approvals:

- Acute myeloblastic and acute lymphoblastic leukemias
- Chronic myelogenous leukemia
- Ewing's sarcoma
- Wilm's tumour
- Reticulosarcoma
- Lymphosarcoma

back to top

D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: Vesicant

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (transient, 6-30%)	I
	Cardiotoxicity	D L
	Flushing (facial; with rapid injection)	I
	Pericarditis / myocarditis	E
Dermatological	Alopecia (common)	E
	Radiation recall reaction (rare)	I
	Rash	I E

	Skin hyperpigmentation (or nail)	E
Gastrointestinal	Abdominal pain	E
	Anorexia	E
	Constipation	E
	Diarrhea	E
	Mucositis	E
	Nausea, vomiting (85%)	I
Hematological	Myelosuppression ± infection, bleeding (may be severe; nadir 10-14 days, recovery around 21 days)	E
Hepatobiliary	↑ LFTs (may be severe)	E D
Hypersensitivity	Hypersensitivity	I
Injection site	Injection site reaction (pain, burning – may be severe; flare reaction - histamine release)	I
Metabolic / Endocrine	Hyperuricemia (during periods of active cell lysis)	I
Neoplastic	Leukemia (secondary)	L
Renal	Renal failure (rare)	E
Reproductive and breast disorders	Infertility	L
Urinary	Urine discoloration (red, for 1-2 days)	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)

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 patents the urine may be alkalinized, by addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

Cardiac toxicity includes either an acute, transient or delayed onset type (related to cumulative dose). The acute type is uncommon; it usually occurs after a single dose/course and involves non-dose related electrocardiographic abnormalities (e.g. ST-T wave changes, QT prolongation) and arrhythmias. Pericarditis and myocarditis have been reported rarely. The non-specific electrocardiographic changes are reversible and do not generally indicate impending development of cardiomyopathy.

Delayed cardiotoxicity is irreversible, reflecting a progressive injury and loss of cardiac myocytes leading to left ventricular dysfunction, conduction disturbances, arrhythmias or heart failure. The risk

factors are high cumulative dose (1-2% CHF incidence at a total cumulative dose of 550 mg/m^2 in adults), thoracic radiation, pre-existing heart disease and prior therapy with anthracyclines or other cardiotoxic drugs. Management of daunorubicin-induced CHF is discontinuation of the anthracycline and standard treatment of CHF. Cardiac dysfunction may appear several months to years after anthracycline therapy, therefore monitoring should continue after therapy is complete.

Clinical cardiotoxicity in children increases rapidly at a cumulative dose of about 300 mg/m^2 (children > 2 years of age), but individual patients may have a lower threshold and develop toxicity at a significantly lower dose. Impaired left ventricular systolic performance, contractility or CHF may occur in pediatric patients months to years after anthracycline discontinuation. Pediatric patients with daunorubicin-induced CHF are very sensitive to digitalis. Consult pediatric specific guidelines for dosing and recommendations regarding monitoring of cardiac function.

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 inspected carefully.

Daunorubicin produces more **vomiting** than doxorubicin, with 85% of patients in one study treated with 1 mg/kg per day for 5 days reporting either nausea or vomiting.

Daunorubicin 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 daunorubicin. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

back to top

E - Dosing

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 white blood cell count.

Dosage should be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy or when given in combination with other cytotoxics. Total cumulative doses should not exceed:

- 10 mg/kg (children of less than 2 years)
- 300mg/m^2 (children 2 years or older)
- 550mg/m^2 (adults)
- 400mg/m^2 (adults who are elderly or with history of arterial hypertension, concurrent/previous thoracic radiation or cardiac risk factors such as prior anthracycline or cardiotoxic drugs)

Adults:

Various dosing schedules used; refer to specific local regimens for details.

For example, as single agent: 30-60 mg/m^2 per day IV x 3-6 days

Management of Infusion-related reactions with Anthracyclines:

he 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:

Also consider dose modification with increased transaminases.

Bilirubin	% usual dose
1-2 x ULN	75%
2-4 x ULN	50%
> 4 ULN	OMIT

Dosage with Renal Impairment:

Reduce dose to 50% if creatinine greater than 2 x ULN.

Dosage in the elderly:

May have higher risk of cardiotoxicity. Use should be avoided in patients ≥ 75 years of age.

Children:

Refer to local regimens for details. Cardiotoxicity may be more frequent in children; long-term cardiac follow-up is recommended.

back to top

F - Administration Guidelines

- Some centres administer daunorubicin as a slow push through sidearm of free flowing IV (5% Dextrose, Normal Saline) over 3 to 10 minutes, depending on the dose, volume and vein condition
- May be mixed in 50 mL minibag (5% Dextrose, Normal Saline); Infuse through sidearm of free flowing IV over 10-15 minutes.
- Slow down injection rate if erythematous streaking or facial flushing occurs.
- Do not use if solution turns blue or purple.
- Do not admix with other drugs; incompatible with heparin, dexamethasone sodium phosphate, and aluminum
- Protect drug from light.

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

back to top

G - Special Precautions

Other:

Daunorubicin should not be used in patients who have/had:

- pre-existing myelosuppression or severe infection
- impaired cardiac function or severe cardiac arrhythmias
- severe liver and renal dysfunction
- previous hypersensitivity to this drug, any excipients, or to other anthracyclines, anthracenediones
- reached the lifetime cumulative dose of any combination of anthracyclines and/or anthracenediones.
- other cardiotoxic drugs or have an active viral infection

Cardiac toxicity is cumulative across the members of the anthracycline (doxorubicin, epirubicin, idarubicin, daunorubicin) and anthracenedione (mitoxantrone) classes of drugs. Patients who have received these agents, mediastinal radiotherapy or other cardiotoxic drugs, who are elderly, or who have other cardiac risk factors are at increased risk of toxicity, and should be carefully monitored.

Radiation recall reactions may occur. Live vaccines should be avoided.

Daunorubicin has **mutagenic, teratogenic, fetotoxic, abortifacient** and **carcinogenic** effects.. It should not be used in pregnancy. Adequate contraception should be used by both sexes during treatment and for at least 6 months after the last dose. **Fertility** can be affected, is dose-dependent and may be irreversible. Other anthracyclines have been observed to excrete in breast milk; therefore, **breastfeeding** is not recommended.

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cardiotoxic drugs (e.g. cyclophosphamide, trastuzumab) or drugs that decrease heart contractility	↑ cardiotoxic effect	Additive	Caution; Avoid anthracycline-based therapy for up to 24 weeks after stopping trastuzumab
Hepatotoxic medications (e.g. methotrexate)	↑ risk of hepatotoxicity	Additive, or may impair hepatic metabolism and biliary excretion of daunorubicin	Avoid

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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and regular
Renal function tests	Baseline and regular
CBC	Baseline and regular
Cardiac function tests (Echo, RNA and/or MUGA scans)	Baseline
Cardiac tests for all patients with cardiac risk factors and cumulative doses ≥ 450 mg/m^2	periodic
Clinical toxicity assessment for stomatitis, infection, bleeding, cardiotoxicity, arrhythmia, nausea/vomiting, local reactions, hypersensitivity, tumour lysis syndrome	At each visit

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

back to top

K - References

Data Sheet: Daunorubicin Injection. Pfizer New Zealand Ltd., February 23, 2011.

Drug Monograph: Daunorubicin. British Columbia Cancer Agency Cancer Drug Manual, August 1, 2013.

McEvoy GK, editor. AHFS Drug Information 2013. Bethesda: American Society of Health-System Pharmacists, p. 982-8.

Product Monograph: Daunorubicin. Erfa Canada Inc., August 15, 2012.

Product Monograph: Daunorubicin. Novopharm Ltd. May 26, 1997.

Summary of Product Characteristics: Daunorubicin. Winthrop Pharmaceuticals (UK). July 19, 2011.

September 2019 Updated infusion reaction information in Dosing section.

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