

DRUG NAME: DAUNORUBICIN**SYNONYM(S):** daunomycin, DNR, rubidomycin**COMMON TRADE NAME(S):** CERUBIDINE®**CLASSIFICATION:** Anthracycline topoisomerase inhibitor, cytotoxic¹*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Daunorubicin is an anthracycline antibiotic which damages DNA by intercalating between base pairs resulting in uncoiling of the helix, ultimately inhibiting DNA synthesis and DNA-dependent RNA synthesis.¹ Daunorubicin may also act by inhibiting polymerase activity, affecting regulation of gene expression and generating free radicals. Cytotoxic activity is cell cycle phase non-specific, although it exerts maximal cytotoxic effects in the S-phase.

PHARMACOKINETICS:

Interpatient variability	no information found	
Distribution	highest levels in kidney, pancreas and liver; lowest levels in fat, crosses placenta. ²	
	cross blood brain barrier?	no evidence that it crosses blood brain barrier
	volume of distribution ^{1,3}	1006-1725 L/m ²
	plasma protein binding	50-60%
Metabolism	extensively in liver and other tissues	
	active metabolite(s)	daunorubicinol (major metabolite – 60%)
	inactive metabolite(s)	yes
Excretion	urine	14-25%
	feces	hepatobiliary secretion in feces is predominant route of elimination (40%)
	terminal half life	18.5 h
	clearance	236-1117 mL/min/m ²
Gender	no information found	
Elderly	no information found	
Children	no information found	
Race	no information found	

Adapted from references 1 and 4 unless specified otherwise.

USES^{1,4}:**Primary uses:**

*Ewing's sarcoma
 *Leukemia, acute lymphocytic
 *Leukemia, acute myeloid
 *Leukemia, chronic myelogenous
 *Lymphoma, non-Hodgkin's

Other uses:

Kaposi's sarcoma
 Lymphoma, Hodgkin's disease
 *Lymphosarcoma
 Rhabdomyosarcoma
 Wilm's tumour

*Health Canada Therapeutic Products Directorate approved indication

SPECIAL PRECAUTIONS:

Carcinogenicity: Potentially carcinogenic; mammary tumours and fibrosarcomas have been reported in rat and mice models.¹

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* tests.¹ Daunorubicin is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.

Fertility: Gonadal suppression resulting in amenorrhea, zoospermia and testicular atrophy in male dogs.⁵

Pregnancy: FDA Pregnancy Category D.⁵ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, 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.⁵

SIDE EFFECTS:

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in <i>bold, italics</i> I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
allergy/immunology	anaphylactoid-type I (rare)	I			
	rash	I			
blood/bone marrow febrile neutropenia	<i>myelosuppression</i> nadir 10-14 days, recovery 21-24 days		E		
cardiovascular (arrhythmia)	arrhythmias due to acute cardiac toxicity – uncommon (ECG changes, AV block, bundle branch block)	I			
	transient arrhythmias (6-30%)	I			
	arrhythmias due to late onset cardiac toxicity				L
cardiovascular (general)	<i>congestive heart failure</i> (rare, dose related)			D	
	<i>cardiomyopathy</i> (rare, dose related)			D	L
	abnormal systolic function on echocardiogram (18-38%) ¹				L
dermatology/skin	<i>extravasation hazard: vesicant</i>				

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in <i>bold, italics</i> I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
	alopecia (very common)		E		
	facial flushing with rapid injection	I			
	flare reaction (histamine release)	I			
	hyperpigmentation		E		
	nail changes		E		
	pain on injection	I			
	radiation recall reaction (rare)	I			
gastrointestinal	<i>emetogenic potential</i> : moderate high				
	diarrhea		E		
	nausea and vomiting (85%)	I			
	<i>stomatitis</i> ²		E		
metabolic/laboratory	hyperuricemia (during periods of active cell lysis)	I			
neurology	neuropathy (13%)		E		
renal/genitourinary	red colouration of urine	I			

Adverse effects adapted from references 1 and 5 unless specified otherwise

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (eg, 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 if tumour lysis is expected.

Tissue necrosis may be caused by extravasation of anthracyclines. These agents may bind to DNA and recycle locally to cause a progressive slough of tissue or ulceration over several weeks, requiring excision and skin grafting. For more details on the prevention and management of anthracycline extravasation, refer to BC Cancer Agency [Extravasation Guidelines](#).

Flare reaction is a painless local reaction along the vein or near the intact injection of anthracyclines. It is characterized by immediate red blotches, streaks and local wheals, probably due to histamine release.⁶ Edema may sometimes occur.⁶ Patients may or may not experience pruritus or irritation.⁶ Symptoms usually subside with or without treatment 30 minutes after the infusion is stopped, although they may last for 1-2 hours and rarely more than 24 hours.⁷ For more details on the prevention and management of anthracycline flare reaction, refer to BC Cancer Agency [Extravasation Guidelines](#).

Cardiac toxicity⁸: 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 are at increased risk of toxicity and should be carefully monitored.

- **Acute cardiotoxicity**⁸: Early, non-dose-related electrocardiographic abnormalities are uncommon. The electrocardiographic changes are reversible and do not indicate impending development of cardiomyopathy. Diminished QRS voltage may be dose-related. These changes are usually transient, but may result in pericardial effusion, decreased myocardial contractility and possible cardiac failure.

- **Chronic cardiotoxicity**⁸: Cardiomyopathy may be dose dependant. Cumulative doses greater than 400 mg/m² increases the risk, with a 1-2% incidence at a total lifetime dose of 550 mg/m² and a 12% incidence at 1000 mg/m² total lifetime dose. Other risk factors include thoracic radiation, pre-existing heart disease and prior anthracycline therapy. The mortality associated with daunorubicin-induced congestive heart failure (CHF) may be high (79%). Management of daunorubicin-induced CHF includes discontinuation of the drug and standard treatment of CHF.
- **Late onset cardiotoxicity**⁸: May occur years to decades following discontinuation of therapy. This condition may be precipitated by stressful situations (eg, surgery, pregnancy, exercise, viral infection). Monitoring for cardiac toxicity should continue after daunorubicin therapy is complete.
- **Children**⁹: Increase risk of cardiotoxicity with cumulative doses of 300mg/m² in children >2 years old and >10 mg/kg in children < 2 years old. Children with daunorubicin-induced CHF are very sensitive to digitalis; the total digitalizing dose (TDD) required is 0.01-0.02 mg/kg of digoxin; maintenance dose is 1/7 to 1/4 of the TDD. For children receiving anthracyclines, the Cardiology Committee of the Children's Cancer Group recommends the following monitoring of cardiac function¹⁰:
 1. Echocardiogram (echo) or radionuclide angiocardigraphy (RNA) at baseline.
 2. An echo should be done at 3, 6 and 12 months following therapy, with RNA as a confirmatory test, if possible, at 12 months following therapy.
 3. Echo before every other subsequent course of anthracycline when the cumulative dose is < 300 mg/m².
 4. Echo (or RNA) before each course of anthracycline when the total cumulative dose is ≥ 300 mg/m² plus mediastinal radiation > 1000 rads.
 5. Echo and RNA before each course of anthracycline when the total course is ≥ 400 mg/m².

There is some evidence supporting the use of agents for cardiac prophylaxis to prevent daunorubicin cardiotoxicity including dexrazoxane¹¹⁻¹³ and adenosine.^{14,15}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ciprofloxacin ¹⁶	may decrease the effect of ciprofloxacin	may decrease ciprofloxacin absorption by altering the intestinal mucosa	monitor patient, increase ciprofloxacin dose if necessary

SUPPLY AND STORAGE:

Injection^{1,4}: 20 mg vial. Store at room temperature.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on solution preparation and compatibility, see [Chemotherapy Chart in Appendix](#).

Reconstitute powder with 4 mL SWI to yield a final concentration of 5 mg/mL.^{4,17}

Reconstitute solution for injection¹: Clear, red solution. Stable for 24 hours at room temperature and for 48 hours when refrigerated¹; may be stable for 7 days at room temperature.¹⁸ A colour change from red to blue-purple indicates decomposition; these solutions should be discarded. Contact between daunorubicin and aluminium may result in darkening of the solution and formation of black patches on the aluminium surface after 12-24 hours.¹⁷ Daunorubicin should not be stored in contact with aluminium but it may be injected safely through an aluminium-hubbed needle.

Diluted solution for infusion¹⁷: Stable at concentrations of 20-100 mg/L in NS, D5W, dextrose-saline combinations, or Lactated Ringer's for at least 4 weeks at room temperature, protected from light.

Compatibility¹⁷: The following are compatible via Y-site injection¹⁷: filgrastim, melphalan, methotrexate and ondansetron, sodium bicarbonate, teniposide, vinorelbine. The following are compatible in the same infusion solution:

Primary drug	Test drug	Test Solution	Stability
daunorubicin 33mg/L	cytarabine 267mg/L etoposide 400mg/L	D51/2S	72 h
daunorubicin 200mg/L	hydrocortisone 500mg/L	D5W	4 h

Incompatibility¹⁷: The following are incompatible via Y-site injection: allopurinol, aztreonam, cefepime, fludarabine, piperacillin-tazobactam. The following are incompatible in the same infusion solution: dexamethasone, heparin.

PARENTERAL ADMINISTRATION:

BCCA administration standard noted in **bold, italics**

Subcutaneous	not used due to corrosive nature ¹
Intramuscular	not used due to corrosive nature ¹
Direct intravenous	preferred method due to need for frequent monitoring for signs of extravasation. ¹ May be diluted with 10 to 15 mL of NS and injected over 2-3 min using a small (21 or 23) gauge needle into tubing of running IV. Give via syringe using side arm method; dilute in 5-15 mL NS and infuse into tubing of a free flowing IC at a rate of 20 mg every 1-3 min. Push slowly so that drip of IV solution does not stop or reverse. Check for blood return before administration and after every 2-3 mL of drug. If no blood return, stop the injection and assess the IV site. Flush with a 20 mL solution after administration to clear any remaining drug from tubing.
Intermittent infusion	in 50mL NS or D5W over 10 to 15 min or in 100 mL NS or D5W over 30-45 min. ^{1,17} For children, in sufficient volume to run over 30-60 min.
Continuous infusion	dilute in a convenient volume of NS or D5W and infuse through a central venous catheter
Intraperitoneal	not used due to corrosive nature ¹
Intrapleural	not used due to corrosive nature ¹
Intrathecal	not used due to corrosive nature ¹
Intra-arterial	no information available on this route
Intravesical	no information available on this route

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 in patients with other toxicities.

Adults:

BCCA usual dose noted in ***bold, italics***

<i>Intravenous:</i>	<p>Cycle Length: 3-4 weeks:</p>	<p>initial therapy: <i>monotherapy</i> 30-60mg/m² IV once daily for 3-6 consecutive days starting on day 1 (total dose per cycle 90-360 mg/m²)</p> <p>maximum dose during initial treatment⁴: 45-600mg/m²</p> <p><i>combination therapy</i>¹ 45 mg/m² (30 mg/m² if > 60 y old) IV once daily for 2-3 consecutive days starting on day 1 (total dose per cycle 90-135 mg/m² [60-90 mg/m² if > 60 y old]) maximum dose⁴: 12-20mg/kg per treatment period</p> <p>maintenance⁴: 1 week: 1mg/kg IV for one dose on day 1</p> <p><i>Maximum lifetime dose</i>¹: 900 mg/m² in adults with normal cardiac function, lower doses are recommended if in combination with thoracic radiation or prior anthracycline therapy. Careful cardiac monitoring is important, as cardiotoxicity may occasionally occur at lower cumulative doses. If tumour is responding when lifetime dose is reached, a cardiac consultation should be obtained before continuing treatment.</p>								
<i>Dosage in myelosuppression:</i>		<p>modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"</p>								
<i>Dosage in renal failure:</i>		<p>reduce dose by 50% if creatinine greater than 265 micromol/L</p>								
<i>Dosage in hepatic failure:</i>	<table border="0"> <tr> <td style="text-align: center;">Bilirubin (micromol/L)</td> <td style="text-align: center;">% usual dose</td> </tr> <tr> <td style="text-align: center;">26-51</td> <td style="text-align: center;">75%</td> </tr> <tr> <td style="text-align: center;">52-85</td> <td style="text-align: center;">50%</td> </tr> <tr> <td style="text-align: center;">> 85</td> <td style="text-align: center;">not recommended</td> </tr> </table>	Bilirubin (micromol/L)	% usual dose	26-51	75%	52-85	50%	> 85	not recommended	
Bilirubin (micromol/L)	% usual dose									
26-51	75%									
52-85	50%									
> 85	not recommended									
<i>Dosage in dialysis:</i>		<p>no information found</p>								

Children:

<i>Intravenous:</i>	<p>Cycle Length: 3-4 weeks⁵:</p>	<p>> 2 y old 25-45mg/m² IV, frequency of administration dependent on specific regimen employed < 2 y old or BSA < 0.5 m² calculate dose based on BW rather than BSA (mg/kg dose can be approximated by dividing the mg/m² dose by 30)</p> <p><i>Maximum dose</i>⁵: BW 20 kg: 600 mg/m² BW 30 kg: 750 mg/m² BW 10 kg: 500 mg/m²</p>
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