

## DRUG NAME: Daunorubicin-cytarabine liposome

**SYNONYM(S):** CPX-351 <sup>1</sup>, daunorubicin liposomal-cytarabine liposomal <sup>2</sup>, daunorubicin lipo-cytarabine lipo <sup>2</sup>, daunorubicin and cytarabine liposome <sup>3</sup>

**COMMON TRADE NAME(S):** VYXEOS®

**CLASSIFICATION:** miscellaneous

*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.*

### MECHANISM OF ACTION:

Daunorubicin-cytarabine liposome is a fixed-dose drug combination of daunorubicin and cytarabine encapsulated by a liposomal coating. Daunorubicin and cytarabine are available in a 1:5 molar ratio within the liposome. The purpose of the liposome is to alter the distribution of the drug molecules *in vivo*, leading to controlled drug delivery at the target site and reduced off-target adverse effects. Daunorubicin-cytarabine liposomes exhibit a prolonged half-life following intravenous infusion, with greater than 99% of daunorubicin and cytarabine in the plasma remaining encapsulated within the liposomes. The liposomes accumulate and persist in high concentration in the bone marrow, where they are taken up by leukemia cells in an active engulfment process before releasing their contents within the intracellular environment.

Daunorubicin is a topoisomerase II inhibitor and exerts its antimitotic and cytotoxic effect by inhibiting DNA synthesis activity and producing DNA-damaging free radicals. Cytarabine is converted intracellularly to an active metabolite which exerts its cytotoxic effect primarily by incorporation into DNA and RNA and inhibiting DNA synthesis. Cytarabine is cell cycle-phase specific affecting cells during the S-phase of cell division.<sup>3-6</sup>

### PHARMACOKINETICS:

Distribution	>99% of daunorubicin and cytarabine in plasma remains encapsulated within liposomes	
	cross blood brain barrier?	no information found
	volume of distribution	daunorubicin: 6.6 L cytarabine: 7.1 L
	plasma protein binding	no information found
Metabolism	daunorubicin and cytarabine are extensively metabolized in the body following release from liposomes	
	active metabolite(s)	daunorubicin: daunorubicinol
	inactive metabolite(s)	cytarabine: 1-β-D-arabinofuranosyluracil (AraU)
Excretion	prolonged half-life as liposome (compared to non-liposomal formulations of daunorubicin and cytarabine)	
	urine	daunorubicin/daunorubicinol: 9% cytarabine/AraU: 71%
	feces	no information found
	terminal half life	31.5 h (daunorubicin); 40.4 h (cytarabine)
	clearance	0.16 L/h (daunorubicin); 0.13 L/h (cytarabine)
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Children	no clinically significant difference	

Ethnicity	no clinically significant difference
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Adapted from standard reference <sup>3,4</sup> unless specified otherwise.

**USES:**

**Primary uses:**

\*Leukemia, acute myeloid

\*Health Canada approved indication

**Other uses:**

**SPECIAL PRECAUTIONS:**

**Caution:**

- daunorubicin-cytarabine liposome is a fixed-dose combination product and is **NOT interchangeable** with conventional daunorubicin, conventional cytarabine, daunorubicin liposomal, cytarabine liposomal or other daunorubicin or cytarabine containing products <sup>3,4</sup>
- daunorubicin-cytarabine liposome may induce **hyperuricemia** secondary to rapid lysis of leukemia cells; consider initiating an anti-hyperuricemic agent prior to treatment <sup>3,4</sup>
- daunorubicin has a known risk of **cardiotoxicity**; patients who have had prior therapy with anthracyclines, pre-existing cardiac disease, previous radiotherapy to the mediastinum, or concomitant treatment with other cardiotoxic drugs may be at increased risk <sup>3,4</sup>
- daunorubicin-cytarabine liposome vials contains **copper gluconate** as a nonmedicinal ingredient; use caution in patients with copper-related metabolic disorders (e.g. Wilson's disease) <sup>3,4</sup>

**Special populations:**

- patients **aged 65 years and older** may experience more bleeding events compared to younger patients <sup>3,4</sup>
- in **pediatric patients**, daunorubicin-cytarabine liposome is associated with increased incidence of early onset of cardiotoxicity, rash, grade  $\geq 3$  hyperglycemia, and QT prolongation compared to adults <sup>3</sup>

**Carcinogenicity:** Carcinogenic potential of daunorubicin-cytarabine liposome has not been determined. Conventional daunorubicin is possibly carcinogenic in animals and humans. Mammary tumours have been reported in animal models. Conventional cytarabine is mutagenic and potentially carcinogenic. <sup>3-6</sup>

**Mutagenicity:** Conventional daunorubicin is mutagenic in Ames test and clastogenic in mammalian *in vitro* and *in vivo* chromosome tests. Conventional cytarabine is mutagenic in Ames test and clastogenic in mammalian *in vitro* chromosome test. <sup>3,4</sup>

**Fertility:** In animal studies with conventional daunorubicin, testicular atrophy and total aplasia in spermatocytes in seminiferous tubules were observed at doses approximately 0.12 times those seen following human clinical exposure. In animal studies with conventional cytarabine, sperm-head abnormalities and impaired spermatogenesis were observed. <sup>3,4</sup>

**Pregnancy:** In animal studies with liposomal daunorubicin, embryoletality was observed at doses approximately 0.27 times those seen following human clinical exposure. Fetal malformations were observed at doses approximately 0.04 times those seen following human clinical exposure. Conventional cytarabine was teratogenic in animal studies at exposures approximately 0.06 times those seen following human clinical exposure. Pregnancy tests are recommended prior to starting treatment with daunorubicin-cytarabine liposome for female patients of childbearing potential. Effective contraception is recommended during treatment and for at least six months after the last dose in female patients of childbearing potential and male patients with female partners of childbearing potential. <sup>3,4</sup>

**Breastfeeding** is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for at least two weeks following the last dose. <sup>3,4</sup>

**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.<sup>7-9</sup>

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b><i>bold, italics</i></b>	
blood and lymphatic system/ febrile neutropenia (see paragraph following <b>Side Effects</b> table)	<b><i>febrile neutropenia</i></b> (severe 66%)
	<b><i>neutropenia</i></b> (100%, severe 10-17%); may be prolonged
	<b><i>thrombocytopenia</i></b> (100%, severe 25-28%); may be prolonged
cardiac (see paragraph following <b>Side Effects</b> table)	<b><i>cardiac arrest</i></b> (severe <1%); fatal events reported
	<b><i>cardiac arrhythmia</i></b> (30%, severe 7%)
	<b><i>cardiotoxicity, non-conduction</i></b> (20%, severe 9%)
	chest pain (17%, severe 3%)
	<b><i>congestive heart failure</i></b>
ear and labyrinth	deafness, deafness unilateral (<10%)
endocrine	hypothyroidism (<10%)
eye	eye disorders (conjunctivitis, dry eye syndrome, eye irritation, periorbital edema, eye pain, injected sclera, ocular hyperemia) (<10%) visual impairment (11%)
gastrointestinal	<b><i>emetogenic potential</i></b> : moderate <sup>10-13</sup>
	<b><i>abdominal pain</i></b> (33-36%, severe 2%)
	<b><i>constipation</i></b> (40-43%)
	<b><i>diarrhea/colitis</i></b> (45-66%, severe 3%)
	dyspepsia (<10%)
	hemorrhoids (11%)
	<b><i>mucositis</i></b> (44-50%, severe 1%)
	<b><i>nausea</i></b> (47-52%, severe <1%)
	<b><i>vomiting</i></b> (24-28%)
general disorders and administration site conditions	<b><i>extravasation hazard</i></b> : irritant <sup>14</sup> ; see paragraph following <b>Side Effects</b> table
	catheter/device/injection site reaction (16%)
	chills (23-31%)
	<b><i>edema</i></b> (49-52%, severe <2%)
	<b><i>fatigue</i></b> (32-46%, severe 5-10%)
	pyrexia (17-30%, severe <1%)
	bacteremia, excluding sepsis (24%, severe 23%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
infections and infestations	fungal infection (18-19%, severe 7%)
	<b>infection</b> (69-78%, severe 52-59%); fatal events reported
	pneumonia (26%, severe 20%); fatal events reported
	sepsis (11%); fatal events reported
	upper respiratory tract infection (18%, severe 3%)
injury, poisoning, and procedural complications	<b>infusion-related reactions, hypersensitivity</b> (67%, severe 3%); see paragraph following <b>Side Effects</b> table
investigations	ALT increase (severe 5%)
	hyperbilirubinemia (severe 2-6%)
	hyperuricemia
metabolism and nutrition	<b>appetite decrease</b> (29-34%, severe 1%)
	hypoalbuminemia (severe 2-7%)
	hypokalemia (severe 6-9%)
	hyponatremia (severe 6-14%)
musculoskeletal and connective tissue	<b>musculoskeletal pain</b> (38-46%, severe 3%)
nervous system	dizziness (18%, severe <1%)
	<b>headache</b> (32-33%, severe 1%)
psychiatric	anxiety (14%)
	delirium (16%, severe 3%)
	hallucinations (<10%)
	<b>sleep disorders</b> (25%, severe 1%)
renal and urinary	renal insufficiency (11%, severe 5%)
respiratory, thoracic and mediastinal	cough (33-34%)
	<b>dyspnea</b> (32%, severe 11-13%)
	<b>epistaxis</b> (36%)
	hypoxia (18%, severe 12%)
	pleural effusion (16%, severe 2%)
	pneumonitis (<10%)
	<b>respiratory failure</b> ; fatal events reported
skin and subcutaneous tissue	petechiae (11%)
	pruritus (15%)
vascular	<b>hemorrhage</b> (70%, severe 10-13%); see paragraph following <b>Side Effects</b> table
	hypertension (18%, severe 10%)
	hypotension (20-24%, severe 5%)

Adapted from standard reference<sup>1,3,4</sup> unless specified otherwise.

**Cardiotoxicity** is a known risk of anthracycline treatment and is thought to be due to free radical damage as myocardial tissue is susceptible to these highly reactive species.<sup>15</sup> Patients with pre-existing cardiac disease, previous radiotherapy to the mediastinum, concomitant use of cardiotoxic medications, or those who have had prior therapy with anthracyclines are at increased risk of daunorubicin-induced cardiotoxicity. With daunorubicin-cytarabine liposome, decreased ejection fraction and congestive heart failure are the most frequently reported serious adverse reactions. Daunorubicin-cytarabine liposome is not recommended in patients with left ventricular ejection fraction that is less than normal or in patients whose lifetime anthracycline exposure has reached the maximum cumulative limit. Baseline cardiac evaluation with ECG and ECHO/MUGA scan is recommended prior to starting treatment.<sup>3,4</sup> [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.](#)

Following **extravasation**, conventional daunorubicin has been associated with tissue necrosis at the site of extravasation and it is considered a vesicant. There is limited data about extravasation with daunorubicin-cytarabine liposome. However, injection site reactions have been reported in 16% of patients receiving the liposome formulation. In clinical studies, only one event of extravasation has been reported, but no tissue necrosis was observed.<sup>3,4</sup> For details on the prevention and management of extravasation, refer to BC Cancer Policy III-20 [Prevention and Management of Extravasation of Chemotherapy](#).

**Infusion-related/hypersensitivity reactions**, are reported in up to 67% of patients. The most frequently reported hypersensitivity reaction is rash; however, cases of anaphylaxis and fatal reactions have been reported. Depending on the severity of the reaction, reactions may be managed by interrupting the infusion, slowing the rate of infusion, or permanently discontinuing daunorubicin-cytarabine liposome.<sup>3,4</sup> For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX [Management of Infusion-Related Reactions to Systemic Therapy Agents](#).

Severe **myelosuppression**, resulting in fatal **infections** and **hemorrhagic** events, has been reported. Due to the prolonged half-life of daunorubicin-cytarabine liposome, recovery of neutrophil and platelet counts may be prolonged and additional monitoring may be required. Pneumonia, sepsis, and bacteremia are the most frequently seen serious infections. Consider prophylactic anti-infective treatment in patients at increased risk. Administration of live vaccines may result in serious or fatal infection and should be avoided.<sup>3,4</sup>

**INTERACTIONS:** No known interactions

#### **SUPPLY AND STORAGE:**

**Injection:** Jazz Pharmaceuticals Canada Inc. supplies daunorubicin-cytarabine in a liposome formulation as single-use vials containing 44 mg daunorubicin and 100 mg cytarabine per vial. Non-medicinal ingredients: copper gluconate (100 mg per vial, equivalent to 14 mg elemental copper). Refrigerate. Protect from light.<sup>3</sup>

**Additional information:** Reconstituted daunorubicin-cytarabine liposome contains 5 mg/mL copper gluconate, of which 14% is elemental copper.<sup>3</sup>

**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.**

**Compatibility:** consult detailed reference

**Additional information:** In-line filtration is not required for administration of daunorubicin-cytarabine liposome; however, if an in-line filter is used, minimum pore diameter should be  $\geq 15$  micron.<sup>3</sup>

**PARENTERAL ADMINISTRATION:**

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

Subcutaneous	do NOT use <sup>3</sup>
Intramuscular	do NOT use <sup>3</sup>
Direct intravenous	no information found
Intermittent infusion	over 90 minutes <sup>3</sup>
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	do NOT use <sup>3</sup>
Intra-arterial	no information found
Intravesical	no information found

**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> <sup>3,4</sup>	Cycle Length: n/a:	<p>first induction: daunorubicin 44 mg/m<sup>2</sup> and cytarabine 100 mg/m<sup>2</sup> IV for one dose on days 1, 3, and 5 (total dose for 1<sup>st</sup> induction daunorubicin 132 mg/m<sup>2</sup> and cytarabine 300 mg/m<sup>2</sup>)</p> <p>second induction (if needed, given 2-5 weeks after first induction; max of 2 induction courses):</p> <p>daunorubicin 44 mg/m<sup>2</sup> and cytarabine 100 mg/m<sup>2</sup> IV for one dose on days 1 and 3 (total dose for 2<sup>nd</sup> induction daunorubicin 88 mg/m<sup>2</sup> and cytarabine 200 mg/m<sup>2</sup>)</p> <p>consolidation (given 5-8 weeks after start of induction; if needed, a second consolidation may be given 5-8 weeks after the start of the first consolidation to a max of 2 consolidation courses) :</p> <p>daunorubicin 29 mg/m<sup>2</sup> and cytarabine 65 mg/m<sup>2</sup> IV for one dose on days 1 and 3 (total dose per consolidation daunorubicin 58 mg/m<sup>2</sup> and cytarabine 130 mg/m<sup>2</sup>)</p>
<i>Concurrent radiation:</i>	no information found	

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

<i>Dosage in myelosuppression:</i>	Cycle Length: modify according to protocol by which patient is being treated
<i>Dosage in renal failure:</i> <sup>3,4</sup>	CrCl ≥30 mL/min: no adjustment required CrCl <30 mL/min: no information found  calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$  * For males N=1.23; for females N=1.04
<i>Dosage in hepatic failure:</i> <sup>3,4</sup>	bilirubin ≤50 micromol/L: no adjustment required bilirubin >50 micromol/L: no information found
<i>Dosage in dialysis:</i>	no information found

**Children:**

safety and efficacy in children <1 year of age have not been established<sup>4</sup>

*Intravenous:*<sup>4</sup>

n/a: first induction:  
daunorubicin 44 mg/m<sup>2</sup> and cytarabine 100 mg/m<sup>2</sup> IV for one dose on days 1, 3, and 5  
(total dose for 1<sup>st</sup> induction daunorubicin 132 mg/m<sup>2</sup> and cytarabine 300 mg/m<sup>2</sup>)  
  
second induction:  
daunorubicin 44 mg/m<sup>2</sup> and cytarabine 100 mg/m<sup>2</sup> IV for one dose on days 1 and 3  
(total dose for 2<sup>nd</sup> induction daunorubicin 88 mg/m<sup>2</sup> and cytarabine 200 mg/m<sup>2</sup>)  
  
consolidation:  
daunorubicin 29 mg/m<sup>2</sup> and cytarabine 65 mg/m<sup>2</sup> IV for one dose on days 1 and 3  
(total dose per consolidation daunorubicin 58 mg/m<sup>2</sup> and cytarabine 130 mg/m<sup>2</sup>)

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