Drug Monograph

A - Drug Name

liposomal DAUNOrubicin / liposomal cytarabine

COMMON TRADE NAME(S): Vyxeos®

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B - Mechanism of Action and Pharmacokinetics

Liposomal daunorubicin / liposomal cytarabine is a combination product with a fixed 1:5 (daunorubicin:cytarabine) molar ratio. The liposomal encapsulation protects the drugs from metabolism and elimination, and provides preferential uptake by leukemia cells. After internalization, the liposome undergoes degradation releasing daunorubicin and cytarabine within cancer cells.

Daunorubicin is an anthracycline antibiotic, which damages DNA by intercalation, metal ion chelation, or 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 non-specific.

Cytarabine is metabolized intracellularly into its active triphosphate form, which competes with deoxycytidine triphosphate, the physiologic substrate of DNA polymerase. The active metabolite damages DNA by multiple mechanisms including the inhibition of DNA polymerase or incorporation into DNA. Cytotoxicity is highly specific for the S phase of the cell cycle.

Distribution	Pharmacokinetics appear to be dose-proportional between 0.03-1.3x the recommended dose.	
	PPB	Unknown
Metabolism	Daunorubicin is mostly catalyzed by hepatic and non-hepatic aldo-keto reductase and carbonyl reductase enzymes.	

	Cytarabine is metabolized by cytidine deaminase.	
	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Half-life is prolonged, with > 99% remaining encapsulated in the plasma.	
	Half-life	31.5 h (daunorubicin); 40.4 h (cytarabine)
	Urine	9% (daunorubicin and its active metabolite) 71% (cytarabine and its inactive metabolite)

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C - Indications and Status

Health Canada Approvals:

- Acute myeloid leukemia (AML)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: Vesicant

The following adverse events were reported with an incidence of ≥ 10% in a randomized Phase 3 study comparing liposomal daunorubicin / liposomal cytarabine with conventional cytarabine and daunorubicin (7+3) in patients with newly diagnosed t-AML or AML-MRC. It also includes severe or life-threatening adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (30%) (7% severe)	E
	Cardiotoxicity (20%) (9% severe)	I E D
	Hypertension (18%)	E
	Hypotension (20%)	E
Dermatological	Hand-foot syndrome (<1%)	E
	Rash, pruritus (54%) (5% severe)	E
Gastrointestinal	Abdominal pain (33%) (2% severe)	E
	Anorexia, weight loss (29%)	E
	Constipation (40%)	E
	Diarrhea (45%) (3% severe)	E
	Mucositis (44%) (1% severe)	E
	Nausea, vomiting (47%) (1% severe)	E
General	Edema (49%) (1% severe)	E
	Fatigue (32%)	E
Hematological	Myelosuppression ± infection, bleeding (69%) (66% severe)	E D
Hypersensitivity	Anaphylaxis (rare)	I
Injection site	Infusion site extravasation (<1%)	I E
	Injection site reaction (16%)	E
Metabolic / Endocrine	Hypothyroidism (rare)	E
	Tumor lysis syndrome (8%)	E
Musculoskeletal	Musculoskeletal pain (38%) (3% severe)	E
Nervous System	Anxiety (14%)	E
	Delusions (16%) (or hallucinations)	E
	Dizziness (18%)	E

	Headache (33%) (1% severe)	E
	Sleep disorder (25%)	E
Ophthalmic	Eye disorders (11%)	E
Renal	Nephrotoxicity (11%)	E
Respiratory	Cough, dyspnea (33%)	E
	Pleural effusion (16%)	E
	Pneumonitis (<10%)	E

* "*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)

The most common side effects for liposomal daunorubicin / liposomal cytarabine include myelosuppression ± infection, bleeding, rash, pruritus, edema, nausea, vomiting, diarrhea, mucositis, constipation, musculoskeletal pain, abdominal pain, cough, and dyspnea.

Cardiotoxicity is a known risk of anthracycline (daunorubicin) treatment. Thoracic radiation, pre-existing heart disease, and prior therapy with anthracyclines or other cardiotoxic drugs may increase the risk of daunorubicin-induced cardiac toxicity. Refer to Monitoring section for additional information. Use of liposomal daunorubicin / liposomal cytarabine is not recommended in patients with reduced LVEF or with total cumulative doses of conventional daunorubicin > 550 mg/m^2 (> 400 mg/m^2 in patients in patients with previous thoracic radiation).

Severe **myelosuppression** (including fatal **infections** and **hemorrhagic** events) has been reported in patients receiving liposomal daunorubicin / liposomal cytarabine. Due to the long plasma half-life of liposomal daunorubicin / liposomal cytarabine, time to recovery of ANC and platelets may be prolonged.

Local tissue necrosis occurring with **extravasation** has been associated with conventional daunorubicin. During clinical trials of liposomal daunorubicin / liposomal cytarabine, one event of extravasation occurred, but no local tissue necrosis was observed.

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. Patients at risk of **tumour lysis syndrome** should have adequate prophylaxis and be monitored closely.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Assess cardiac function (e.g., ECG and MUGA / Echo) prior to starting treatment and monitor routinely.

Calculate total cumulative anthracycline doses (daunorubicin or equivalent) prior to each cycle. Total cumulative daunorubicin doses should not exceed:

- 550mg/m^2
- 400mg/m^2 in patients with previous thoracic radiation

In the pivotal trial, patients were required to have, at baseline, a prior lifetime cumulative anthracycline exposure of < 368 mg/m^2 daunorubicin (or equivalent).

Other Supportive Care:

- Consider anti-hyperuricemic therapy (e.g., allopurinol) prior to treatment initiation.
- Consider prophylactic anti-infectives (e.g., anti-bacterials, anti-virals, anti-fungals) for febrile neutropenia prophylaxis.

Adults:

Dose should be determined based on the liposomal daunorubicin component and the individual's BSA.

Induction:

- 1st induction: liposomal daunorubicin 44 mg/m^2 and liposomal cytarabine 100 mg/m^2 IV on days 1, 3 and 5
- 2nd induction*: liposomal daunorubicin 44 mg/m^2 and liposomal cytarabine 100 mg/m^2 IV on days 1 and 3

*May be administered 2-5 weeks after the 1st induction if remission not achieved and no unacceptable toxicity, according to product monograph.

Consolidation -** For patients who achieve complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CRi) during induction:

- Liposomal daunorubicin 29 mg/m^2 and liposomal cytarabine 65 mg/m^2 IV on days 1 and 3

**Administered 5 to 8 weeks after start of the last induction or 1st consolidation, up to a maximum of 2 consolidation cycles, according to product monograph. Do not start consolidation until ANC > 0.5 x 10^9/L and platelets > 50 x 10^9/L.

Dosage with Toxicity:

Toxicity	Action
Cardiotoxicity (i.e., cardiomyopathy, impaired cardiac function)	Discontinue.
Acute copper toxicity	Discontinue.

Management of Infusion-related reactions:

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

Severity	Management	Re-challenge
Mild	• Stop the infusion. • Manage the symptoms. **Restart:** • Once symptoms resolve, restart the infusion at 50% of the prior rate +/- pre-medications (antihistamines and/or corticosteroids).	• Re-challenge with pre-medications.
Moderate	• Stop the infusion. • Manage the symptoms. • Do not restart.	• Pre-medicate with antihistamines and/or corticosteroids. • Re-challenge at the same rate.
Severe	• Stop treatment. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Dosage with Hepatic Impairment:

Liposomal daunorubicin / liposomal cytarabine should only be used in severe hepatic impairment if benefits outweigh risks.

Bilirubin (µmol/L)	Liposomal Daunorubicin / Liposomal Cytarabine Dosage
≤ 50	No dose adjustment required
> 50	No data

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Liposomal Daunorubicin / Liposomal Cytarabine Dosage
≥ 15	No dose adjustment required
< 15	No data. Use only if benefits outweigh risks.

Dosage in the elderly:

No dose adjustment required in patients ≥ 65 years old. Although there were no overall differences in safety between older and younger patients, bleeding events occurred more frequently in patients ≥ 65 years old.

Dosage based on gender:

No clinically important effects were observed based on gender.

Dosage based on ethnicity:

No clinically important effects were observed based on ethnicity.

Children:

The safety and efficacy of liposomal daunorubicin / liposomal cytarabine has not been established in patients < 18 years old.

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F - Administration Guidelines

Liposomal daunorubicin / liposomal cytarabine (Vyxeos®) is **not interchangeable** with other daunorubicin- and/or cytarabine-containing products.

- Dose should be determined based on the liposomal daunorubicin component and the individual's BSA.
- Calculate drug volume based on the concentration of the liposomal daunorubicin component (2.2 mg/mL).
- Reconstitute each vial with SWFI; mix by careful swirling and gentle inversion. Refer to the product monograph for details.
- Dilute in 500mL NS or D5W; mix by gentle inversion.
- Administer as IV infusion over 90 minutes using an infusion pump through a CVC or PICC line. An in-line membrane filter (minimum pore diameter ≥ 15 µm) may be used.
- Daunorubicin is a vesicant. Exercise care to ensure that there is no extravasation when liposomal daunorubicin / liposomal cytarabine is administered.
- Do NOT administer by intramuscular, intrathecal or subcutaneous route.
- Flush line with NS after administration.
- Do not mix with or administer as an infusion with other medications.
- Store unopened vials in the original carton at 2-8°C. Protect from light. Keep in an upright position.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or any of its components

Other Warnings/Precautions:

- Liposomal daunorubicin / liposomal cytarabine is not recommended in patients with reduced LVEF.
- Avoid use of live vaccines in patients receiving liposomal daunorubicin / liposomal cytarabine. Inactivated vaccines may be administered; however, response may be diminished.
- Patients should exercise caution when driving or operating heavy machinery as fatigue and dizziness have been reported with liposomal daunorubicin / liposomal cytarabine.
- Caution in patients with Wilson's disease; the formulation contains copper. A hepatologist and nephrologist should be consulted before starting treatment. Perform serum/urine copper levels and serial neuropsychological assessments at baseline and as clinically indicated.

Other Drug Properties:

- Carcinogenicity: Probable

Pregnancy and Lactation:

- Mutagenicity: Yes
- Clastogenicity: Yes
- Embryotoxicity: Yes
- Teratogenicity: Yes
  Liposomal daunorubicin / liposomal cytarabine is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Probable
  Based on animal studies with cytarabine and daunorubicin, male fertility may be compromised.

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H - Interactions

No interaction studies have been performed. A lower risk of drug interactions is expected with liposomal drug delivery as free-drug concentrations are reduced compared to the conventional formulation.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cardiotoxic agents (e.g., doxorubicin)	↑ cardiotoxic effect (with prior use of anthracyclines)	Additive	Do not administer with other cardiotoxic agents unless cardiac function is closely monitored; avoid anthracycline-based therapy for up to 28 weeks after stopping trastuzumab.
Hepatotoxic agents	↑ risk of liver impairment and toxicity	Changes in hepatic function due to concomitant therapies may affect PK/efficacy/toxicity of liposomal daunorubicin / liposomal cytarabine.	Monitor liver function more frequently when liposomal daunorubicin / liposomal cytarabine is given with hepatotoxic agents.

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Cardiac function tests (e.g., ECG, and MUGA / Echo)	Baseline, prior to consolidation, and as clinically indicated
CBC	Baseline, before each cycle, and as clinically indicated
Liver function tests	Baseline, before each cycle, and as clinically indicated
Renal function tests	Baseline, before each cycle, and as clinically indicated
Clinical toxicity assessment for infusion-related or injection site reactions, tumour lysis syndrome, infections, bleeding, skin, respiratory and GI effects	At each visit

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

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J - Supplementary Public Funding

High Cost Therapy Funding Program

- Liposomal Daunorubicin and Liposomal Cytarabine (Inpatient) - Previously Untreated Acute Myeloid Leukemia

New Drug Funding Program (NDFP Website)

- Liposomal Daunorubicin and Liposomal Cytarabine (Outpatient) - Previously Untreated Acute Myeloid Leukemia

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K - References

Blair, Hannah A. Daunorubicin/Cytarabine Liposome: A Review in Acute Myeloid Leukaemia. Drugs (2018) 78:1903–1910.

Cytarabine drug monograph. Ontario Health (Cancer Care Ontario).

Daunorubicin drug monograph. Ontario Health (Cancer Care Ontario).

Lancet et al. CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. Journal of Clinical Oncology 2018 36:26, 2684-2692.

Mayer LD, Tardi P, Louie AC. CPX-351: a nanoscale liposomal co-formulation of daunorubicin and cytarabine with unique biodistribution and tumor cell uptake properties. Int J Nanomedicine. May 23, 2019.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Antiemesis. Version 2.2022, March 23, 2022.

Product monograph: Vyxeos® (daunorubicin and cytarabine liposome for injection). Jazz Pharmaceuticals Canada Inc. February 2023.

Summary of Product Characteristics: Vyxeos liposomal 44 mg/100 mg powder for concentrate for solution for infusion. Jazz Pharmaceuticals UK limited. March 2022.

December 2023 Modified Dosage in hepatic impairment, Dosage in renal impairment, and Pregnancy/lactation sections

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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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