Drug Monograph

A - Drug Name

pegylated liposomal DOXOrubicin

SYNONYM(S): Doxorubicin Hydrochloride Pegylated Liposomes

COMMON TRADE NAME(S): Caelyx®

back to top

B - Mechanism of Action and Pharmacokinetics

"Pegylated liposomal doxorubicin (Caelyx®) is doxorubicin hydrochloride encapsulated in long-circulating liposomes, microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The Stealth® liposomes are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system and to increase blood circulation time. It is hypothesized that pegylated liposomal doxorubicin molecules are able to penetrate the vasculature of tumours. Incorporation of doxorubicin into a liposomal preparation substantially alters the pharmacokinetic properties of the drug compared with those of the non-liposomal doxorubicin."

Absorption	Oral: No	
Distribution	The pharmacokinetics of pegylated liposomal doxorubicin are non-linear. Pegylated liposomal doxorubicin distributes mainly in intravascular fluid.	
	Volume of distribution	1.93 L/m^2
	Cross blood brain barrier?	yes
	PPB	Approximately 70 % (doxorubicin)
Metabolism	Liposomal doxorubicin undergoes metabolism mainly in the liver.	
	Active metabolites	Doxorubicinol (major metabolite).

	Inactive metabolites	Yes
Elimination	The elimination of doxorubicin is primarily via the biliary system. Very low or absent plasma concentrations of doxorubicin metabolites suggest that either doxorubicin is not released in great extent from the liposomes as they circulate, or the doxorubicinol elimination rate exceeds the release rate.	
	Urine	5% (in 72 hours)
	Half-life	(apparent mean): 74 hours

back to top

C - Indications and Status

Health Canada Approvals:

- Treatment of advanced ovarian carcinoma in women who have failed standard first-line therapy (platinum and paclitaxel based chemotherapy).
- Treatment of patients with AIDS-related Kaposi's sarcoma with CD4 counts < 200/mm^3 and extensive mucocutaneous or visceral disease, who have failed or are intolerant of prior systemic combination chemotherapy (with at least 2 of vinca alkaloid, bleomycin, and doxorubicin or another anthracycline).
- Monotherapy in metastatic breast cancer, for patients with an increased cardiac risk with conventional doxorubicin.

back to top

D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Irritant

The following adverse effects were reported mainly in single agent studies in breast cancer.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<1%)	E D
	Arterial thromboembolism (<1%)	E D

	Cardiotoxicity (3-9%)	E
	Venous thromboembolism (<1%)	E D
Dermatological	Alopecia (20%)	E
	Hand-foot syndrome (48%)	E
	Nail disorder (<5%)	E
	Radiation recall reaction (rare)	E
	Rash (10%) (may be severe)	I
Gastrointestinal	Abdominal pain (8%)	E
	Anorexia (11%)	I
	Constipation (8%)	E
	Diarrhea (7%)	E
	Dyspepsia (<5%)	E
	Mucositis (23%)	E
	Nausea, vomiting (37%)	I
	Weight changes (≤5%)	E
General	Fatigue (12%)	E
	Pain (<5%)	E
Hematological	Myelosuppression ± infection, bleeding (>10%) (may be severe)	E
Hepatobiliary	↑ LFTs (2%)	E
Hypersensitivity	Infusion related reaction (11-13%)	I
Injection site	Phlebitis (rare)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (≤5%)	E
Neoplastic	Secondary malignancy (rare)	D L
Nervous System	Dysgeusia (<5%)	I E
Respiratory	Cough (1-5%)	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 reported were **infusion reactions, hand-foot syndrome, nausea/vomiting, mucositis, alopecia and fatigue.**

In general, **acute hypersensitivity infusion reactions** occur during the first infusion of pegylated liposomal doxorubicin, usually within the first few minutes after the start of the infusion. Symptoms include flushing, rash, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest and throat, and hypotension. These acute reactions do not appear to occur during subsequent cycles of chemotherapy in patients who did not react to the first cycle. Hold the infusion if a patient experiences signs or symptoms of an infusion reaction. These symptoms usually resolve without further therapy; however, some patients may require treatment with antihistamines and/or corticosteroids.

Left ventricular failure is less common than with doxorubicin but is reported and is more common in patients who have received high cumulative lifetime doses of doxorubicin (> 550mg/m^2), other anthracyclines or anthracenediones, who have had doxorubicin doses > 400mg/m^2 plus mediastinal radiation or have other cardiac risk factors. Congestive heart failure and/or myocardiopathy may occur suddenly or may happen several weeks after treatment completion.

A frequent dose-limiting adverse effect of pegylated liposomal doxorubicin is **myelosuppression**, predominantly leukopenia, with higher incidence and greater severity in patients with Kaposi's sarcoma who are immuno-compromised at baseline. In patients with ovarian cancer, myelosuppression is generally mild to moderate, reversible and is not associated with neutropenic infection or sepsis. Growth factor support is infrequently required. Pegylated liposomal doxorubicin does not appear to offer any advantage over standard doxorubicin in terms of hematological adverse events.

Palmar-plantar erythrodysesthesia (PPE; hand-foot syndrome) is another common dose and schedule-related adverse effect associated with pegylated liposomal doxorubicin. The syndrome is characterized by painful, macular reddening skin eruptions, swelling, pain, and, for some patients, desquamation of the skin on the hands and feet. PPE is generally seen after 2 or 3 cycles of treatment but may occur earlier. Strategies to prevent and treat PPE, which may be initiated 4-7 days after treatment, include keeping hands and feet cool, avoiding excessive heat/hot water and keeping them unrestricted. Emollients and petroleum-based balms may also provide some relief.

Pegylated liposomal doxorubicin associated **stomatitis** is dose and schedule-dependent and occurs in up to 39% of patients. Mouth care with regular rinsing should be encouraged as prophylaxis. Mouth sores usually subside with dosage reduction and treatment delay (see Dosing), along with appropriate stomatitis treatment protocol.

Secondary oral cancers, including fatal cases were reported during treatment and up to 6 years following treatment completion. Patients should be monitored regularly for oral ulceration or discomfort.

back to top

E - Dosing

Dose adjustment is required in patients with history of prior anthracyclines use, prior mediastinal irradiation, concurrent cyclophosphamide therapy, or pre-existing cardiovascular disease.

Adults:

Ovarian or breast cancer:

- q4 weeks: 50mg/m^2 IV

AIDS-Kaposi's Sarcoma:

- q2-3 weeks: 20mg/m^2 IV

Dosage with Toxicity:

Dosage modifications for toxicity differ for ovarian cancer and Kaposi's sarcoma. This is due to differences in the population group, immunity status, and dose of pegylated liposomal doxorubicin indicated for specific use.

Non-HIV Indications:

Worst Toxicity & Toxicity on day of planned dosing	**Action*: Week 4-5**	**Action*: Week 6**
Grade 1 skin/stomatitis	If was ≥ grade 3, delay for 1-2 weeks; otherwise treat on time	If still grade 1, ↓ dose by 25%
Grade 2 skin/stomatitis	Delay for 1-2 weeks;	If still grade 1 or 2, ↓ dose by 25%
Grade 3 or 4 skin/stomatitis	Delay for 1-2 weeks;	Discontinue if still ≥ grade 3 Consider discontinuing if was grade 4 Otherwise ↓ dose by 25%
Grade 4 ANC, platelets, febrile neutropenia or thrombocytopenic bleeding	↓ dose by 25%	
Worst Toxicity & Toxicity on day of planned dosing	**Action*: Week 4-5**	**Action*: Week 6**

Significant cardiotoxicity	Discontinue	
Grade 3 other	↓ dose by 25%	
Grade 4 other	Discontinue	
*Do not retreat until ANC > 1.5 x 10^9/L, platelets > 75-100 x 10^9/L and other toxicity ≤ grade 2 / or as indicated above		

HIV/AIDS indication:

Worst Toxicity & Toxicity on day of planned dosing	**Action*: Week 3**	**Action*: Week 4**
Grade 1 skin	If was ≥grade 3, delay for 1 week; otherwise treat on time	If still grade 1, ↓ dose by 25%
Grade 1 stomatitis	Treat on time with no dose modification	Not applicable
Grade 2 skin	Delay for 1 week	If still grade 2, ↓ dose by 50% If grade 1, ↓ dose by 25%
Grade 2 stomatitis	Delay for 1 week	If still grade 2, ↓ dose by 25%
Grade 3 skin	Delay for 1 week	If still grade 3, discontinue If grade 2, then ↓ dose by 50% If grade 1, ↓ dose by 25%
Grade 3 stomatitis	Delay for 1 week	If improved, ↓ dose by 25%
Grade 4 skin	Delay for 1 week	If still ≥ grade 3, discontinue If ≤ grade 2, ↓ dose by 50%
Grade 4 stomatitis	Delay for 1 week	If still grade 4, discontinue If improved, ↓ dose by 50%
Grade 3 myelosuppression	↓ dose by 25%	
Grade 4 ANC, platelets, febrile neutropenia or thrombocytopenic bleeding	↓ dose by 50%	
Worst Toxicity & Toxicity on day of planned dosing	**Action*: Week 3**	**Action*: Week 4**
Significant cardiotoxicity	Discontinue	
Grade 3 other	↓ dose by 25%	

Grade 4 other	Discontinue or ↓ dose by 50%	
*Do not retreat until ANC > 1 x 10^9/L, platelets > 50-100 x 10^9/L and other toxicity ≤ grade 2 / or as indicated above		

Management of Infusion-related reactions with Anthracyclines:

Also refer to the 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:

Bilirubin (µmol/L)	Ovarian, Breast cancer		HIV/AIDS
	% of Standard Dose		
	Cycle 1 (% normal dose)	Cycle 2 onwards if cycle 1 tolerated with no changes in liver function tests (% normal dose)	Each cycle (% normal dose)
21-51	75%	100%	50%
>51	50%	75%*	25%

* The dosage can be increased for subsequent cycles if tolerated.

Dosage with Renal Impairment:

No modifications are necessary for mild to moderate renal impairment (creatinine clearance > 30 mL/min). No studies have been done in patients with severe renal impairment.

Dosage in the elderly:

Limited information in patients ≥ 60 years. Use with caution.

Children:

Safety and efficacy not established.

back to top

F - Administration Guidelines

Pegylated liposomal doxorubicin must **not** be given by the intramuscular or subcutaneous route.

- For dose < 90mg, dilute drug in 250mL D5W.
- For dose ≥ 90mg, dilute drug in 500mL D5W.
- Only use 5% Dextrose solution for further dilution. Use of other diluents or ones containing bacteriostatic agents (i.e. benzyl alcohol) may cause drug precipitation.
- Do not administer as a bolus injection or undiluted solution. The Caelyx® infusion line can be connected through the side port of a 5% Dextrose infusion for further diluent, or to minimize risk of thrombosis or extravasation.
- Do not use in-line filters. Do not admix Caelyx® with other drugs.
- To minimize the risk of infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent infusions may be administered over 60-minutes (in ovarian or breast cancer) and 30 minutes (for Kaposi's sarcoma patients).
- The following graduated rate was used for patients who experienced an infusion reaction in the breast clinical trial: 5% of the total dose infused IV over 15 minutes. If tolerated, double the infusion rate for the next 15 minutes. If tolerated, complete the infusion over the next hour for a total infusion time of 90 minutes.
- Avoid extravasation. It may occur with or without an accompanying stinging or burning sensation, and even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation occur, the injection or infusion should be immediately terminated and restarted in another vein. Any known or suspected extravasation should be managed promptly.

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

back to top

G - Special Precautions

Contraindications:

- Patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin, other anthracyclines, anthracenediones, or components of the pegylated liposome
- Patients with Kaposi's Sarcoma and HIV who have had splenectomy (no experience)

Other Warnings/Precautions:

-
  - Use with caution in patients with a history of cardiovascular disease and/or prior anthracycline use
  - care should be exercised in patients with diabetes as the infusate is dextrose water
  - pegylated liposomal doxorubicin (Caelyx) is a unique formulation of doxorubicin and should never be used interchangeably with other formulations of doxorubicin

Other Drug Properties:

- Carcinogenicity: Probable

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Teratogenicity: Probable
  Pegylated liposomal doxorubicin is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- Breastfeeding:
  Pegylated liposomal doxorubicin is contraindicated in breastfeeding.

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
barbiturates	↓ efficacy of doxorubicin	↑ clearance of doxorubicin	monitor
cyclophosphamide	exacerbation of hemorrhagic cystitis	uncertain	Caution
cyclophosphamide	↑ cardiotoxicity	uncertain	monitor, adjust as needed
digoxin	↓ digoxin levels	↓ digoxin absorption	monitor digoxin levels and patient
mercaptopurine	↑ hepatotoxicity	uncertain	monitor
quinolones	↓ efficacy of quinolones	↓ absorption of quinolones	monitor, may need to modify dose of quinolones
High dose progesterone	↑ hematologic toxicity	unknown	caution
Calcium channel blockers	↑ cardiotoxicity	additive	avoid
Sorafenib	possibly ↑ doxorubicin toxicity	↑ doxorubicin exposure	caution
cyclosporine	↑ hematologic toxicity	↓ doxorubicin clearance or metabolism	caution
cytarabine	typhlitis	uncertain	caution; treat appropriately
Streptozocin	↑ toxicity of doxorubicin	liver damage due to streptozocin decreasing metabolism of doxorubicin	caution
zidovudine	↓ effect of zidovudine	doxorubicin decreases intracellular activation	avoid
stavudine	↓ effect of stavudine	inhibits stavudine phosphorylation/metabolism	avoid
radiation	↑ toxicity	radiation sensitizer	caution; consider dose modification, especially in patients with prior mediastinal radiation

Paclitaxel followed by doxorubicin	↑ neutropenia and stomatitis	↓ doxorubicin clearance	use paclitaxel after doxorubicin
Dactinomycin	↑ radiation recall pneumonitis	additive effects	caution
phenytoin	↓ phenytoin levels	↑ phenytoin metabolism	caution, check levels
Trastuzumab	↑ cardiotoxicity	additive	avoid anthracycline-based therapy for up to 24 weeks after stopping Trastuzumab
Vincristine	seizures	unknown	caution

back to top

I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors. Regular cardiac function tests before each additional dose over the cumulative dose **threshold** of **450 mg/m^2**. (Cumulative dose lower for high risk patients)	Baseline and as clinically indicated
CBC	Baseline and at each visit
Liver function tests	Baseline and at each visit
Clinical toxicity assessment for stomatitis, rash, hand-foot syndrome, hypersensitivity, infection, bleeding and cardiac symptoms	At each visit

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

back to top

J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Liposomal Doxorubicin - Platinum-Resistant Ovarian Fallopian Tube or Primary Peritoneal Cancer
- Liposomal DOXOrubicin - Single Agent Treatment of Platinum Sensitive Ovarian Fallopian Tube or Primary Peritoneal Cancer
- Liposomal Doxorubicin with Carboplatin - Platinum-Sensitive Recurrent Ovarian Fallopian Tube and Primary Peritoneal Cancer
- Liposomal Doxorubicin - HIV-positive Kaposi's Sarcoma

back to top

K - References

McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, p. 1046-55.

Doxorubicin drug monograph, Cancer Care Ontario, 2011.

Product Monograph: Caelyx® (pegylated liposomal doxorubicin). Janssen Inc., October 10, 2013.

December 2019 Updated NDFP form titles

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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management

information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top