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A DRUG NAME: LIPOSOMAL DOXORUBICIN

SYNONYM(S): Doxorubicin Hydrochloride Liposomes

COMMON TRADE NAME(S): Myocet® (Sopherion Therapeutics)

B MECHANISM OF ACTION AND PHARMACOKINETICS

Liposomal doxorubicin (Myocet®) is doxorubicin hydrochloride encapsulated in liposomes that are composed of egg phosphatidylcholine and cholesterol, but which are not pegylated. Liposomal encapsulation prolongs exposure to doxorubicin, although pegylation results in longer exposure than non-pegylated liposomal doxorubicin. Doxorubicin molecules encapsulated in liposomes can extravasate into tumours with abnormal vascular endothelium but may not penetrate normal tissues. Both prolonged exposure and differential tissue/tumour penetration may alter the therapeutic index and toxicity. Free doxorubicin damages DNA by intercalation of the anthracycline portion, metal ion chelation, or by generation of free radicals. Doxorubicin has also been shown to inhibit DNA topoisomerase II which is critical to DNA function. Cytotoxic activity is cell cycle phase non-specific.

Oral Absorption	No	
Distribution	Compared to conventional doxorubicin, plasma levels are higher, clearance is less (9 times) and volume of distribution is less (25 times).	
	Cross blood brain barrier?	Not clear
	PPB	Approximately 70% (doxorubicin)
Metabolism	Liposomal doxorubicin undergoes metabolism similar to that of doxorubicin. Doxorubicin is metabolised mainly in the liver but doxorubicinol appears later than with non liposomal doxorubicin.	
	Active metabolite(s)	Doxorubicinol (major metabolite)
	Inactive metabolite(s)	Yes
Excretion	The elimination of doxorubicin is primarily via the biliary system	
	t _{1/2} (terminal)	52.6 hrs
	Urine	6.44% of doxorubicin (after 48 hours)

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C INDICATIONS AND STATUS

* First-line treatment of metastatic breast cancer in combination with cyclophosphamide

* Health Canada approved indication

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D ADVERSE EFFECTS

ORGAN SITE	SIDE EFFECT*	ONSET**
Cardiovascular	<u>Cardiac failure</u> (5%- 750mg cumulative dose)	E D L
	Arrhythmia, chest pain, pericardial effusion (<5%)	E
Dermatologic and Hypersensitivity	Alopecia (91%)	E
	Injection site reaction (5%)	I
	Nail disorder (<5%)	E
	Rash, pruritis, folliculitis (11%)	I E
	Low grade radiation recall reaction (<1%)	E
Extravasation hazard (refer to Appendix 2)	Irritant	I
Gastrointestinal	<u>Nausea and Vomiting</u> (84%, grade 3 or 4; 21%)	I E
	<u>Stomatitis</u> (40%; grade 3 or 4; 7%)	E
	Diarrhea (28%, grade 3 or 4; 3%)	E
	Constipation, anorexia, weight loss (<5%)	E
	Gastric ulcer (<5%)	E
Hepatic/Metabolic	Abnormal LFTs (<5%)	E
	Hypokalemia, hyperglycemia (<5%)	E
Musculoskeletal	Back pain, muscle weakness (< 5%)	E
	Myalgia (<5%)	E
Pulmonary	Dyspnea, pneumonitis (<5%)	E
Renal	Oliguria, hemorrhagic cystitis (<5%)	E
Neurological	Gait abnormality, dysphonia (<5%)	E
	Insomnia, somnolence, agitation, dizziness (<5%)	E

D ADVERSE EFFECTS (continued)		
ORGAN SITE	SIDE EFFECT*	ONSET**
Generalized	Fatigue (42%, grade 3 or 4; 6%)	E
	Infusion reactions (<5%) – hot flushes, dyspnea, fever, headache, facial swelling, back pain, chills, hypotension	I
Hematologic	<u>Neutropenia</u> (grade 4 ; 61%)	E
	<u>Thrombocytopenia</u> (4% < 20,000)	E
	<u>Anemia</u> (23%)	E
	Febrile neutropenia (10%), Infection (grade 3 or 4; 11%)	E
	Bleeding, purpura, lymphopenia (<5%)	E

* Dose-limiting side effects are underlined.

** I = immediate (onset in hours to days)

E = early (days to weeks)

D = delayed (weeks to months)

L = late (months to years)

All common side effects (> 5%) are incidences associated with liposomal doxorubicin (75mg/m²) when given with cyclophosphamide. Toxicity is less frequent with lower doses.

Myelosuppression is the most common and dose limiting side effect associated with liposomal doxorubicin. Hematologic toxicity may require dose reductions or delays. Therapy with colony-simulating factors may also be considered. Prolonged and / or severe **mucositis** or **gastrointestinal side effects** also warrant dose reduction.

Left ventricular failure is less common than with conventional doxorubicin but is reported and is more common in patients who have received high cumulative lifetime doses of doxorubicin (> 750mg/m²), other anthracyclines or anthracenediones, or who have received mediastinal radiation or have other cardiac risk factors. Caution should be exercised when lifetime cumulative dose is reached. This lifetime cumulative dose could be comprised of both conventional doxorubicin and liposomal doxorubicin, or it could be exclusively liposomal doxorubicin.

Occasional **infusion reactions** have been reported with liposomal doxorubicin infusion. This may be avoided by moderating or slowing the drug infusion rate. Premedication is usually not required. Hand foot syndrome has not been commonly described.

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DOSING

Refer to protocol by which patient is being treated.

Adults: 60- 75 mg/m² in combination with cyclophosphamide (600mg/m²) administered every 3 weeks

Dosage in myelosuppression: Growth factors OR dose modification should be instituted for grade 4 neutropenia > 7 days duration or febrile neutropenia.

ANC (10 ⁹ /L)		Platelet (10 ⁹ /L)		Hemoglobin	Modification for liposomal doxorubicin and cyclophosphamide
<1.2	And / Or	<100	And / Or	Grade 4	Delay until ANC ≥ 1.2, platelets ≥ 100, Hemoglobin ≤ Grade 2
< 0.5 ≥ 7 days or febrile neutropenia					Reduce subsequent cycles by one dose level* or use growth factor support
		<25			Reduce subsequent cycles by one dose level*

Dosage with mucositis and GI toxicity:

Mucositis		Other GI toxicity	Modification for liposomal doxorubicin and cyclophosphamide
Grade 3 (lasting 3 or more days) or Grade 4	Or	Persistent Grade 3 or 4	Wait until Mucositis or other GI toxicity recovered to grade 2; reduce subsequent cycles by one dose level*

* Dose Level Reduction: Liposomal doxorubicin : 75mg/m² → 60 mg/m² → 50 mg/m² → 40 mg/m²
Cyclophosphamide : 600mg/m² → 500mg/m² → 400 mg/m²

Dosage with renal impairment: no adjustment required

Dosage with hepatic impairment:

Bilirubin (µmol/L)	% usual dose
1-2.5 x ULN	50%
> 2.5 x ULN	25%

Dosage in the elderly: Use with caution

Children: Safety and efficacy not established.

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ADMINISTRATION GUIDELINES (see [Appendix 3a](#))

- Follow manufacturer's instructions for reconstitution.
- Dilute drug in 250-500mL NS or D5W. (May dilute drug maximally up to 50 times.)
- Infuse over 1 hour.
- Avoid extravasations.
- Do not administer as a bolus injection or undiluted solution.
- Liposomal doxorubicin must **not** be given by the intramuscular or subcutaneous route.

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G SPECIAL PRECAUTIONS

Cardiotoxicity precautions for doxorubicin, anthracyclines or anthracenediones should be observed for liposomal doxorubicin even though the incidence appears lower. Extreme caution should be exercised if dosed above a lifetime cumulative (both conventional and liposomal) doxorubicin dose of 750mg/m². Patients with a history of **cardiovascular disease** should be administered liposomal doxorubicin only when the potential benefit of treatment outweighs the risk.

Liposomal doxorubicin is **contraindicated** in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin, other anthracyclines or anthracenediones or components of the liposome, including egg and egg products.

Liposomal doxorubicin is **embryotoxic**, may be **teratogenic** and is an **abortifacient** and should not be administered to **pregnant** women. Women of childbearing potential should be advised to avoid pregnancy while they or their male partner are receiving liposomal doxorubicin and in the 6 months following discontinuation of liposomal doxorubicin. It is not known whether this drug is excreted in human milk. Mothers should discontinue **nursing** prior to taking this drug.

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H INTERACTIONS

AGENT	EFFECT	MECHANISM	MANAGEMENT
Barbiturates	efficacy of doxorubicin decreased	increased clearance of doxorubicin	monitor
Cyclophosphamide	exacerbation of hemorrhagic cystitis	uncertain	caution
Cyclophosphamide	increased cardiotoxicity	uncertain	monitor, adjust as needed
Digoxin	decreased digoxin levels	decreased digoxin absorption	monitor digoxin levels and patient
Mercaptopurine	enhanced hepatotoxicity	uncertain	monitor
Quinolones	decreased efficacy of quinolones	decreased quinolones absorption	monitor, may need to modify dose quinolones
Cytarabine	Typhlitis	uncertain, treat appropriately	caution
Streptozocin	increased toxicity of doxorubicin	decreases metabolism of doxorubicin	caution
Zidovudine	decreased effect of zidovudine	Doxorubicin ↓ intracellular activation	avoid

H	INTERACTIONS (continued)			
	AGENT	EFFECT	MECHANISM	MANAGEMENT
	Radiation	increased toxicity	radiation sensitizer	
	Paclitaxel followed by doxorubicin	increased neutropenia and stomatitis	reduced doxorubicin clearance	use paclitaxel after doxorubicin
	Dactinomycin	increased radiation recall pneumonitis		caution
	Phenytoin	reduced phenytoin levels		caution, check levels
	Cyclosporin	increased hematologic toxicity	reduced doxorubicin clearance/metabolism	caution
	High dose progesterone	increased hematologic toxicity	unknown	caution
	Cucurmin (Turmeric)	May reduce effect of Doxorubicin	Inhibits Doxorubicin induced apoptosis	Avoid concomitant use
	Vincristine	Seizure	Unknown	caution

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I	RECOMMENDED CLINICAL MONITORING	
	<u>Recommended Clinical Monitoring</u>	<u>Suggested Clinical Monitoring</u>
	<ul style="list-style-type: none"> Regular clinical assessment and grading of stomatitis and CHF. Baseline and regular liver function tests Baseline and regular CBC Baseline cardiac function tests (Echo, RNA and/or MUGA scans) for all patients Periodic cardiac function tests for all patients with cardiac risk factors or patients at or above the lifetime cumulative doxorubicin dose of 300mg/m² 	<ul style="list-style-type: none"> Periodic cardiac function tests after completion of therapy in patient with clinical cardiac symptoms.

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J REFERENCES

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