DRUG NAME: Doxorubicin pegylated liposomal

SYNONYM(S): PLD, pegylated liposomal doxorubicin [1]

COMMON TRADE NAME(S): CAELYX®, DOXIL® (USA), LIPODOX® (USA)

CLASSIFICATION: antitumour antibiotic (anthracycline)

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

MECHANISM OF ACTION:

Liposomal anthracyclines were developed to decrease the risk of cardiotoxicity experienced with conventional doxorubicin while preserving the anti-tumour efficacy. Liposomal anthracyclines achieve lower cardiotoxicity by changing tissue distribution and by decreasing rate of drug release. Liposomes cannot escape from the vascular space in areas that have narrow capillary junctions, such as the heart muscle, but they can reach tissues and organs that do not have narrow capillary junctions such as areas of tumour growth. [2] Liposomal doxorubicin formulations include liposomal doxorubicin and pegylated liposomal doxorubicin. Pegylated liposomal doxorubicin (PLD) is a formulation of doxorubicin in polyethylene glycol (PEG) coated Stealth® liposomes. [3] "Pegylation" is the process whereby the doxorubicin-containing liposomes are enclosed within a PEG layer. [2] Pegylation protects the liposomes from detection by the mononuclear phagocyte system [2] and provides a stabilization effect that reduces adhesion to cells, blood vessel walls and other surfaces. [4] During circulation, at least 90% of PLD remains encapsulated within the liposomes, resulting in an extended half life compared to conventional doxorubicin [4,5] The active ingredient of the formulation is doxorubicin (refer also to doxorubicin monograph).

PHARMACOKINETICS:

Interpatient variability	no information found	
Distribution	confined mostly to the vascular fluid volume	
	cross blood brain barrier?	no [6]
	volume of distribution	1.93 L/m^2 (range 0.96-3.85 L/m^2)
	plasma protein binding	no information found [5]
	active metabolite(s)	doxorubicinol detected in plasma after administration at very low levels [5]
	inactive metabolite(s)	no information found
	urine	5.5% recovered in urine after 72 h [5]
	feces	no information found
	terminal half life	73.9 h (range 24-231 h)
	clearance	0.03 L/h/m^2 (range 0.008-0.152 L/h/m^2)
Gender	no information found	
Elderly	does not affect the pharmacokinetics of this drug	
Children	no information found	
Ethnicity	not evaluated [6]	

Adapted from standard reference [7] unless specified otherwise.

USES:

Primary uses: ***Other uses:***

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*Breast cancer
*Kaposi's sarcoma
*Ovarian cancer

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to conventional formulation of doxorubicin or any components of the PLD preparation [7]

Caution:
- ***PLD formulations are not interchangeable*** with conventional doxorubicin or with other liposomal anthracyclines. [8] Care must be taken to avoid mistaking PLD for conventional doxorubicin or other liposomal anthracyclines, and PLD should be stored separately from conventional doxorubicin. [9]
- ***Cardiac toxicity*** has been seen with PLD at cumulative doses both above and below 550 mg/m^2, although at a significantly lower frequency than with conventional doxorubicin. [7]

Carcinogenicity: Carcinogenic potential of PLD has not been determined; however, conventional doxorubicin is carcinogenic in animals and is potentially carcinogenic in humans. [5]

Mutagenicity: Conventional doxorubicin is mutagenic and clastogenic (refer to doxorubicin monograph). The STEALTH® Liposome component of PLD tested negative for the Ames test and mammalian *in vitro* mutation test. The liposome component was found to be non-clastogenic in mammalian *in vitro* and *in vivo* chromosome tests. [7]

Fertility: Although not specific to PLD, conventional doxorubicin may produce gonadal suppression, resulting in amenorrhea or azoospermia. [5]

Pregnancy: Pegylated liposomal doxorubicin is embryotoxic and abortifacient in animal studies and may be teratogenic. [10] Women of childbearing potential should avoid pregnancy while they or their male partners are receiving treatment and for six months following discontinuation. [7]

Breastfeeding is not recommended due to the potential secretion into breast milk. [7]

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. [11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	***acute infusion reactions*** (5-10%) [6,9]; see paragraph following **Side Effects** table
	allergic reaction, anaphylactoid reaction (1-5%) [7]
blood/bone marrow/ febrile neutropenia	***anemia*** (6-74%); reaching nadir 10-14 days after treatment, recovery usually by days 21-28.
	ecchymosis, small hemorrhagic spots (1-10%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hemolysis (1-5%)
	leukopenia (36%) [7]
	neutropenia (12-62%) [7]
	thrombocytopenia (13-65%) [7]
cardiovascular (general) (see paragraph following **Side Effects** table)	hypotension (1-10%)
	pallor (1-10%)
	peripheral edema (≤11%)
	pericardial effusion (<1%)
	tachycardia (1-10%)
	thrombophlebitis (1-10%) [7]
	vasodilatation (1-10%)
	ventricular arrhythmia (<1%)
coagulation	prothrombin time increased (1-5%)
constitutional symptoms	diaphoresis, profuse sweating (1-10%)
	fever (8-12%)
	flu-like syndrome (1-5%) [7]
	weakness (7-40%)
	weight loss (1-5%) [7]
dermatology/skin	acne, dry skin (1-10%)
	alopecia, mild (6%) [3,4,8]
	herpes simplex/zoster (1-10%) [7]
	palmar-plantar erythrodysesthesia (≤51% in ovarian cancer, 4% in Kaposi's sarcoma); see paragraph following **Side Effects** table
	pruritus (1-5%) [7]
	rash (≤29% in ovarian cancer, ≤5% in Kaposi's sarcoma)
gastrointestinal	*emetogenic potential:* low [12]
	anorexia (<20%)
	ascites (1-10%)
	cachexia (1-10%)
	constipation (≤30%)
	diarrhea (5-21%)
	dyspepsia (≤12%)
	dysphagia (1-5%) [7]
	esophagitis (1-10%)
	flatulence (1-10%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	gingivitis (1-10%)
	glossitis (1-5%) [7]
	ileus (1-10%)
	liver failure (<1%)
	mouth ulceration (1-10%)
	mucositis (≤14%)
	nausea (18-46%)
	intestinal obstruction (≤11%)
	stomatitis (5-41%); see paragraph following **Side Effects** table
	taste changes (1-10%)
	vomiting (8-33%)
	weight loss (1-10%)
	xerostomia (1-10%)
general disorders and administration site conditions	*extravasation hazard:* irritant [13]
hemorrhage	epistaxis, nosebleed (1-10%)
	rectal bleeding (1-10%)
	vaginal bleeding (1-10%)
infection	infection (1-5%) [7]
	moniliasis, white vaginal discharge (1-10%)
metabolic/laboratory	dehydration (1-10%)
	electrolyte disturbances (i.e., decreased calcium, potassium, sodium) or increased glucose (1-10%)
musculoskeletal	arthralgia (1-10%)
	hypertonia (1-10%)
	myalgia (1-10%)
	neuralgia (1-10%)
	paresthesia (≤10%)
	pathological fracture (1-10%)
neurology	acute brain syndrome (<1%)
	agitation, anxiety (1-10%)
	chills (1-10%)
	confusion (1-10%)
	depression (1-10%)
	dizziness (1-10%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	emotional lability (1-10%)
	seizure (<1%)
	somnolence (1-10%)
	vertigo (1-10%)
ocular/visual	abnormal vision (<1%)
	blindness (<1%)
	conjunctivitis (1-10%)
	dry eyes (1-10%)
	retinitis (1-5%) [7]
pain	back pain (≤12%)
	ear pain (1-10%)
	headache (≤11%)
	general pain (≤21%)
	pelvic pain (1-10%)
pulmonary	cough, increased (≤10%)
	dyspnea (≤15%)
	pleural effusion (1-10%)
	pharyngitis (≤16%)
	pneumonia (1-5%) [7]
	sinusitis (1-10%)
renal/genitourinary	albuminuria (1-5%) [7]
	cystitis (1-10%)
	dysuria (1-10%)
	hematuria (1-10%)
	kidney failure (<1%)
	polyuria (1-10%)
secondary malignancy	secondary acute myelogenous leukemia; reported in patients treated with topoisomerase II inhibitors, including anthracyclines [5]

Adapted from standard reference [8] unless specified otherwise.

Acute infusion reactions can be serious and sometimes life-threatening. These occur within minutes of starting the PLD infusion. [7] The earliest and most common symptoms of this reaction are shortness of breath, light-headedness, perspiration, and hypotension. [9] Other symptoms include facial edema, vasodilatation, urticaria, back pain, chest pain, chills, fever, tachycardia, nausea, pharyngitis, rash and pruritus. [7] At the first sign of an acute infusion reaction, the infusion rate should be reduced or temporarily interrupted. [9] Slowing the rate or interrupting the infusion will usually resolve the symptoms, although antihistamines, IV H_2-blockers, or steroids are required for some patients. [4,7,9] In most patients, treatment can be resumed after all symptoms have resolved. To minimize the risk of infusion

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reactions the initial dose should be administered at a rate no greater than 1 mg/minute. [4,7] Infusion reactions rarely recur after the first infusion and subsequent infusions may be administered over a 60 minute period. [7] Unlike an IgE-mediated (type I) allergic reaction, this reaction occurs with first exposure to the drug without prior sensitization. [14] The lipid component rather than the doxorubicin is likely responsible for these acute infusion reactions. [7,9,14]

Cardiac toxicity has been seen with PLD at cumulative doses both above and below 550 mg/m^2, although at a significantly lower frequency than with conventional doxorubicin. [7] One study comparing the use of PLD with conventional doxorubicin in patients with metastatic breast cancer found a frequency of 3.9% cardiotoxicity in patients treated with PLD compared to a frequency of 18.8% in patients treated with conventional doxorubicin. Cardiotoxicity was defined as a pre-specified reduction in resting left ventricular ejection fraction. In this study no patients receiving PLD developed symptomatic congestive heart failure (CHF), while 3.9% of the patients receiving conventional doxorubicin developed CHF. [15] Retrospective and prospective trials have not identified a maximum "cardiac safe" cumulative dose of PLD above which CHF is expected to occur, despite doses exceeding 2,000 mg/m^2 in some patients. [5] Caution should be observed in patients who have received other anthracyclines or anthracenediones and in patients who have a history of cardiovascular disease. [7] Baseline MUGA scans should be performed on all patients treated with PLD. [9] Repeat MUGA scans should be performed after cumulative dose reaches 400 mg/m^2, and again at every 100-120 mg/m^2 cumulative dose increase. In patients who have received prior anthracycline treatment or have other pre-disposing risk factors, MUGA scans should be performed more frequently. 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.

Palmar-Plantar Erythrodysesthesia (PPE), also called *hand-foot skin reaction,* is characterized by painful, macular reddening skin eruptions which include swelling, pain and sometimes desquamation of the skin on the hands and feet. PPE can affect other parts of the body, including axilla and groin area or wherever the skin surface is warm. PPE is generally seen after 2 or 3 cycles of treatment but can occur earlier. [7] Patients usually experience slight numbness and tingling days or even weeks before erythema. [9] In most patients the reaction is mild and will resolve in one to two weeks with or without treatment using corticosteroids. Some patients will require a dose reduction to manage PPE, while patients with severe and debilitating PPE require discontinuation of therapy. [7] Patients should be asked at every visit whether they experienced numbness or tingling anywhere on their bodies since the last dose. If numbness or tingling has occurred the dosing interval should be prolonged. [4,9] Pyridoxine at a dose of 50-150 mg per day has been used for the prophylaxis and treatment of PPE without interfering with the anti-tumour efficacy of PLD. [4,7] Corticosteroids may also reduce the incidence of PPE during PLD treatment. [4] Early measures to prevent or minimize PPE include avoiding all of the following for 3 days after PLD therapy [9]:

- Tape on skin
- Tight clothing (especially around waist, groin, wrists and fingers)
- Tight jewelry [16]
- Pressure or friction on skin
- Hot water (including showers or dishwashing), beginning 24 hours before treatment
- Sun exposure, sun block recommended [16]
- Vigorous activities such as aerobics, heavy cleaning and gardening
- Leaning on bony prominences such as elbows

See dosing guidelines for suggested dose modifications related to PPE.

Stomatitis can occur at any dose of PLD, but higher doses are associated with increased risk of stomatitis. Other risk factors include: prior alcohol and tobacco use, nutritional status, poor dental hygiene and concomitant use of drugs such as antihistamines, anticholinergics, phenytoin and steroids. [9] See dosing guidelines for suggested dose modifications related to stomatitis.

INTERACTIONS:

No drug interaction studies have been conducted with PLD. PLD may interact with drugs known to interact with conventional doxorubicin; e.g., digoxin and cyclosporine. See doxorubicin monograph for more details. In patients who received cyclophosphamide or taxanes, no new toxicities were noted. [7]

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SUPPLY AND STORAGE:

Injection:
Janssen supplies doxorubicin in a pegylated liposomal formulation as 20 mg ready-to-use, single-use (preservative free) vials in a concentration of 2 mg/mL. Doxorubicin is encapsulated in STEALTH® liposome carriers to form a liposomal dispersion. Refrigerate. [17]

Taro Pharmaceuticals Inc. supplies doxorubicin in a pegylated liposomal formulation as 20 mg and 50 mg ready-to-use, single-use (preservative free) vials in a concentration of 2 mg/mL. Doxorubicin is encapsulated in liposome carriers to form a liposomal dispersion. Refrigerate. [10]

Additional information:
- pegylated liposomal doxorubicin is red in colour and translucent; discard if solution is discoloured or particulates are present. [17]

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.

Additional information:
- do NOT use with in-line filters [10]
- dilute in D5W only [10]
- pegylated liposomal doxorubicin is not compatible with any bacteriostatic agent such as benzyl alcohol [10]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

	BC Cancer administration guideline noted in ***bold***, ***italics***
Subcutaneous [7]	not used due to corrosive nature
Intramuscular [7]	not used due to corrosive nature
Direct intravenous [7]	do not administer as a bolus injection or undiluted solution
Intermittent infusion	***initial dose*** administered at a ***rate no greater than 1 mg/minute;*** subsequent infusions may be administered over 60 minutes if no infusion reaction is observed [1,18,19] ***OR*** ***over 30-60 minutes*** [20-25]
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

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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***

Intravenous:

Cycle Length:

2**-3 **weeks [17,24,26]: ***20 mg/m² IV for one dose on day 1 (total dose per cycle 20 mg/m²)***

4 weeks [4,17,27-29] ***40**-50 **mg/m² IV for one dose on day 1*** (total dose per cycle 40-50 mg/m²)

3-***4 weeks*** [4,30,31]: ***30 mg/m² IV for one dose on day 1*** (total dose per cycle 30 mg/m²)

Intervals <10 days should be avoided due to possible drug accumulation. [7]

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure [1]*:* no adjustment required

Dosage in hepatic failure: Adjustment required. Refer to protocol by which patient is being treated. If no guidelines are available, see suggested dose modifications below:

For **breast or ovarian** patients [1,18,19]

Total Bilirubin (micromol/L)	Dose
<21	100%
21-51	75%
>51	50%
If first dose is tolerated without further increases in bilirubin and/or liver enzymes, subsequent doses may be increased by one dosage level as clinically indicated. [1]	

For **Kaposi's Sarcoma** patients [1,25]

Bilirubin (micromol/L)	Dose
<21	100%
21-51	50%
>51	25%

Dosage in dialysis: no information found

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Dosage in PPE/stomatitis: Adjustment required. Refer to protocol by which patient is being treated. If no guidelines are available, use suggested dose modifications below:

For **breast or ovarian** patients [7]

Palmar-Plantar Erythrodysesthesia (PPE)			
Grade	Adverse event	Week after prior PLD dose Weeks 4&5	Week 6
1	mild erythema, swelling, or desquamation not interfering with daily activities	redose unless patient has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week	decrease dose by 25%; return to 4 week interval
2	erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter	delay one week	decrease by 25%; return to 4 week interval
3	blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	delay one week	discontinue
4	diffuse or local process causing infectious complications, or a bedridden state or hospitalization	delay one week	discontinue
Stomatitis			
Grade	Adverse event	Week after prior PLD dose Weeks 4&5	Week 6
1	painful ulcers, erythema or mild soreness	redose unless patient has experienced a previous Grade 3 or 4 stomatitis in which case wait an additional week	decrease dose by 25%; return to 4 week interval or discontinue per physician's assessment
2	painful erythema, edema or ulcers but can eat	delay one week	decrease dose by 25%; return to 4 week interval or discontinue per physician's assessment
3	painful erythema, edema or ulcers but cannot eat	delay one week	discontinue
4	requires parenteral or enteral support	delay one week	discontinue

For **Kaposi's Sarcoma** patients [7]

Palmar-Plantar Erythrodysesthesia (PPE)			
Grade	Adverse Event	Week after prior PLD dose Week 3	Week 4
	no symptoms	redose at 2 to 3-week interval	redose at 2 to 3-week interval
1	mild erythema, swelling or desquamation not interfering with daily activities	redose unless patient has experienced a previous grade 3 or 4 skin toxicity in which case wait an additional week	redose at 25% dose reduction; return to 3-week interval

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For **Kaposi's Sarcoma** patients [7]

Palmar-Plantar Erythrodysesthesia (PPE)			
Grade	Adverse Event	Week after prior PLD dose Week 3	Week 4
2	erythema, desquamation or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter	delay one week	redose at 50% dose reduction; return to 3-week interval
3	blistering, ulceration or swelling interfering with walking or normal daily activities; cannot wear regular clothing	delay one week	discontinue
4	diffuse or local process causing infectious complications, or a bedridden state or hospitalization	delay one week	discontinue

Stomatitis		
Grade	Adverse Event	Modification
1	painless ulcers, erythema or mild soreness	none
2	painful erythema, edema or ulcers but can eat	delay one week and if symptoms improve redose at 100%
3	painful erythema, edema or ulcers and cannot eat	delay one week and if symptoms improve redose at 25% dose reduction
4	requires parenteral or enteral support	delay one week and if symptoms improve redose at 50% dose reduction

Children: being studied in children; dosing guidelines have not yet been established.

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Developed: January 2006
Limited Revision: 1 March 2025