

DRUG NAME: Pegylated liposomal doxorubicin**SYNONYM(S):** PLD**COMMON TRADE NAME(S):** CAELYX®, DOXIL®**CLASSIFICATION:** anthracycline antineoplastic antibiotic¹, cytotoxic²*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.³ 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.³ Liposomal doxorubicin formulations include:

- liposomal doxorubicin
- pegylated liposomal doxorubicin

Pegylated liposomal doxorubicin (PLD) is a formulation of doxorubicin in polyethylene glycol (PEG) coated STEALTH® liposomes.⁴ “Pegylation” is the process whereby the doxorubicin-containing liposomes are enclosed within a PEG layer.³ Pegylation protects the liposomes from detection by the mononuclear phagocyte system³ and provides a stabilization effect that reduces adhesion to cells, blood vessel walls and other surfaces.⁵ During circulation, at least 90% of PLD remains encapsulated within the liposomes, resulting in an extended half life compared to conventional doxorubicin^{5,6} The active ingredient of the formulation is doxorubicin (see doxorubicin monograph).

PHARMACOKINETICS:

Interpatient variability	no information found	
Distribution	confined mostly to the vascular fluid volume	
	cross blood brain barrier?	no ¹
	volume of distribution	1.93 L/m ² (range 0.96-3.85 L/m ²)
	plasma protein binding	no information found ⁷
	active metabolite(s)	doxorubicinol detected in plasma after administration at very low levels ⁷
	inactive metabolite(s)	no information found
	urine	5.5% recovered in urine after 72 h ⁷
	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 ¹	

Adapted from standard reference⁸ unless specified otherwise.

USES:**Primary uses:**

- *Breast cancer
- *Kaposi's sarcoma
- *Ovarian cancer

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindicated in patients with the following conditions⁸:

- hypersensitivity to conventional formulation of doxorubicin
- hypersensitivity to any components of the PLD preparation

Cardiac toxicity has been seen with PLD at cumulative doses both above and below 550 mg/m², although at a significantly lower frequency than with conventional doxorubicin.⁸ 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.⁹ Cardiotoxicity was defined as a pre-specified reduction in resting left ventricular ejection fraction.⁹ In this study no patients receiving PLD developed symptomatic congestive heart failure (CHF), while 3.9% of the patients receiving conventional doxorubicin developed CHF.⁹

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/m² in some patients.¹⁰ Caution should be observed in patients who have received other anthracyclines or anthracenediones and in patients who have a history of cardiovascular disease.⁸ Baseline MUGA scans should be performed on all patients treated with PLD.¹² Repeat MUGA scans should be performed after cumulative dose reaches 400 mg/m², and again at every 100-120 mg/m² 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.

Carcinogenicity: Carcinogenic potential of PLD has not been determined; however, conventional doxorubicin is carcinogenic in animals and is potentially carcinogenic in humans.¹⁰

Mutagenicity: Conventional doxorubicin is mutagenic and clastogenic (see doxorubicin monograph). The STEALTH® Liposome component of PLD tested negative for the Ames test and mammalian *in vitro* mutation test.⁸ The liposome component was found to be non-clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.⁸

Fertility: Although not specific to PLD, conventional doxorubicin may produce gonadal suppression, resulting in amenorrhea or azoospermia.¹⁰

Pregnancy: FDA Pregnancy Category D. Women of childbearing age should be advised to avoid pregnancy while they or their male partners are receiving PLD and for six months following discontinuation.⁸ Although there is positive evidence of human fetal risk, the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.⁸

PLD formulations are not interchangeable with conventional doxorubicin or with other liposomal anthracyclines.¹¹ Care must be taken to avoid mistaking PLD for conventional doxorubicin or other liposomal anthracyclines, and PLD should be stored separately from conventional doxorubicin.¹²

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.¹³

ORGAN SITE	SIDE EFFECT	ONSET			
Clinically important side effects are in bold, italics I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
allergy/immunology	acute infusion reactions (5-10%)^{1,12}	I			
	allergic reaction, anaphylactoid reaction (1-5%) ⁸	I			
blood/bone marrow/ febrile neutropenia	myelosuppression: neutropenia (12-62%)⁸ , leukopenia (36%) ⁸ , thrombocytopenia (13-65%) ⁸ , anemia (6-74%) reaching nadir 10-14 days after treatment; recovery usually by days 21-28.		E		
	ecchymosis, small hemorrhagic spots (1-10%)		E		
	hemolysis (1-5%)		E		
cardiovascular (general)	hypotension (1-10%)	I			
	pallor (1-10%)		E		
	peripheral edema (up to 11%)			D	
	pericardial effusion (<1%)			D	
	tachycardia (1-10%)	I			
	thrombophlebitis (1-10%) ⁸		E		
	vasodilatation (1-10%)			D	
	ventricular arrhythmia (<1%)	I			
coagulation	prothrombin time increased (1-5%)		E		
constitutional symptoms	diaphoresis, profuse sweating (1-10%)		E		
	fever (8-12%)		E		
	flu-like syndrome (1-5%) ⁸		E		
	weakness (7-40%)		E		
	weight loss (1-5%) ⁸			D	
dermatology/skin	extravasation hazard: irritant				
	alopecia, mild (6%) ^{4,5,11}		E		
	acne, dry skin (1-10%)		E		
	herpes simplex/zoster (1-10%) ⁸			D	
	palmar-plantar erythrodysesthesia (up to 51% in ovarian cancer, 4% in Kaposi's sarcoma)		E		
	pruritus (1-5%) ⁸		E		
	rash (up to 29% in ovarian, up to 5% in Kaposi's sarcoma)		E		
gastrointestinal	emetogenic potential¹⁴: low				
	ascites (1-10%)			D	

ORGAN SITE	SIDE EFFECT	ONSET			
<p>Clinically important side effects are in <i>bold, italics</i> I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)</p>					
	anorexia (up to 20%)			D	
	cachexia (1-10%)			D	
	constipation (up to 30%)			D	
	diarrhea (5-21%)			D	
	dyspepsia (up to 12%)		E		
	dysphagia (1-5%) ⁸		E		
	esophagitis (1-10%)		E		
	flatulence (1-10%)		E		
	gingivitis (1-10%)		E		
	glossitis (1-5%) ⁸		E		
	ileus (1-10%)			D	
	liver failure (<1%)				L
	mouth ulceration (1-10%)			D	
	mucositis (up to 14%)			D	
	nausea (18-46%)		E		
	intestinal obstruction (up to 11%)			D	
	<i>stomatitis (5-41%)</i>		<i>E</i>		
	taste changes (1-10)			D	
	vomiting (8-33%)		E		
	weight loss (1-10%)			D	
xerostomia (1-10%)			D		
hemorrhage	epistaxis, nosebleed (1-10%)		E		
	rectal bleeding (1-10%)			D	
	vaginal bleeding (1-10%)		E		
infection	infection (1-5%) ⁸			D	
	moniliasis, white vaginal discharge (1-10%)			D	
metabolic/laboratory	dehydration (1-10%)		E		
	electrolyte disturbances (i.e., calcium decreased, glucose increased, potassium decreased, sodium decreased) (1-10%)		E		
musculoskeletal	arthralgia (1-10%)		E		
	hypertonia (1-10%)		E		
	myalgia (1-10%)		E		
	neuralgia (1-10%)		E		
	paresthesia (up to 10%)		E		
	pathological fracture (1-10%)		E		

ORGAN SITE	SIDE EFFECT	ONSET			
<p style="text-align: center;">Clinically important side effects are in <i>bold, italics</i> I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)</p>					
neurology	acute brain syndrome (<1%)			D	
	agitation, anxiety (1-10%)		E		
	chills (1-10%)		E		
	confusion (1-10%)	I			
	depression (1-10%)			D	
	dizziness (1-10%)	I			
	emotional lability (1-10%)		E		
	seizure (<1%)	I			
	somnolence (1-10%)		E		
	vertigo (1-10%)	I			
ocular/visual	abnormal vision (<1%)		E		
	blindness (<1%)			D	
	conjunctivitis (1-10%)		E		
	dry eyes (1-10%)		E		
	retinitis (1-5%) ⁸		E		
pain	back pain (up to 12%)		E		
	ear pain (1-10%)			D	
	headache (up to 11%)		E		
	general pain (up to 21%)		E		
	pelvic pain (1-10%)		E		
pulmonary	cough increased (up to 10%)		E		
	dyspnea (up to 15%)	I			
	pleural effusion (1-10%)			D	
	pharyngitis (up to 16%)		E		
	pneumonia (1-5%) ⁸			D	
	sinusitis (1-10%)			D	
renal/genitourinary	albuminuria (1-5%) ⁸		E		
	cystitis (1-10%)		E		
	dysuria (1-10%)		E		
	hematuria (1-10%)		E		
	kidney failure (<1%)			D	
	polyuria (1-10%)		E		
secondary malignancy	secondary acute myelogenous leukemia has been reported in patients treated with topoisomerase II inhibitors, including anthracyclines ⁷				L

Adapted from standard reference¹¹ unless specified otherwise.

Acute infusion reactions can be serious and sometimes life-threatening.⁸ These occur within minutes of starting the PLD infusion.⁸ The earliest and most common symptoms of this reaction are shortness of breath, light-headedness, perspiration, and hypotension.¹² Other symptoms include facial edema, vasodilatation, urticaria, back pain, chest pain, chills, fever, tachycardia, nausea, pharyngitis, rash and pruritus.⁸ At the first sign of an acute infusion reaction, the infusion rate should be reduced or temporarily interrupted.¹² Slowing the rate or interrupting the infusion will usually resolve the symptoms,⁸ although antihistamines, IV H₂-blockers,¹² or steroids are required for some patients.⁵ In most patients, treatment can be resumed after all symptoms have resolved. To minimize the risk of infusion reactions the initial dose should be administered at a rate no greater than 1 mg/minute.^{5,8} Infusion reactions rarely recur after the first infusion and subsequent infusions may be administered over a 60 minute period.⁸ Unlike an IgE-mediated (type I) allergic reaction, this reaction occurs with first exposure to the drug without prior sensitization.¹⁵ The lipid component rather than the doxorubicin is likely responsible for these acute infusion reactions.^{12,15}

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.⁸ 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.⁸ Patients usually experience slight numbness and tingling days or even weeks before erythema.¹² In most patients the reaction is mild and will resolve in one to two weeks with or without treatment using corticosteroids.⁸ Some patients will require a dose reduction to manage PPE, while patients with severe and debilitating PPE require discontinuation of therapy.⁸ At every visit patients should be asked whether they experienced numbness or tingling anywhere on their bodies since the last dose.^{5,12} If numbness or tingling has occurred the dosing interval should be prolonged.⁵ 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.^{5,8} Corticosteroids may also reduce the incidence of PPE during PLD treatment.⁵ Early measures to prevent or minimize PPE include avoiding all of the following for 3 days after PLD therapy¹²:

- Tape on skin
- Tight clothing (especially around waist, groin, wrists and fingers)
- Tight jewelry¹⁶
- Pressure or friction on skin
- Hot water (including showers or dishwashing), beginning 24 hours before treatment
- Sun exposure, sun block recommended¹⁶
- 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.¹² 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.¹² See dosing guidelines for suggested dose modifications related to stomatitis.

INTERACTIONS⁸:

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.

SUPPLY AND STORAGE:

Injection⁸: Supplied as a preservative-free, sterile, translucent, red liposomal dispersion of 10 and 25 mL single-use vials. The doxorubicin is encapsulated in STEALTH® liposomes in a pegylated liposomal formulation at a concentration of 2 mg/mL in water for injection and a pH of 6-7. Unopened vials should be stored at 2-8°C. Avoid freezing. Discard unused portion after puncture.⁸

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on solution preparation and compatibility, see [Chemotherapy Chart in Appendix](#).

Diluted solution for infusion⁸: For doses less than 90 mg, dilute in preservative-free 250 mL **D5W (only)**, for doses \geq 90 mg dilute in preservative-free 500 mL **D5W (only)**. Do not use with diluent other than Dextrose Injection as stated by the manufacturer. Diluted solutions should be used immediately or refrigerated at 2-8°C and administered within 24 hours. Do not use in-line filters.

Compatibility¹⁷: The following are compatible **via Y-site injection**: acyclovir, allopurinol, aminophylline, ampicillin, aztreonam, bleomycin, butorphanol, calcium, carboplatin, cefazolin, cefepime, ceftioxin, ceftizoxime, ceftriaxone, chlorpromazine, cimetidine, ciprofloxacin, cisplatin, clindamycin, cyclophosphamide, cytarabine, dacarbazine, dexamethasone, diphenhydramine, dobutamine, dopamine, droperidol, enalaprilat, etoposide, famotidine, fluconazole, fluorouracil, furosemide, ganciclovir, gentamicin, granisetron, haloperidol, heparin, hydrocortisone, hydromorphone, ifosfamide, leucovorin, leucovorin, lorazepam, magnesium, mesna, methotrexate, methylprednisolone, metronidazole, netilmicin, ondansetron, piperacillin, potassium chloride, prochlorperazine, ranitidine, ticarcillin, ticarcillin-clavulanate, tobramycin, trimethoprim-sulfamethoxazole, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine.

Incompatibility¹⁷: The following are incompatible **via Y-site injection**: amphotericin B, amphotericin B complex, buprenorphine, cefoperazone, ceftazidime, docetaxel, hydroxyzine, mannitol, meperidine, metoclopramide, mitoxantrone, ofloxacin, paclitaxel, piperacillin, promethazine, sodium bicarbonate.

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in **bold, italics**

Subcutaneous ⁸	not used due to corrosive nature
Intramuscular ⁸	not used due to corrosive nature
Direct intravenous ⁸	do not administer as a bolus injection or undiluted solution
<i>Intermittent infusion</i>	<i><90 mg in 250 D5W ; \geq90 mg in 500 mL D5W⁸ initial dose administered at a rate no greater than 1 mg/minute; if no infusion reaction is observed, subsequent infusions administered over 60 minutes⁸</i>
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

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:

BCCA usual dose noted in **bold, italics**

Cycle Length:

Intervals <10 days should be avoided due to possible drug accumulation.⁸

<i>Intravenous:</i>	2 weeks:	20 mg/m² IV for one dose on day 1 (total dose per cycle 20 mg/m²)¹⁸
	4 weeks:	50 mg/m ² IV for one dose on day 1 (total dose per cycle 50 mg/m ²) ⁸
<i>Concurrent radiation:</i>	no information found	
<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
<i>Dosage in renal failure:</i>	no adjustment required ⁸	
<i>Dosage in hepatic failure:</i>	adjustment required, see table to follow	
<i>Dosage in PPE:</i>	adjustment required, see table to follow	
<i>Dosage in stomatitis:</i>	adjustment required, see table to follow	
<i>Dosage in dialysis:</i>	no information found	

Children:

PLD is being studied in children, but dosing guidelines have not yet been established.

DOSE MODIFICATIONS FOR BREAST OR OVARIAN PATIENTS⁸

Grade	Adverse event	Week after prior PLD dose Weeks 4&5	Week 6
Palmar-Plantar Erythrodysesthesia (PPE)			
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	delay one week	decrease by 25%; return to 4 week interval

DOSE MODIFICATIONS FOR BREAST OR OVARIAN PATIENTS⁸

Grade	Adverse event	Week after prior PLD dose Weeks 4&5	Week 6
	diameter		
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			
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

DOSE MODIFICATIONS FOR KAPOSI'S SARCOMA PATIENTS⁸

Grade	Adverse Event	Week after prior PLD dose Week 3	Week 4
Palmar-Plantar Erythrodysesthesia (PPE)			
	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
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		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	

DOSE MODIFICATIONS FOR KAPOSI'S SARCOMA PATIENTS⁸

Grade	Adverse Event	Week after prior PLD dose Week 3	Week 4
Palmar-Plantar Erythrodysesthesia (PPE)			
4	requires parenteral or enteral support	delay one week and if symptoms improve redose at 50% dose reduction	

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