Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

EPIrubicin

COMMON TRADE NAME(S): Pharmorubicin PFS®

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B - Mechanism of Action and Pharmacokinetics

Epirubicin is an anthracycline antineoplastic agent whose mechanism of action appears to be related to its ability to bind to nucleic acids. It forms a complex with DNA by intercalation of the planar ring with the DNA double helix resulting in inhibition of DNA and RNA synthesis. Binding to cell membranes as well as to plasma proteins may also be involved. Epirubicin is cell cycle phase non-specific.

Distribution	Rapidly and widely distributed into tissues. Also concentrates in red blood cells.	
	Cross blood brain barrier?	No
	PPB	77%
Metabolism	Rapidly and extensively metabolized in liver, other organs and cells (i.e. red blood cells).	
	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Urine	9-10% within 48 hours
	Bile	40% of dose recovered in bile within 72

	hours
Half-life	$t_{½}$ (terminal) = 30-40 hours

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C - Indications and Status

Health Canada Approvals:

For the treatment of:

- Metastatic breast cancer
- Early stage breast cancer (adjuvant treatment)
- Small cell lung cancer (both limited and extensive disease)
- Advanced non-small cell lung cancer
- Lymphoma, non-Hodgkin's
- Lymphoma, Hodgkin's
- Ovarian carcinoma, stage III and IV (FIGO)
- Gastric carcinoma, metastatic and locally unresectable

Other Uses:

- Soft tissue sarcoma
- Prostate cancer
- Primary unknown

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D - Adverse Effects

Emetogenic Potential: High (> 90 mg/ m2)
Moderate (≤ 90 mg/ m2)

Extravasation Potential: Vesicant

The following pooled adverse effects were reported from combination therapy Phase III studies for adjuvant breast cancer. Severe, life-threatening and post-marketing adverse effects are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**

Cardiovascular	Arterial thromboembolism (rare)	E D
	Cardiotoxicity (3%)	I D L
	Venous thromboembolism (rare)	E D
Dermatological	Alopecia (96%) (57% severe)***	E
	Photosensitivity (rare)	I
	Radiation recall reaction (rare)	I
	Rash, pruritus (9%)	I E
	Skin hyperpigmentation (including nail hyperpigmentation - rare)	I
Gastrointestinal	Anorexia (3%)	E
	Diarrhea (25%)	E
	GI hemorrhage (rare)	E
	Mucositis (59%)	E
	Nausea, vomiting (92%) ***	I E
General	Fatigue (46%)	E
	Fever (5%)	E
Hematological	Myelosuppression ± infection, bleeding (80%) (67% severe)***	E
Hypersensitivity	Anaphylaxis (rare)	I
Injection site	Injection site reaction (20%)	I
Metabolic / Endocrine	Hyperuricemia (rare)	I
Neoplastic	Leukemia (secondary) (1%) (at 8 years)	L
Ophthalmic	Conjunctivitis (15%) (also keratitis)	E
Reproductive and breast disorders	Menopausal symptoms (72%)	E D
Respiratory	Pneumonitis (rare)	E
Urinary	Urine discoloration (red, for 1-2 days)	I

* "*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)

***Incidences are lower when administered in a weekly schedule (Gasparini 1991)

The most common side effects for epirubicin include alopecia, nausea, vomiting, myelosuppression ± infection, bleeding, menopausal symptoms, mucositis, fatigue, diarrhea, injection site reaction,

conjunctivitis.

Myelosuppression is the major dose-limiting toxicity and may be severe and even life-threatening.

Epirubicin is associated with **cardiac toxicity**. It may manifest as an initial, **acute** effect of tachyarrhythmias and/or ECG abnormalities. These effects are usually reversible, unrelated to total dose, not considered indications for suspension of therapy and do not predict subsequent development of delayed cardiotoxicity. The onset of cardiomyopathy may be **delayed**, occurring 2-3 months to years after therapy and present as decreased left ventricular ejection fraction (LVEF) and/or signs/symptoms of CHF. Serious, irreversible cardiomyopathy, often unresponsive to therapy, is possible as the cumulative dose approaches 1000 mg/m^2. Cardiac monitoring is advised when cumulative dose exceeds 650 mg/m^2 (see Recommended Clinical Monitoring section). The risk of cardiomyopathy is increased at a lower cumulative dose when patients are older, have received prior treatment with trastuzumab, anthracycline/ anthracenediones/ mitomycin C, have received mediastinal radiation or have pre-existing cardiac risk factors.

Hyperuricemia may result from cell lysis by epirubicin resulting in tumor lysis syndrome (TLS). Hydration and antihyperuricemic prophylaxis may minimize potential TLS complications.

Erythematous streaking (a histamine release phenomenon) along the vein proximal to the site of injection has been reported, and must be differentiated from an extravasation event. This '**epirubicin flare**' reaction usually subsides within 30 minutes. The injection may be continued, more slowly in the same site or may be changed to another site. Local protocols should be followed regarding management.

The tissue necrosis that happens with **extravasation** may happen days to weeks after the treatment. Extravasation may be asymptomatic initially, and occur even if blood returns well on aspiration of the infusion needle. Patients must be observed for delayed reactions and prior injection sites carefully inspected. Local protocols should be followed regarding management and should include application of ice to the affected area; dexrazoxane has been studied in the treatment of anthracycline extravasation (Mouridsen et al).

Epirubicin has the potential to enhance radiation injury to tissues. While often called **radiation recall reactions**, the timing of the radiation may be before, concurrent with or even after the administration of epirubicin. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

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E - Dosing

Refer to protocol by which patient is being treated.

Numerous dosing schedules exist and depend on disease, toxicity, response and concomitant therapy. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy or bone marrow infiltration. Patients should have recovered

from toxicity before re-treatment.

Dosage is usually calculated on the basis of body surface area.

Prophylactic treatment consisting of hydration, urine alkalinization, and allopurinol should be considered for patients at high-risk of tumor lysis syndrome.

Adults:

Cycle Length	Epirubicin Dose (mg/m^2)
Weekly	12.5 to 25
2 Weeks	35
3-4 Weeks	50-150*
4 Weeks	60 for one dose on days 1 and 8

*Recommended single dose may be divided over 2 successive days

Maximum lifetime cumulative dose:

- 650 mg/m^2 for patients with cardiac risk factors and
- 900-1000mg/m^2 for patients with no cardiac risk factors

Dosage with Toxicity:

Suggested dose levels: 90, 75, 50 mg/m^2

Worst Toxicity / Counts in Prior Cycle	Epirubicin Dose for Next Cycle
Febrile neutropenia / Thrombocytopenic bleeding / ANC grade 4 ≥ 7 days	↓ 1 dose level*
Cardiotoxicity**	Discontinue
Grade 3 related organ / non-hematologic	↓ 1 dose level*
Grade 4 related organ / non-hematologic	Discontinue

*Do not start new cycle until organ toxicity ≤ grade 2, platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x 10^9/L

**including any signs and symptoms of heart failure, > 10% decline in LVEF to below the lower limit of normal, > 20% decline in LVEF from any level, or LVEF ≤ 45%.

Dosage with Hepatic Impairment:

Hepatic Impairment	% of Epirubicin recommended starting Dose
Bilirubin 21-51 micromol/L or AST 2-4 x ULN	50
Bilirubin > 51 micromol/L or AST > 4 x ULN	25
Severe	Use is contraindicated

Dosage with Renal Impairment:

Adjust dose with severe renal impairment (creatinine > 442 micromol/L).

Dosage in the elderly:

Use with caution; no adjustment required. Plasma clearance of epirubicin in female patients > 70 years of age was noted to be reduced by 35%.

Children:

Safety and effectiveness have not been established. May be at greater risk for anthracycline-induced acute or chronic cardiotoxicity.

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F - Administration Guidelines

- Slow push through sidearm of free flowing IV (5% Dextrose, Normal Saline). Doses of 100-120 mg/m^2 should be infused over 15-20 minutes. For lower dose volumes, the infusion time may be proportionally decreased to no less than 3-5 minutes.
- Do not admix with other drugs. Incompatible with heparin.
- Avoid contact with alkaline solutions since this can lead to hydrolysis of epirubicin.
- Slow down injection rate if erythematous streaking or facial flushing occurs.
- 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 as per local guidelines and should include application of ice to the affected area.
- Keep refrigerated (2-8^{o}C). Protect from light.

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G - Special Precautions

Contraindications:

- Hypersensitivity to epirubicin, any components of the product, other anthracyclines or anthracenediones
- Severe myelosuppression induced by prior chemotherapy or radiotherapy
- Severe hepatic impairment
- Severe myocardial insufficiency
- Recent myocardial infarction
- Severe arrhythmias
- History of severe cardiac disease
- Previous treatment with maximum cumulative doses of anthracyclines or anthracenediones

Other Warnings/Precautions:

- Avoid live vaccines; use may result in serious infections in immunocompromised patients.
- Patients who have received mediastinal radiotherapy, other anthracycline/ anthracenediones/ cardiotoxic drugs, pre-existing heart disease are at increased risk of cardiotoxicity

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Mutagenicity: Yes
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Epirubicin is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** (general recommendation) after the last dose.
- Excretion into breast milk: Probable
  Breastfeeding is not recommended.
- Fertility effects: Probable

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cimetidine and other drugs affecting hepatic metabolism	↑ epirubicin exposure by 50% and decreased clearance by 30%	↓ metabolism	Avoid concomitant use
radiation	↑ skin reaction	radiation sensitizer	Use with caution
Verapamil, other calcium channel blockers	↑ risk of heart failure	↓ cardiac function	Caution, monitor
Cytotoxic drugs	↑ hematologic and GI toxicity	Additive	Caution, monitor
Trastuzumab	↑ cardiotoxicity	Additive	Avoid anthracycline-based therapy for up to 28 weeks after stopping trastuzumab
Taxanes (i.e.	↑ systemic exposure to	Taxane or Cremophor	Caution if used in

paclitaxel, docetaxel)	epirubicin or its metabolites. May be schedule dependent.	EL possibly competes with epirubicin for biliary excretion	combination; give epirubicin first, taxane at least 24 hours later

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each cycle
Liver and renal function tests	Baseline, before each cycle and as clinically indicated
Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors and cumulative doses > 650mg/m^2	Baseline and as clinically indicated
Clinical toxicity assessment of GI effects, dermatologic effects, tumor lysis syndrome, infection, bleeding, ocular effects, cardiotoxicity, local toxicity	At each visit

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

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K - References

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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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