DRUG NAME: Epirubicin

SYNONYM(S): 4'-epidoxorubicin,[1] IMI-28,[1] NSC-256942[1]

COMMON TRADE NAME(S): PHARMORUBICIN®,[2] ELLENCE®[3]

CLASSIFICATION: anthracycline antineoplastic antibiotic[4]

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

MECHANISM OF ACTION:

The mechanism of action of epirubicin appears to be related to its ability to bind to nucleic acids.[2] It forms a complex with DNA by intercalation between base pairs, resulting in inhibition of DNA and RNA synthesis.[4] Intercalation also triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity.[3,4] Binding to cell membranes and plasma proteins may also be involved.[2] Epirubicin also generates cytotoxic free radicals.[3,4] Epirubicin is the 4'-epimer of doxorubicin; i.e., there is a different spatial orientation of the hydroxyl group at the 4' carbon of the sugar moiety.[4] This difference may account for faster elimination and reduced toxicity.[2]

PHARMACOKINETICS:

Distribution	rapidly and widely distributed into tissues[3]; may concentrate in red blood cells, whole blood concentrations are approximately twice those of plasma[3]	
	cross blood brain barrier?	no
	volume of distribution[3]	21-27 L/kg
	plasma protein binding[3]	77%
Metabolism	extensive hepatic metabolism; also metabolized by other organs and cells, including red blood cells[3]	
	active metabolite(s)	epirubicinol (13-OH epirubicin)[3]; cytotoxic activity one-tenth that of epirubicin; plasma levels consistently lower than epirubicin
	inactive metabolite(s)	glucuronides of epirubicin and epirubicinol; doxorubicin; aglycones of doxorubicinol, 7-deoxydoxorubicin, and 7-deoxydoxorubicinol[3]
Excretion	predominantly hepatobiliary; rapid elimination of parent compound from plasma	
	urine	9-10% within 48 h[2]; 20-27% within 4 days[3]
	feces	40% of dose recovered in bile within 72 h
	terminal half life[3]	33 h
	clearance[3]	65-83 L/h
Gender	no differences observed[3]	
Elderly	clearance may be decreased in elderly women[3]	

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:
* Breast cancer
* Gastric cancer
* Lung cancer, non-small cell
* Lung cancer, small cell
* Lymphoma, Hodgkin's
* Lymphoma, non-Hodgkin's
* Ovarian cancer

Other uses:
Bladder cancer[5,6]
Pediatric, soft tissue sarcoma[7]
Soft tissue sarcoma[8-10]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindicated in patients with the following conditions[3]:
- hypersensitivity to epirubicin or any component of the product
- hypersensitivity to other anthracyclines (e.g., daunorubicin, doxorubicin)
- hypersensitivity to anthracenediones (e.g., mitoxantrone, mitomycin)
- severe hepatic impairment
- severe myocardial insufficiency
- recent myocardial infarction
- severe arrhythmias
- history of severe cardiac disease
- previous therapy with high cumulative doses of anthracyclines (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin)
- previous therapy with high cumulative doses of some anthracenediones (e.g., mitoxantrone)

Cardiac toxicity is a risk of epirubicin therapy that may be manifested by early (acute) or late (delayed) effects.[4] Cardiac function should be assessed at baseline and continue during treatment; refer to Side Effects section for more information. Risk factors for developing epirubicin-induced cardiotoxicity include[3]:

- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- concomitant use of drugs that can suppress cardiac contraction

Carcinogenicity: Epirubicin has been associated with an increased risk of secondary leukemia in human trials.[3]

Mutagenicity: Epirubicin is mutagenic and clastogenic in animals, and may induce chromosomal damage in human spermatozoa.[3]

Fertility: Dose-related infertility has been observed in mammals of both sexes.[3] Epirubicin may cause premature menopause in premenopausal women.

Pregnancy: FDA Pregnancy Category D.[3] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk. Chemotherapy protocols including epirubicin have been administered during pregnancy to treat breast cancer.[11-15] For more information, please refer to The BC Cancer Agency Cancer Management Guidelines for Breast Cancer in Pregnancy.

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

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.[16]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	anaphylaxis
	chills, fever, shock, urticaria
blood/bone marrow/ febrile neutropenia	anemia (13-72%)
	leukopenia (50-80%, severe 2-59%), ***neutropenia*** (54-80%, severe 10-67%); nadir 10-14 days after treatment; recovery by day 21
	neutropenic fever (6%)
	thrombocytopenia (5-49%)
cardiovascular (arrhythmia)	acute transient ECG changes, sinus tachycardia; see discussion following table
cardiovascular (general)	***congestive heart failure***, symptomatic[3] (0.9-3.3%, dose-related); risk increases steeply after cumulative dose of 900 mg/m^2; see paragraph following **Side Effects** table
	decreased left ventricular ejection fraction, asymptomatic (1-3%); see paragraph following **Side Effects** table
	thromboembolism (including fatal pulmonary embolism), thrombophlebitis, venous sclerosis
constitutional symptoms	fever (1-5%)
	fatigue/lethargy (1-46%)
	malaise/asthenia
dermatology/skin	*extravasation hazard: vesicant*
	alopecia (70-96%), regrowth occurs 2-3 months after discontinuing epirubicin therapy[3]
	flushing
	injection site reactions (2-20%)
	photosensitivity
	radiation recall reaction
	rash/itch (1-9%)
	skin changes (1-5%)
	skin and nail hyperpigmentation
endocrine	hot flashes(5-39%)
gastrointestinal	*emetogenic potential: dose-related[17]; high-moderate for > 90 mg/m^2, low-moderate for ≤ 90 mg/m^2*
	anorexia (2-3%)
	dehydration
	diarrhea (7-25%)
	dyspepsia
	hyperpigmentation of the oral mucosa
	mucositis (9-58%)
	nausea/vomiting (83-92%)
hemorrhage	bleeding, GI

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
hepatic	increased transaminases[18]
infection	***infection*** (15-22%)
metabolic/laboratory	hyperuricemia
ocular/visual	conjunctivitis (1-15%), keratitis
renal/genitourinary	red colouration of urine for 1-2 days after administration
secondary malignancy	acute myeloid leukemia, myelodysplastic syndrome (0.3-0.6%)
sexual/reproductive function	amenorrhea (69-72%), premature menopause
syndromes	tumour lysis syndrome

Adapted from standard reference[3] unless specified otherwise.

Cardiotoxicity is thought to be due to free radical damage as myocardial tissue is susceptible to these highly reactive species.[19] Anthracycline cardiotoxicity may present with early or late effects.[20,21] The following information applies to all anthracyclines, anthracenediones and mitoxantrone.[19,21,22]

Early cardiotoxic effects are not dose-related and may present from mild ECG changes to life-threatening arrhythmias.[19,20,22] These events may occur during or immediately after a single dose of anthracycline treatment,[19,22] but do not predict subsequent development of delayed cardiotoxicity and are not considered indications for suspension of therapy.[19,20,22-25]

Late cardiotoxic effects, which are dose-related and clinically the most important type of cardiotoxic effect, present as reduced LVEF or symptomatic CHF, and typically occur weeks to years after completion of treatment.[19,21-24] Abnormalities in LVEF are associated with all the anthracyclines and their derivatives.[21] LVEF changes are related to the total cumulative dose, are irreversible and refractory to medical therapy. [19,26]

Prevention and treatment: Cardiac assessment should occur at baseline and throughout therapy. Monitor for symptomatic congestive heart failure (CHF) or reduced left ventricular ejection fraction (LVEF). Sensitive, non-invasive methods to measure LVEF include radionucleotide angiography (RNA), MUGA, or echocardiogram.[21] Late cardiotoxic effects may be prevented by stopping treatment with the associated anthracycline once patients have reached the suggested maximum cumulative dose.[19,26] Management of anthracycline cardiotoxicity includes discontinuation of the drug and initiating standard treatment of CHF.[21]

Cardiotoxicity risk can be reduced but not eliminated with the use of alternative anthracyclines (i.e., epirubicin or liposomal doxorubicin) or by altering the frequency of administration (once a week vs. once every 3 weeks, or continuous infusion).[21] Cardioprotectant therapy with dexrazoxane may be considered for patients with cumulative doxorubicin-equivalent doses greater than 300 mg/m^2.[22,27,28]

Cumulative doses should be calculated using the following table, taking into account all previous anthracyclines or anthracenediones received during the patient's lifetime.

AGENT	SUGGESTED CONVERSION FACTOR TO DOXORUBICIN DOSE[29-31]*	SUGGESTED MONITORING THRESHOLD[20,21,32,33]**
DAUNOrubicin	x 0.5-0.83	450 mg/m^2
DOXOrubicin	x 1	300 mg/m^2
epirubicin	x 0.5-0.67	600 mg/m^2
IDArubicin	x 2-5	150 mg/m^2
mitoXANTRONE	x 2.2-4	140 mg/m^2

* based on relative hematological toxicities[30]

** Treatment may continue beyond these doses in selected patients, if the clinician has considered the potential risks and benefits. The addition of dexrazoxane may be considered, and monitoring should be increased. Maximum tolerated doses are variable; some patients may tolerate doxorubicin equivalent doses exceeding 1000 mg/m^2 while other patients exhibit symptomatic CHF at doxorubicin equivalent doses doses less than 300 mg/m^2.

Local effects: Extravasation of epirubicin can occur with or without accompanying stinging or burning sensation, and even if blood returns well on aspiration of the infusion needle.[3] Severe local tissue necrosis may occur. To minimize the risk of thrombosis or perivenous extravasation, the usual administration time should be 15 to 20 minutes, and never less than 3 minutes.[3] For more information on prevention and treatment of extravasation with doxorubicin refer to BC Cancer Agency Provincial Systemic Therapy Program: Prevention and Management of Extravasation of Chemotherapy. Also, monitor for local erythematous streaking along vein and/or facial flushing which may indicate a too rapid infusion rate.[34] This has traditionally been called the "epirubicin flare."[35,36]

Hyperuricemia may result from cell lysis by epirubicin and may lead to electrolyte disturbances or acute renal failure.[37] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[38]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[39] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminium hydroxide has been added, discontinue sodium bicarbonate.[40]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
bevacizumab[41]	anthracycline-induced cardiotoxicity may be increased	unknown	monitor cardiac function throughout treatment
calcium channel blockers (e.g., verapamil)[2,4]	anthracycline-induced cardiotoxicity may be increased	additive toxicity	monitor cardiac function throughout treatment
cimetidine[2,3,42]	increases AUC of epirubicin by 50% and decreases clearance of epirubicin by 30%	unknown; does not seem to be related to cytochrome P450	discontinue cimetidine and choose alternate therapy; e.g., ranitidine
gemcitabine[43]	no influence on epirubicin pharmacokinetics		

AGENT	EFFECT	MECHANISM	MANAGEMENT
taxanes[43-49] (e.g., docetaxel, paclitaxel)	toxicity of both agents may be increased when given concurrently, regardless of which drug is given first; lower neutrophil and platelet nadirs, and slower neutrophil recovery have been observed	increased levels of epirubicin metabolites, decreased taxane clearance	separate administration by 24 hours if possible
trastuzumab[50]	anthracycline-induced cardiotoxicity may be increased	unknown	monitor cardiac function throughout treatment

SUPPLY AND STORAGE:

***Injection**:* Sterile solution for injection, 2 mg/mL, in 5 mL, 25 mL, and 100 mL glass vials and polypropylene vials.[3] Store vials between 2-8ºC and protect from light (keep intact vials in their carton until use). Discard unused portion within 8 hours after puncture.

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous[2]	must not be used due to corrosive nature
Intramuscular[2]	must not be used due to corrosive nature
Direct intravenous	***over at least 3 minutes (usual 3-20 minutes);*** ***Preferred method*** due to need for frequent monitoring for signs of extravasation***: via small (21 or 23) gauge needle into tubing of running IV. Push slowly, so that drip of IV solution does not stop or reverse. Check for blood return before administration and after every 2-3 mL of drug. If no blood return, stop the injection and assess the IV site. Flush with 20 mL NS or D5W after administration to clear any remaining drug from tubing.***
Intermittent infusion[51-56]	has been used
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found

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

Intravesical[6,57-61]	has been instilled in the bladder as a single dose postoperatively OR as induction doses of 50-100 mg in 25-100 mL NS weekly for 6 to 8 weeks, followed by monthly maintenance doses to 1 year; solutions are retained for 1-2 h after instillation

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***

Intravenous:

Cycle Length:

2 weeks[2]: 35 mg/m^2 IV for one dose on day 1
(total dose per cycle 35 mg/m^2)

3 weeks[62]: ***100 mg/m^2 IV for one dose on day 1***
(total dose per cycle 100 mg/m^2)

3-4 weeks[2]: 50-150 mg/m^2 IV for one dose on day 1
(total dose per cycle 50-150 mg/m^2)

4 weeks[63-65]: ***60 mg/m^2 IV for one dose on days 1 and 8***
(total dose per cycle 120 mg/m^2)

4 weeks[66-68]: ***when given as a dose-dense regimen with filgrastim (G-CSF) support:***
60 mg/m^2 IV for one dose on days 1 and 15
(total dose per cycle 120 mg/m^2)

Suggested maximum cumulative doses[3,62]: 720-1000 mg/m^2

Concurrent radiation: generally not administered concurrently due to additive toxicity[4]

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[2]: lower starting doses are necessary if serum creatinine > 442 µmol/L

Dosage in hepatic failure[2]:

AST		Bilirubin	Dose
2-4 X ULN	or	21-51 µmol/L	50%
> 4 x ULN	or	> 51 µmol/L	25%

contraindicated in severe hepatic impairment

Dosage in dialysis: no information found

Children: safety and effectiveness in children has not been studied[3]

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