

DRUG NAME: Estramustine**SYNONYM(S):** Estramustine sodium phosphate,¹ EMP^{1,2}**COMMON TRADE NAME(S):** EMCYT®**CLASSIFICATION:** alkylating agent, cytotoxic³*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Estramustine is a complex of 17-beta-estradiol and nitrogen mustard linked by a carbamate ester bridge¹; therefore, it has both cytotoxic and antigonadotropic effects.⁴ Estramustine sodium phosphate is a pro-drug. After oral administration, it is rapidly converted to estramustine, most of which is oxidized to another cytotoxic metabolite, estromustine. Estramustine and estromustine exert their cytotoxic effect by binding to tubulin and/or microtubule-associated proteins, inducing depolymerization and cellular metaphase arrest.^{1,4,5} Estramustine levels are reportedly higher in tumour tissue than plasma, possibly demonstrating selective uptake and accumulation of estramustine and its cytotoxic metabolites in tumour tissues.¹ Limited data suggest that estramustine may also induce oxygen radicals,⁶ damage cell membranes, promote DNA breakage and interference with DNA replication, and induce cellular apoptosis in cell lines.^{4,6} Estramustine and estromustine are metabolized to estradiol and estrone, respectively, which may cause the antigonadotropic effects reported (including decreased plasma concentrations of testosterone, dihydrotestosterone, gonadotropins, cholesterol and 17-hydroxyprogesterone; and increased concentrations of prolactin and cortisol).⁴ Estramustine is cell cycle phase-nonspecific.^{1,5,6} Estramustine is an immunosuppressive agent.^{1,7}

PHARMACOKINETICS:

Oral Absorption	37-75% ^{1,5,6} ; reduced by food and calcium ^{1,6,8}	
Distribution	peak serum levels in 2-3 h ⁷ ; estramustine levels 5-10 times higher in tumour tissue than in plasma ¹ ; accumulates in adipose tissue ⁶	
	cross blood brain barrier?	yes ^{5,6}
	volume of distribution	0.11 L/kg
	plasma protein binding	highly bound when given intravenously ^{2,6}
Metabolism	extensive first pass metabolism; rapid initial dephosphorylation in GI tract, followed by oxidation and hydrolysis in liver ^{5,7}	
	active metabolite(s)	primarily estramustine and estromustine ¹ ; 10-20% of estramustine and estromustine metabolized to estradiol and estrone, respectively ^{1,4,6}
	inactive metabolite(s)	no information found
Excretion	mainly in the feces ⁵	
	urine	less than 1% of conjugated estradiol and estrone excreted in urine ^{4,5}
	feces	3-5% as unchanged drug ⁷ ; estramustine, estromustine, and their metabolites excreted principally in bile ^{4,6}
	terminal half life	15-20 h (estramustine and estromustine)
	clearance ⁶	4.2-5.5 L/h

Adapted from standard reference¹ unless specified otherwise.**USES:****Primary uses:**

*Prostate cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to estramustine, estradiol, or nitrogen mustard¹
- severe hepatic or cardiac disease¹
- active thrombophlebitis or thromboembolic disorders¹
- not intended for use in women^{4,7}

Caution:

- history of thrombophlebitis, thrombosis, or **thromboembolic disorders**, especially if associated with estrogen therapy¹
- **cerebrovascular disease** or coronary artery disease¹
- **diabetics** may have decreased glucose tolerance¹
- avoid in **peptic ulcer disease**⁹
- **hypertension** may occur; monitor blood pressure periodically during treatment¹
- **fluid retention** may exacerbate pre-existing or incipient peripheral edema and congestive heart disease¹
- **impaired liver function** may affect drug metabolism; monitor liver function tests regularly¹
- considered unsafe in **porphyria**; associated with acute attacks^{9,10}
- **calcium and phosphorus** metabolism may be affected^{1,4}; monitor calcium levels in metabolic bone diseases, renal insufficiency, or osteoblastic metastases¹
- avoid **vaccination** with live or live-attenuated vaccines; possibly diminished response to killed or inactivated vaccines¹

Carcinogenicity: No information found.

Mutagenicity: Not mutagenic in Ames test¹; both estradiol and nitrogen mustard are known to be mutagenic.¹

Fertility: Atrophy of reproductive organs shown in mammalian testing.¹

Pregnancy: FDA Pregnancy Category X.¹ Studies in animals have shown fetal abnormalities and the risk of use of the drug in pregnant women clearly outweighs any possible benefit.¹ Contraindicated in women who are or may become pregnant.^{1,4} Men undergoing treatment with partners of childbearing potential should utilize effective contraceptive measures.¹

Breastfeeding is not recommended. Not intended for use in women.⁴

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^{11,12}.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	angioedema ($\leq 1\%$) ^{1,7} ; with or without concomitant therapy; discontinue treatment immediately
	pruritis ⁴ (2%)
blood/bone marrow/ febrile neutropenia	leukopenia (1-4%) ^{4,7} ; reversible with dose reduction or temporary withdrawal ¹ ; usually not significant with monotherapy ⁵

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	thrombocytopenia ($\geq 1\%$) ^{4,7} ; reversible with dose reduction or temporary withdrawal ¹ ; usually not significant with monotherapy ⁵
cardiovascular (general)	angina (1%) ^{4,7}
	congestive heart failure (3%) ^{4,7}
	coronary thrombotic event ⁵ ($\leq 10\%$)
	fluid retention/edema (19-20%) ^{4,7}
	ischemic heart disease ($\leq 1\%$) ⁷
	flushing ^{4,7} ($\geq 1\%$)
	hypertension ($\leq 1\%$)
	myocardial infarction (2-3%) ^{4,7}
coagulation	thromboembolism ($\leq 1\%$)
	thrombophlebitis ^{4,7} (2-3%)
constitutional symptoms	lethargy (1-4%) ^{4,7}
	thirst ^{4,7} (1%)
dermatology/skin	<i>extravasation hazard: none</i> ¹³
	bruising ^{4,7} (1-3%)
	dry skin ^{4,7} ($\geq 1\%$)
	hair thinning ^{4,7} ($\geq 1\%$)
	pruritis ^{4,7} (2%)
	rash ^{4,7} (1%)
	skin peeling, at fingertips ^{4,7} ($\geq 1\%$)
endocrine	glucose tolerance , decreased ($\leq 1\%$) ⁷
	gynecomastia (mild 60%; moderate 10%) ⁴ ; (75%) ⁷
gastrointestinal	<i>emetogenic potential: rare</i> ¹⁴
	anorexia ^{4,7} (4%)
	burning throat ^{4,7} (1%)
	diarrhea (12-13%) ^{4,7} ; usually within two weeks ¹ ; often mild; if severe, may require dose reduction or withdrawal ⁶
	flatulence ^{4,7} (2%)
	gastrointestinal bleed ^{4,7} (1%); avoid in peptic ulcer disease ⁹
	gastrointestinal upset ^{4,7} (11-12%)
	nausea (15-16%) ^{4,7} ; usually within two weeks, transient ^{1,15} ; if severe, may require dose reduction or withdrawal ⁶
	vomiting (1%) ^{4,7} ; usually within two weeks ^{1,15}
metabolic/laboratory	AST and/or LDH elevation (2-33%) ^{4,5,7} ; see paragraph following Side Effects table
	hyperbilirubinemia (1-2%) ^{4,7} ; see paragraph following Side Effects table
	hypercalcemia ($\leq 1\%$) ⁷

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	hypocalcemia, asymptomatic ($\leq 20\%$) ⁵
	hypocalcemia, clinically significant, acute ($\leq 1\%$) ⁵
neurology	anxiety ^{4,7} ($\geq 1\%$)
	cerebrovascular accident (2-10%) ^{4,5,7}
	cerebrovascular ischemia ⁷ ($\leq 1\%$)
	emotional lability ^{4,7} (1-2%)
	headache ($\geq 1\%$) ^{4,7}
	insomnia (1-3%) ^{4,7}
	ocular/visual
pain	breast tenderness or pain (66-71%) ^{4,7}
	chest pain ($\geq 1\%$) ⁴
	leg cramps ^{4,7} (8-9%)
pulmonary	dyspnea ^{4,7} (1-12%)
	hoarseness ^{4,7} ($\geq 1\%$)
	pulmonary embolus ^{4,5,7} (2-10%)
	upper respiratory discharge ^{4,7} ($\geq 1\%$)
sexual/reproductive function	impotence ($\leq 93\%$) ^{7,16} ; reversible upon withdrawal ⁶
	libido , reduced ($>10\%$) ⁷
vascular	venous thrombosis ⁷ ($\leq 10\%$) ⁵

Adapted from standard reference¹ unless specified otherwise.

Severe liver dysfunction is rare.⁶ Elevated transaminases and bilirubin are seldom serious enough to require cessation of therapy and are reversible with dose reduction or temporary withdrawal (1-2 weeks).¹ Liver function tests should be repeated at intervals during treatment, and again two months after cessation of treatment.^{1,4} Patients with hepatic impairment may have decreased metabolism of estramustine.^{1,4}

INTERACTIONS :

AGENT	EFFECT	MECHANISM	MANAGEMENT
ACE inhibitors ^{1,17}	angioedema	unknown	discontinue estramustine ^{1,18}
calcium-containing food, beverages, or drugs ^{1,4,8}	decreased absorption	formation of a poorly soluble calcium complex	avoid concurrent administration; administer on empty stomach (1 h before meals or 2 h after meals)
clodronate ¹⁹	increased serum estramustine levels	possibly increased bioavailability	monitor for increased estramustine toxicity

Estrogens have been reported to increase therapeutic activity and toxicity of tricyclic antidepressants (TCA), probably via inhibition of metabolism.¹ Although estramustine has not been reported to interact with tricyclic antidepressants, approximately 10-20% of

estramustine and estromustine is metabolized to estradiol and estrone, respectively.^{4,6} Elevated estradiol levels may appear as early as one week after treatment initiation and persist 7-12 weeks after cessation.⁴ Monitoring for increased TCA toxicity is suggested with concurrent therapy.

SUPPLY AND STORAGE:

Oral: Pfizer Canada Inc. supplies estramustine sodium phosphate as 140 mg capsules. Refrigerate. Capsules should not be opened.¹ Capsules are bisulfite-, gluten-, lactose- and tartrazine-free.¹⁸

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:

Oral:	14 mg/kg^{1,20} (range 10-16 mg/kg) daily, in 3 or 4 divided doses. Administer on an empty stomach (one hour before or after meals) with water. ¹ BCCA usual dose noted in bold, italics
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"
Dosage in renal failure:	no information found
Dosage in hepatic failure:	no information found
Dosage in dialysis:	no information found
<u>Children:</u>	no information found

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