DRUG NAME: Etoposide

SYNONYM(S): VP-16[1]

COMMON TRADE NAME: VEPESID®, ETOPOPHOS® (etoposide phosphate)

CLASSIFICATION: topoisomerase II inhibitor[1]

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

MECHANISM OF ACTION:

Etoposide is a semisynthetic derivative of the podophyllotoxins, an epipodophyllotoxin. It inhibits DNA topoisomerase II, thereby inhibiting DNA synthesis. Etoposide is cell cycle dependent and phase specific, affecting mainly the S and G_2 phases.[1]

PHARMACOKINETICS:

Interpatient variability	bioavailability	
Oral Absorption	dose-dependent; absorption decreases as etoposide dose increases; mean 50%.[1] daily doses greater than 200 mg should be divided (BID) absorption does not appear to be altered by food or changes in stomach pH and emptying[2]; however manufacturer recommends drug be taken on an empty stomach.	
	time to peak plasma concentration	1-1.5 h
Distribution	detected in saliva, liver, spleen, kidney, myometrium, healthy brain tissue, and brain tumour tissue, minimally in pleural fluid	
	cross blood brain barrier?	in low and variable concentrations[1]
	volume of distribution	7-17 L/m^2, 32% of body weight
	plasma protein binding	95%[3]
Metabolism	hepatic biotransformation[1]	
	active metabolite[1]	yes
	inactive metabolite[1]	yes
Excretion	fecal and urinary excretion	
	urine	44-60% (67% of that unchanged)[1]
	feces	up to 16% (as unchanged drug and metabolites)[1]
	biliary	≤6%[1]
	terminal half life	7 h (range, 3-12)[1]
	clearance	19-28 mL/min/m^2
Gender	no clinically important differences	
Elderly	no clinically important differences	
Children	volume of distribution 5-10 L/m^2; terminal half life 3-5.8 h	

Adapted from standard references[4,5] unless specified otherwise.

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USES:

Primary uses:
Bladder cancer
Brain tumours
Cervical cancer
Ependyoma
Germ cell tumour
Gestational trophoblastic neoplasia
Head and neck cancer
*Lung cancer, small cell
*Lung cancer, non-small cell
*Lymphoma
Ovarian cancer
Prostate cancer
*Testicular cancer

Other uses:
Ewings's sarcoma
Hepatoma
Kaposi's sarcoma, AIDS-related
Leukemia, acute myeloid
Leukemia, acute lymphocytic
Neuroblastoma
Rhabdomyosarcoma
Wilm's tumour

*Health Canada approved indication

Adapted from standard reference[4,6] unless specified otherwise.

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reactions to etoposide[6]

Caution:
- etoposide phosphate (ETOPOPHOS®) is ***NOT interchangeable*** with other etoposide formulations and should not be substituted

Carcinogenicity: Etoposide is potentially carcinogenic.[4]

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* mutation test. Etoposide is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[1]

Fertility: The effect of etoposide on fertility in humans is not known.[4]

Pregnancy: FDA Pregnancy Category D.[1] There is positive evidence of human fetal risk, but 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 should be discontinued as etoposide is excreted in human milk.[6]

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.[7]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	***type 1 hypersensitivity*** reaction during or immediately after IV administration (1-3%)[8]
blood/bone marrow febrile neutropenia	***myelosuppression*** (WBC nadir 7-14 days, platelet nadir 9-16 days, recovery 20 days)
cardiovascular	congestive heart failure
	hypotension with rapid IV administration (1-2%)
	myocardial infarction
constitutional symptoms	***fatigue***
	fever
dermatology/skin	*extravasation hazard:* irritant[9]
	alopecia (8-66%)
	anal irritation or fissures[10]
	epidermal necrolysis, toxic (one fatal case reported)
	nail changes[10]
	palmar-plantar erythema[10]
	pigmentation
	pruritus, severe
	rash
	urticaria
gastrointestinal	*emetogenic potential:* low moderate[11]
	anorexia (10-13%)
	constipation
	diarrhea (1-13%)
	dysphagia
	esophagitis
	mucositis
	nausea and vomiting (31-43%)
	parotitis
	stomatitis (1-6%)
	taste alteration
hepatic	hepatotoxicity (0-3%) in higher than recommended doses
metabolic/laboratory	metabolic acidosis in higher than recommended doses
musculoskeletal	muscle cramps
	weakness
neurology	transient mental confusion
	peripheral neuropathy (1-2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	seizure
	transient vertigo
ocular/visual	transient cortical blindness
	optic neuritis
pain	abdominal pain (0-2%)
	headache
pulmonary	interstitial pneumonitis
	pulmonary fibrosis
secondary malignancy	***acute leukemia*** (onset 2-3 years) reported[1]
syndromes	Stevens-Johnson syndrome

Adapted from standard references[4,6] unless specified otherwise.

Allergic reactions are rare but can be life threatening.[12] Usually include chest discomfort, dyspnoea, bronchospasm, hypotension and/or skin flushing. In most patients the reactions occur within 5-10 minutes of the infusions with complete recovery once the infusion is discontinued. There are reports of reactions occurring several hours after administration. Reactions are very rare with oral capsules.[6] Treatment should be symptomatic and can include pressor agents, corticosteroids, antihistamines, or volume expanders.[6] The subsequent management of patients experiencing a hypersensitivity reaction is usually to omit etoposide from the chemotherapy regimen.[8] Higher rates of anaphylactoid reactions are reported in children receiving etoposide infusions at higher than recommended concentrations.[4]

Congestive heart failure and myocardial infarction occurred in patients receiving etoposide by continuous IV infusion over 5 days. Some of these patients had pre-existing cardiovascular disease, and these cardiovascular side effects were attributed to the large volumes of NS used as the diluent for administration of the drug.[4]

Hypotension can occur following rapid IV administration.[6] Etoposide should be administered over at least 30 minutes (usually 30-60 minutes).[6] Longer infusion times may be required based on patient tolerance. Hypotension usually responds to stopping the infusion, and administration of IV fluids or other supportive therapy as needed. When restarting the infusion a slower rate should be used. Geriatric patients may be more susceptible to etoposide-induced hypotension.[4] Delayed hypotension has occurred following slow IV infusion at higher than recommended doses.

Gastrointestinal side effects occur at a slightly higher incidence with oral administration compared to IV administration.[4]

Acute reactions to products containing polysorbate 80 have been reported. In premature infants, a life threatening syndrome of liver and renal failure, pulmonary deterioration, thrombocytopenia and ascites has been associated with injectable vitamin E product containing polysorbate 80.[6]

Excipient-related side effects have been hypothesized[10];
- Polysorbate 80 may be responsible for the immediate side effects including hypotension and hypertension, tachycardia, dyspnoea, bronchospasm, flushing and exanthema.
- Ethanol, benzyl alcohol, polysorbate 80 and polyethylene glycol may be responsible for the cardiovascular, neurological and/or respiratory side effects.
- Dextrans are often associated with allergic reactions.

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
aprepitant[13]	elevated etoposide plasma levels	inhibition of cytochrome P450-mediated metabolism of etoposide by aprepitant	closely monitor for etoposide toxicities
atovaquone[14]	possible increase in plasma level of etoposide	unknown	closely monitor for etoposide toxicities
cisplatin[6]	synergistic antineoplastic activity against testicular, small cell lung and, non-small cell lung cancers	possible impaired elimination of etoposide in patients previously treated with cisplatin	some protocols are designed to take advantage of this effect; monitor toxicity closely
high dose cyclosporine with oral etoposide[14]	increase in plasma level in etoposide	decrease in clearance of etoposide	etoposide dose should be reduced by 50% with concurrent use of high-dose cyclosporine infusion[13]
glucosamine[15]	may cause resistance to topoisomerase-II inhibitors	induction of the glucose-regulated stress response	avoid use of glucosamine during cancer chemotherapy treatments
grapefruit juice[16,17]	etoposide AUC reduced by 26% and mean absolute bioavailability reduced by 21%; large interpatient variability	possible alteration of intestinal P-glycoprotein mediated transport	avoid grapefruit juice for 48 hours before and on day of dose
St John's Wort[13]	reduced effectiveness of etoposide	induction of CYP3A4 which metabolizes etoposide	avoid concomitant use of St John's Wort with etoposide
warfarin[14]	suspected increased anticoagulant effect of warfarin	may decrease warfarin metabolism	monitor INR or PT closely

Adapted from standard references[4,6] unless specified otherwise.

SUPPLY AND STORAGE:

Oral:

Xediton Pharmaceuticals Inc. (for Cheplapharm Arzneimittel GmbH Germany) supplies etoposide as 50 mg liquid-filled soft gelatin capsules (vehicle contains citric acid, glycerol, polyethylene glycol 400, and water). Store at room temperature.[18]

Injection:
Sandoz Canada Inc. supplies etoposide injection as 100 mg, 200 mg, 500 mg, and 1 g ready-to-use multi-dose vials in a concentration of 20 mg/mL. Benzyl alcohol is included as preservative. Store at room temperature. Protect from light.[19]

Teva Canada Limited supplies etoposide injection as 100 mg, 200 mg, 500 mg, and 1 g ready-to-use preservative-free vials in a concentration of 20 mg/mL. Store at room temperature. Protect from light.[20]

Xediton Pharmaceuticals Inc. (for Cheplapharm Arzneimittel GmbH Germany) supplies etoposide phosphate (ETOPOPHOS®) as 100 mg single dose (preservative-free) vials of lyophilized powder. Refrigerate. Protect from light.[21-23]

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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:

Etoposide injection:

- Cracking and leaking of plastic containers made of acrylic or ABS (a polymer made of acrylonitrile, butadiene and styrene) have been reported when used with undiluted etoposide injection.[6] The reports include BURRON® chemo-dispensing pin, plastic port on a disposable cassette for the OMNI-FLOW 4000® pump (acrylic plastic), connector on a minimal volume extension set (ABS/acrylic plastic) and rigid plastics in general (e.g. ABS, acrylics, polycarbonates, etc.).[24]
- Diluted solution for infusion:
    - Etoposide injection is lipid soluble and contains various excipients including the surfactant polysorbate 80. Polysorbate 80 leaches the plasticizer diethylhexyl phthalate [DEHP] from polyvinyl chloride [PVC][25] containers and tubing into etoposide IV solution.[25,26] The amount of DEHP leached from PVC containers and tubing is dependent on surfactant concentration, bag size and contact time.[27] Actual hazardous exposure levels to this substance are not known,[28,29] however DEHP is hepatotoxic and exposure should be minimized.[26] The standard practice at BC Cancer (1 October 2005) and many other hospitals is to prepare etoposide IV infusions in non-DEHP containers[30-35] and administer using non-DEHP tubing.[36] Bristol-Myers Squibb Canada states that the use of non-DEHP containers and tubing remains an individual choice at this time.[24]
    - When etoposide is diluted to 0.4 mg/mL or greater the use of peristaltic pumps should be avoided as they can exacerbate precipitation.[27] Volumetric pumps are recommended. Etoposide is most stable at pH of about 3.5 to 6.
    - Etoposide solutions of 0.1-0.4 mg/mL in D5W or NS have been filtered using several commercially available filters (such as the 0.22 micron Millex-GS or Millex) without filter decomposition.[27]
    - Administer using 0.22 micron in-line filters.[37]

Etoposide phosphate injection (ETOPOPHOS®):

- Etoposide phosphate is a water soluble ester of etoposide which lessens the potential for precipitation following dilution and intravenous administration.[38]
- ETOPOPHOS® does *not* contain polysorbate 80[38]; non-DEHP containers and tubing are not required.

Preparation of Oral Solution:

VEPESID® for injection can be administered orally to patients unable to swallow capsules; the capsules should NOT be punctured and the liquid inside removed for these patients. There is no significant difference in bioavailability between taking the capsule and drinking the injection.[24]

- Dilute etoposide injection with Sodium Chloride 0.9% injection to a concentration of 10 mg/mL.[39]
- Store the prepared solution in oral syringes or in amber glass bottles.
- Solution is stable for 22 days at room temperature.[39] Chemical stability information applies to oral etoposide solution diluted with bacteriostatic NS,[39-42] though preservative-free NS has also been used.[43-45]
- Shake well before use.
- Solution can be further diluted immediately prior to administration in apple juice, orange juice or lemonade (NOT grapefruit juice).[24] To enhance taste, concentration should be less than 0.4 mg/mL. For example: Dilute 50 mg (5 mL) oral solution to at least 125 mL fruit juice. More concentrated solutions in fruit juice may result in precipitation in less than 3 hours.[46]

Some hospital pharmacies dispense the etoposide injection undiluted, either in the original vial[47] or in pre-drawn syringes.[45]

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PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	not to be administered by direct IV route[4,38]
Intermittent infusion	**etoposide injection:** • dilute to final concentration of 0.2-0.4 mg/mL[1] • ***by slow IV infusion (usually over 30-60 minutes)***[6] • use non-DEHP administration sets and in-line filter[37] **etoposide phosphate:** • dilute to final concentration of 0.1 mg/mL or greater[38] • over 5 minutes to 3.5 hours[38] (e.g., over 30 minutes)[48] • non-DEHP administration sets and in-line filters are not required.
Continuous infusion	**etoposide injection:** • dilute to final concentration of 0.2-0.4 mg/mL[1] • ***over 24 h[49], 26 h[50] or 34 h[51-53]*** • has been administered by continuous infusion over 5 days[4] • use non-DEHP administration sets and in-line filter[37]
Intraperitoneal	has been used[3], not recommended[4]
Intrapleural	has been used[3], not recommended[4]
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. 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***

	Cycle Length:	
Oral:	2-3 weeks:	***50 mg – 100 mg PO once daily for 3-10 days*** (total dose per cycle 150 mg-1000 mg/m^2) Round dose to the nearest 50 mg. Administer on an empty stomach as stated in the package insert[6]; may also be taken with food if needed.[2,4,54] Daily doses greater than 200 mg should be given in divided doses (BID).[6]

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Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Some protocols combine IV and oral etoposide:	2 weeks:	***80 mg/m^2 IV daily on day 1*** (total IV dose per cycle 80 mg/m^2) **with** ***160 mg/m^2 PO daily on day 2***
	3-4 weeks	***100 mg/m^2 IV daily on day 1*** **with** ***100 mg mg/m^2 PO daily on day 3 and day 5*** (total PO dose per cycle 200mg/ m^2)
	4 weeks:	***60 mg/m^2 IV for one dose on days 1 to 3*** (total IV dose per cycle 180 mg/m^2) **with** ***50 mg PO days 4 to 10*** (total PO dose per cycle 350 mg/m^2)
	4 weeks:	***50 mg/m^2 IV for one dose on day 8*** **with** ***100 mg/ m^2 PO daily on day 9-12***
Intravenous:	3 weeks:	***100 mg/m^2 IV once daily*** for 2 consecutive days starting on day 1
	3-6 weeks:	***75-100 mg/m^2 IV for one dose on days 1 to 5*** (total dose per cycle 375-500 mg/m^2)
	3 weeks:	***75 mg/m^2 IV for one dose on days 21 and day 22***
	3-4 weeks:	***50 mg/ m^2 IV for one dose daily on days 3-5*** (total dose per cycle 150mg/ m^2)
	4 weeks:	***100 mg/m^2 IV for one dose on day 1***
	3-7 weeks:	***100 mg/m^2 IV for one dose on days 1 to 3***
High dose protocols with or without bone marrow transplant:		1800-2400 mg/m^2 IV continuous infusion over 24-34 h (total dose per cycle 1800-2400 mg/m^2)[49-53,55]
Concurrent radiation:	3 weeks	***100 mg/m² IV on day 1*** **with** ***100 mg/m²/day PO on day 3 and 5***[56,57]
	3 weeks	***100 mg/m²/day x 3 days***[58,59]
Dosage in myelosuppression:		modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

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Dosage in renal failure[60,61]*:*

Suggested dose modification

Measured creatinine clearance (mL/min)	Dose
>50	100 %
10-50	75 %
<10	50 %

Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{Serum Creatinine in } \mu\text{mol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure[60,62]:

Suggested dose modification

Serum bilirubin (µmol/L)	Dose
< 25	100 %
25 to 50	50 %
50 to 85	25 %
> 85	Do not administer

Minor alterations in liver function, such as transaminase elevations, do not require dose reductions if renal function is normal.

Dosage in dialysis: not appreciably dialyzable[4]

Children:

	Cycle Length:	
Oral[63]:	4 weeks	50 mg daily for 21 days
Intravenous[63]:	3-6 weeks	60-120 mg/m^2 daily for 3-5 days

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