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.[1] Etoposide phosphate is a prodrug of etoposide and is converted *in vivo* to etoposide (its active moiety) by dephosphorylation.[2] Etoposide 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	50% (mean); dose-dependent (absorption decreases as etoposide dose increases)[1]; however, absorption does not appear to be altered by food or changes in stomach pH and emptying[3]	
	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%[4]
Metabolism	metabolism of etoposide occurs via hepatic biotransformation[1]; etoposide phosphate is rapidly and completely converted to etoposide in plasma[2]	
	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[5,6] unless specified otherwise.

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USES:

Primary uses:

Adrenocortical cancer[7]
Brain tumours[8]
Ependymoma[9]
Ewing sarcoma[7]
Germ cell tumour[7]
Gestational trophoblastic tumour[7]
Head and neck cancer[7]
*Lung cancer, small cell
*Lung cancer, non-small cell
*Lymphoma
Merkel cell carcinoma[7]
Neuroendocrine tumour[7]
Ovarian cancer[7]
Prostate cancer[7]
Sarcoma[7]
*Testicular cancer
Thymoma[7]

Other uses:

Breast cancer[7]
Kaposi's sarcoma, AIDS-related[7]
Leukemia, acute myeloid[7]
Leukemia, acute lymphocytic[7]
Multiple myeloma[7]
Rhabdomyosarcoma[7]
Wilms' tumour[7]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Carcinogenicity: Chronic toxicity studies in animals have shown etoposide to be potentially oncogenic. Based on its mechanism of action, etoposide is considered a possible carcinogen in humans. Secondary malignancies and chromosome abnormalities have been seen in patients treated with epipodophyllotoxins in association with other antineoplastic drugs.[11]

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: In animal studies, etoposide has caused absent or reduced spermatogenesis and reduced testes and ovarian weights. Consider genetic consultation and sperm preservation prior to treatment for patients of reproductive potential.[11]

Pregnancy: In animal studies, etoposide has been shown to be embryotoxic and teratogenic. Decreased fetal weights and fetal abnormalities such as major skeletal and cranial abnormalities (e.g., exencephaly, encephalocele, anophthalmia) and retarded ossification were observed. Etoposide induced aberrations in chromosome number and structure were reported in embryonic cells. Etoposide may cause fetal harm if administered to pregnant women. Contraception is recommended during treatment and for up to 6 months after treatment has ended for male and female patients of reproductive potential.[11]

Breastfeeding is not recommended as etoposide is excreted in human milk.[11]

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

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were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[12]

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%)[13]; see paragraph following ***Side Effects*** table
blood/bone marrow	***myelosuppression*** (WBC nadir 7-14 days, platelet nadir 9-16 days, recovery 20 days)
febrile neutropenia	
cardiovascular	congestive heart failure; see paragraph following ***Side Effects*** table
	hypotension with rapid IV administration (1-2%); see paragraph following ***Side Effects*** table
	myocardial infarction; see paragraph following ***Side Effects*** table
constitutional symptoms	***fatigue***
	fever
dermatology/skin	*extravasation hazard:* irritant[2,7,14]*;* see paragraph following ***Side Effects*** table
	alopecia (8-66%)
	anal irritation or fissures[15]
	epidermal necrolysis, toxic (one fatal case reported)
	nail changes[15]
	palmar-plantar erythema[15]
	pigmentation
	pruritus, severe
	rash
	urticaria
gastrointestinal	*emetogenic potential:* moderate[16]
	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

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
neurology	transient mental confusion
	peripheral neuropathy (1-2%)
	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[5,10] unless specified otherwise.

Allergic reactions are rare but can be life threatening. Higher rates of anaphylactoid reactions are reported in children receiving etoposide infusions at higher than recommended concentrations.[17] Reactions usually include chest discomfort, dyspnoea, bronchospasm, hypotension and/or skin flushing. In most patients the reactions occur within 5-10 minutes of the infusion with complete recovery once the infusion is discontinued. There are some reports of reactions occurring several hours after administration.[13] Reactions are very rare with oral capsules. Treatment should be symptomatic and can include pressor agents, corticosteroids, antihistamines, or volume expanders.[17] The subsequent management of patients experiencing a hypersensitivity reaction is usually to omit etoposide from the chemotherapy regimen.[13] When etoposide cannot be used due to severe hypersensitivity reaction, etoposide phosphate may be considered as an alternative.[13,18,19]

Excipient-related side effects have been hypothesized[15]:
- Polysorbate 80 may be responsible for the immediate side effects including hypotension and hypertension, tachycardia, dyspnoea, bronchospasm, flushing and exanthema. 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.[10]
- Ethanol, benzyl alcohol, and polyethylene glycol may be responsible for the cardiovascular, neurological and/or respiratory side effects.
- Dextrans are often associated with allergic reactions.

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.[5]

If ***extravasated,*** etoposide and etoposide phosphate may be irritants.[2,7] Extravasation of etoposide has occasionally resulted in soft tissue irritation and inflammation, but ulceration is generally not seen.[11] Etoposide phosphate extravasation may cause local soft tissue toxicity, and swelling, pain, cellulitis, and necrosis may occur.[20] Monitor injection site for extravasation.[2,7] Do not administer etoposide or etoposide phosphate by bolus or rapid intravenous injection.[11,20]

Gastrointestinal side effects occur at a slightly higher incidence with oral administration compared to IV administration.[5]

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Hypotension can occur following rapid IV administration and delayed hypotension has occurred following slow IV infusion at higher than recommended doses. Geriatric patients may be more susceptible to etoposide-induced hypotension.[5] Etoposide should be administered over at least 30 minutes (usually over 30-60 minutes).[10] 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.[5]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
aprepitant[21]	elevated etoposide plasma levels	inhibition of cytochrome P450-mediated metabolism of etoposide by aprepitant	closely monitor for etoposide toxicities
atovaquone[22]	possible increase in plasma level of etoposide	unknown	closely monitor for etoposide toxicities
cisplatin[10]	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[22]	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[21]
glucosamine[23]	may cause resistance to topoisomerase-II inhibitors	induction of the glucose-regulated stress response	avoid use of glucosamine during cancer chemotherapy treatments
grapefruit juice[24,25]	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[21]	reduced effectiveness of etoposide	induction of CYP3A4 which metabolizes etoposide	avoid concomitant use of St John's Wort with etoposide
warfarin[22]	suspected increased anticoagulant effect of warfarin	may decrease warfarin metabolism	monitor INR or PT closely

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.[17]

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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.[26]

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.[11]

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.[27-29]

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.[10] 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.).[30]
- 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) containers and tubing into etoposide IV solution.[31,32] The amount of DEHP leached from PVC containers/tubing is dependent on surfactant concentration, bag size, and contact time.[33] Actual hazardous exposure levels to this substance are not known,[34,35] however DEHP is hepatotoxic and exposure should be minimized.[31] The standard of practice at BC Cancer (as of October 1, 2005) and many other hospitals is to prepare etoposide IV infusions in non-DEHP containers[36-41] and administer using non-DEHP tubing.[42] Bristol-Myers Squibb Canada states that the use of non-DEHP containers and tubing remains an individual choice at this time.[30]
  - When etoposide is diluted to 0.4 mg/mL or greater the use of peristaltic pumps should be avoided as they can exacerbate precipitation.[33] Volumetric pumps are recommended. Etoposide is most stable at pH of approximately 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.[33]
  - Administer using 0.22 micron in-line filters.[43]

Etoposide phosphate injection (ETOPOPHOS®):
- Etoposide phosphate is a water soluble ester of etoposide which lessens the potential for precipitation following dilution and intravenous administration.[44]
- ETOPOPHOS® does NOT contain polysorbate 80[44]; 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.[30]
- Dilute etoposide injection with Sodium Chloride 0.9% injection to a concentration of 10 mg/mL.[45]
- Store the prepared solution in oral syringes or in amber glass bottles.[45]

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- Solution is stable for 22 days at room temperature.[45] Chemical stability information applies to oral etoposide solution diluted with bacteriostatic NS,[45-48] though preservative-free NS has also been used.[49-51]
- Shake well before use.[45]
- Solution can be further diluted immediately prior to administration in apple juice, orange juice or lemonade (NOT grapefruit juice).[30] 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.[52]

Some hospital pharmacies dispense the etoposide injection undiluted, either in the original vial[53] or in pre-drawn syringes.[51]

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[5,44]
Intermittent infusion	**etoposide injection:** • by slow IV infusion (usually ***over 30-60 min***)[11] • use non-DEHP administration sets and in-line filter[43] **etoposide phosphate:** • over 5 minutes to 3.5 hours[44] (e.g., ***over 30-60 min***)[11] • non-DEHP administration sets and in-line filters are NOT required.
Continuous infusion	**etoposide injection:** • ***over 24 h***[54]***, 26 h***[55] ***or 34 h***[56-58] • has been administered by continuous infusion over 5 days[5] • use non-DEHP administration sets and in-line filter[43]
Intraperitoneal	has been used[4]; not recommended[5]
Intrapleural	has been used[4]; not recommended[5]
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.

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

	Cycle Length:	
Oral:	***4 weeks***[8,59,60]:	***50 mg PO once daily for 21 consecutive days*** starting on day 1 (total dose per cycle 1050 mg) Administer on an empty stomach[11] (one hour before or after breakfast); may also be taken with food if needed.[3,61]

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

Cycle Length:

4 weeks[62,63]: ***50 mg/m² PO once daily for 2 consecutive days*** starting on day 1
(total dose per cycle 100 mg/m²)

Round dose to the nearest 50 mg.[11]
Daily doses greater than 200 mg should be given in divided doses (BID).[11]
Administer on an empty stomach[11] (one hour before or after breakfast); may also be taken with food if needed.[3,61]

3 weeks[64,65]: ***50 mg PO twice daily for 7 consecutive days*** starting on day 1
(total dose per cycle 700 mg)

Administer on an empty stomach[11] (one hour before or after breakfast); may also be taken with food if needed.[3,61]

3-4 weeks[17,66]: ***100***-200 ***mg/m² PO once daily for 3-5 consecutive days*** starting on day 1
(total dose per cycle 300-1000 mg/m²)

Round dose to the nearest 50 mg.[11]
Daily doses greater than 200 mg should be given in divided doses (BID).[11]
Administer on an empty stomach[11] (one hour before or after breakfast); may also be taken with food if needed.[3,61]

Intravenous:

when converting from etoposide to etoposide phosphate, equivalent doses should be used (e.g., 100 mg of etoposide phosphate is equivalent to 100 mg of etoposide)[2]

3-4 weeks[11,67]: ***50-100 mg/m² IV once daily for 5 consecutive days*** starting on day 1 (days 1-5)
(total dose per cycle 250-500 mg/m²)

3-4 weeks[68-71]: ***50-150 mg/m² IV once daily for 3 consecutive days*** starting on day 1 (days 1-3)
(total dose per cycle 150-450 mg/m²)

2 weeks[72-74]: ***100 mg/m² IV once daily for 2 consecutive days starting on day 1***
(total dose per cycle 200 mg/m²)

4 weeks[8,75]: ***100 mg/m² IV for one dose on day 1***
(total dose per cycle 100 mg/m²)

Concurrent radiation:

4 weeks[76-78]: ***50 mg/m² IV once daily for 5 consecutive days starting on day 1*** (days 1-5)
(total IV dose per cycle 250 mg/m²)

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

Cycle Length:

3-4 weeks[79-83]: ***100 mg/m² IV once daily for 3 consecutive days starting on day 1*** (days 1-3)
(total IV dose per cycle 300 mg/m²)

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[84]*:* modify according to protocol by which patient is being treated; if no guidelines available, the following suggested dose modification may be used:

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

calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

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

Dosage in hepatic failure[85,86]*:* modify according to protocol by which patient is being treated; if no guidelines available, the following suggested dose modification may be used:

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

Dosage in dialysis: not appreciably dialyzable[4]

modify according to protocol by which patient is being treated; if no guidelines available, the following suggested dose modification may be used:
hemodialysis[7]: reduce dose by 50%; not removed by hemodialysis, so dose may be administered before or after dialysis
peritoneal dialysis[7]: reduce dose by 50%; supplemental dose is not necessary

Children:

Cycle Length:

Oral[87-90]:
4 weeks: 50 mg/m² PO once daily for 21 consecutive days
(total dose per cycle 1050 mg/m²)

Intravenous[7,90]:
3-6 weeks: 60-120 mg/m² IV once daily for 3-5 days
(total dose per cycle 180-600 mg/m²)

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