Drug Monograph

A - Drug Name

etoposide

SYNONYM(S): VP-16

COMMON TRADE NAME(S): Vepesid®

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B - Mechanism of Action and Pharmacokinetics

In 1861, Bentley reported cytotoxic activity for podophyllin, which in a later report (1942) was useful as a topical solution in oil for treating condyloma acuminatum. Etoposide is a semisynthetic podophyllotoxin derived from the root of Podophyllum peltatum (the May apple or mandrake). It is known to cause single-strand breaks in DNA. Etoposide also causes DNA damage through inhibition of topoisomerase II and activation of oxidation-reduction reactions to produce derivatives that bind directly to DNA. Topoisomerase II carries out breakage and reunion reactions of DNA which are necessary for normal cellular function. Etoposide is cell cycle phase-specific with predominant activity occurring in late S phase and G2.

Absorption	Bioavailability	• oral: 50 % availability (range 25-75%) • Large inter- and intrapatient variability • Absorption not altered by food or other chemotherapy • Bioavailability of low oral doses of 100 mg may be better than higher oral doses
Distribution	Saliva, liver, spleen, kidneys, myometrium, cardiac tissue and brain tumour	

	tissue.	
	Cross blood brain barrier?	trace
	Volume of distribution	18-29 L
	PPB	94-97%
Metabolism	Metabolized in the liver via the cytochrome p450 system (CYP3A4 involved).	
	Active metabolites	yes
	Inactive metabolites	yes
Elimination	Elimination described by two-compartment open model, primary route of elimination is renal. Biliary excretion accounts for up to 44% recovery in feces.	
	Urine	56%, 45% as unchanged drug
	Half-life	t ½ ß: 11 hours (IV), 6.8 hours (PO)

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C - Indications and Status

Health Canada Approvals:

- Lung cancer - small cell (first-line, in combination; second-line, in combination or single agent)
- Lung cancer – non-small cell (advanced inoperable; single agent or adjuvant in combination)
- Malignant lymphomas (first-line, combination)
- Testicular cancer (germ cell and seminoma; first-line or salvage combination therapy)

Other Uses:

- Small cell carcinomas (multiple sites)
- Adrenal cancer
- Gynecological cancers (GTD, others)
- Sarcomas (Wilm's tumour, Soft tissue, Ewing's)

- CNS cancers
- Thymoma
- Merkel cell
- Leukemias

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D - Adverse Effects

Low (IV)
Emetogenic Potential: Low – No routine prophylaxis; PRN recommended (PO)

Extravasation Potential: Irritant

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare)	E
	Arterial thromboembolism (rare)	E
	Flushing	E
	Hypertension	E
	Hypotension (2%) (with rapid IV infusion)	I
Dermatological	Alopecia (66%)	E
	Nail discoloration (<1%)	D
	Radiation recall reaction (rare)	I E
	Rash (erythematous maculopapular rash, palmar erythema- high dose protocols)	I
	Skin discolouration (<1%)	D
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Abdominal pain (2%)	E
	Anorexia (13%)	E
	Constipation (rare)	E
	Diarrhea (13%)	E
	Mucositis (6%) (especially with high dose protocols >1 g/m2)	E
	Nausea (or vomiting - 43%)	I
General	Fatigue (3%) (weakness)	
	Fever (<1%)	
Hematological	Leukopenia (17%) (grade 4)	E
	Thrombocytopenia (20%) (grade 3/4)	E

Hepatobiliary	↑ LFTs (3%) (may be severe with high dose protocols)	E
Hypersensitivity	Drug reaction (2%) (type 1 - anaphylactoid)	I
Injection site	Phlebitis (rare)	I
Metabolic / Endocrine	Acidosis (compensated metabolic acidosis- high dose protocols)	E L
	Tumor lysis syndrome (rare)	I
Neoplastic	Leukemia (secondary)	L
Nervous System	Depression (<1%)	E
	Dizziness (<1%)	E
	Dysgeusia (rare)	E
	Encephalopathy (PRES - rare)	E
	Peripheral neuropathy (2%)	E
	Seizure (rare)	E
	Somnolence (rare)	E
Ophthalmic	Eye disorders (cortical blindness- rare)	D
	Optic nerve disorder (rare)	D
Respiratory	Apnea (following infusion- rare)	
	Pneumonitis (rare)	

* "*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)

Myelosuppression is dose-related, dose-limiting and may be fatal, but does not appear to be cumulative.

Etoposide has an appreciable risk of causing **hypersensitivity reactions**. Anaphylactoid reactions occur in up to 3% of patients. Fewer hypersensitivity reactions may occur if the infusion rate is slow (i.e. over at least 30 minutes). Hypersensitivity reactions occur rarely with oral administration. These reactions may be severe and fatal bronchospasm has been reported. If a reaction occurs, the drug should be held and vasopressors, corticosteroids, antihistamines or plasma volume expanders administered. If deemed appropriate by the physician, patients may be re-challenged at a slower infusion rate. For Grade 3 or 4 reactions, consider desensitization if re-challenge is necessary.

Transient hypotension during infusion occurs in 1-2% of patients and is usually associated with rapid infusion and/or high doses. It has not been associated with cardiotoxicity or ECG changes, and usually responds to cessation of the infusion and/or other appropriate supportive therapy. Rarely, etoposide may cause an increase in blood pressure. Cases of **myocardial infarction**

(some fatal) and arrhythmia have been reported.

Stomatitis is likely to occur in patients treated with radiation to the head and neck region and has been the dose-limiting toxicity in high-dose etoposide protocols. **Adverse gastrointestinal effects** occur more frequently following oral administration.

Phlebitis has occurred following the administration of undiluted etoposide.

The use of etoposide has been associated with the development of secondary acute myelogenous leukemia (AML); some included 11q23 chromosome changes. This secondary AML typically presents 2 to 4 years after the primary diagnosis of malignancies in children treated with epipodophyllotoxins.

Posterior Reversible Encephalopathy Syndrome (PRES) has been reported in patients treated with etoposide in association with other antineoplastic agents.

Cases of **tumour lysis syndrome** (including deaths) have been reported following the use of etoposide with other antineoplastic agents.

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E - Dosing

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 white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

Adults:

Intravenous:

- q4w: 50-100mg/m^2 daily for 5 days

Oral:

- q3-4w: 100-200 mg/m^2/day x 5 days. Doses greater than 200mg should be given in divided doses (BID). Many protocols use IV day 1 and PO on subsequent days (e.g., days 2-5 or days 3, 5). Usual dose is twice the IV dose to the nearest 50 mg.

Dosage with Toxicity:

Discontinue if grade 4 organ toxicity.

Dosage in myelosuppression:

- Modify according to protocol by which patient is being treated.

Toxicity	Count level (x 10^9/L)	Action for next cycle (blood counts expressed in 10^9/L)
Platelets	< 50	*Reduce dose; 50% ↓ if platelets < 25 or bleeding
	≥ 50	*Consider dose reduction if platelets 50 – 75, especially heavily pretreated or debilitated patients
ANC	< 0.5	*Reduce dose; 50% ↓ if febrile neutropenia
WBC	2 - 3	*No change
*Do not retreat until ANC > 1.5 x 10^9/L and platelets > 100 x 10^9/L.		

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time.	• Consider switch to oral etoposide. • Pre-medications with corticosteroids and H1-receptor antagonists. • Slow infusion rate (infuse over 60-120 minutes).
3 or 4	• Stop treatment. • Aggressively	• Consider switch to oral etoposide. • Cross-reactivity reported between

	manage symptoms.	etoposide and teniposide. • Consider desensitization.

Dosage with Hepatic Impairment:

Patients with bilirubin > 25 µmol/L may have higher exposure to unbound etoposide as its concentrations are significantly higher due to lower albumin binding. Unbound etoposide clearance is lower in this patient population than in patients with normal bilirubin levels.

Suggested dose adjustments:

Bilirubin (µmol/L)	% usual dose
1-2 x ULN	50
>2-4 x ULN	25
>4 x ULN	Discontinue

Dosage with Renal Impairment:

Creatinine clearance (mL/min)	% usual dose
15-50	75
<15	50, or discontinue

Dosage in the elderly:

No dose adjustment required.

Children:

Safety and efficacy not established.

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F - Administration Guidelines

Always wear impervious gloves when handling etoposide.

IV ETOPOSIDE:

- Maximum diluted concentration of 0.4 mg/mL
- All premixed bag(s) should be attached to (0.22 micron) in-line filter.
- Precipitation is unpredictable, depending on concentration, time after dilution, presence of crystallization nuclei, agitation, contact with incompatible surfaces and other factors.
- Monitor solutions for precipitation before and during administration.
- Dilute doses ≤100 mg in 250 mL NS or D5W, doses >100 mg to ≤200 mg in 500 mL, and doses> 200 mg in 1000 mL
- The use of non-DEHP [non-di(2-ethylhexyl) phthalate] containers and tubing is recommended, due to the potential for DEHP leaching from infusion containers and tubings into etoposide solutions with polysorbate 80.
- Larger volumes may be used for prehydration for Cisplatin or Ifosfamide dose.
- Infuse over 30 to 60 minutes; Adjust rate if blood pressure drops. Etoposide **should not** be given by rapid IV injection.
- May observe patient for 30 minutes after dose, to watch for hypotension.
- Acrylic or ABS (a polymer composed of acrylonitrile, butadiene and styrene) infusion devices may crack if exposed to undiluted etoposide.

ORAL ETOPOSIDE:

- Oral self-administration; drug available by outpatient prescription.
- Capsules should be taken on empty stomach.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to etoposide or to any component of the formulation (polysorbate 80).
- Patients with severe myelosuppression.
- Patients with severe hepatic and/or renal impairment.
- Do not use live vaccines.

Other Warnings/Precautions:

- Patients with low serum albumin may be at an increased risk of toxicity.
- Polysorbate 80 is associated with life-threatening organ failure in preterm infants.
- Etoposide injection contains benzyl alcohol and should not be used in neonates.

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Teratogenicity: Yes
- Mutagenicity: Yes
  Etoposide is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- Excretion into breast milk: Yes
  Breastfeeding is not recommended.
- Fertility effects: Yes
  Preservation of sperm may be considered for later fatherhood. Genetic consultation is recommended after treatment ends.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Levamisole, drugs which inhibit phosphatase	↑ toxicity		Use with caution
vincristine	↑ in incidence and severity of neurotoxicity	Unknown	Caution
P-glycoprotein inhibitors (i.e. quinidine, cyclosporine)	↑ etoposide toxicity	reduced clearance with increased etoposide AUC	Avoid concurrent use or consider dose reduction (e.g. decrease etoposide dose by 50% when used with high-dose cyclosporine)
CYP3A4 inhibitors (i.e. ketoconazole, voriconazole, clarithromycin, ritonavir)	↑ etoposide plasma levels	may inhibit metabolism of etoposide	Caution; may require dose adjustment
CYP3A4 inducers (i.e. phenytoin, rifampin,	↓ etoposide effect	↑ metabolism of etoposide	Caution; dose of etoposide may require adjustment

dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)			
warfarin	possible increased anticoagulant effect	Unknown	Monitor PT/INR closely and anticoagulant dose adjusted accordingly
Glucosamine	↓ etoposide effectiveness	↓ in topoisomerase II level suggested	Avoid concomitant use
Grapefruit juice	↑ etoposide exposure (theoretical); ↓ PO bioavailability / exposure observed in humans	↑ exposure due to ↓CYP3A4 metabolism (theoretical); ↓ exposure possibly via OATP2 inhibition or alteration of P-glycoprotein mediated transport	Avoid concurrent use
Live virus vaccines	May result in severe systemic infection	Immunosuppression	Avoid concurrent use

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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
Renal function tests	Baseline and before each cycle
Liver function tests	Baseline and before each cycle
Blood pressure - monitor for hypertension	Baseline and at each treatment
Clinical assessment of stomatitis (oral examination upon patient complaint of sore mouth), bleeding, infection, infusion reactions, tumour lysis syndrome, encephalopathy	At each visit

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

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- etoposide - oral capsules ()

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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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