

Etoposide

Class:

Antineoplastic Agent, Podophyllotoxin Derivative; Antineoplastic Agent, Topoisomerase II Inhibitor

Indications:

- _ Small cell lung cancer
- _ Testicular cancer
- _ Non-Hodgkin lymphoma

Unlabeled uses:

- _ Hematopoietic stem cell transplant conditioning regimen, lymphoid malignancies
- _ Non small cell lung cancer
- _ Ovarian cancer, refractory
- _ Testicular cancer
- _ Thymoma
- _ Unknown primary adenocarcinoma

Available dosage form in the hospital: 100 mg AMP , 100 mg CAP.

Trade Names: Toposar , Vepesid.

Doses: Details concerning dosing in combination regimens should also be consulted:

*U.S. labeling:

-Small cell lung cancer (combination chemotherapy):

- I.V.: 35 mg/m²/day for 4 days, up to 50 mg/m²/day for 5 days every 3-4 weeks
- Oral: Due to poor bioavailability, oral doses should be twice the I.V. dose (and rounded to the nearest 50 mg)

-Testicular cancer (combination chemotherapy): I.V.: 50-100 mg/m²/day for days 1-5 or 100 mg/m²/day on days 1, 3, and 5 repeated every 3-4 weeks

*Canadian labeling:

-Non-Hodgkin lymphoma (in combination with other agents), non small cell lung cancer (alone or in combination), small cell lung cancer (first-line in combination; second-line alone or in combination), testicular cancer (in combination; oral therapy for refractory disease):

- I.V.: 50-100 mg/m²/day for 5 days
- Oral: 100-200 mg/m²/day for 5 days; administer daily doses >200 mg in 2 divided doses.

**Adult unlabeled uses and/or dosing:

-Hematopoietic stem cell transplant conditioning regimen, lymphoid malignancies: I.V.: 60 mg/kg over 4 hours as a single dose 3 or 4 days prior to transplantation (Horning, 1994; Snyder, 1993; Weaver, 1994)

-Non small cell lung cancer: I.V.: 100 mg/m² days 1, 2, and 3 every 3 weeks for 4 cycles or every 4 weeks for 3-4 cycles (in combination with cisplatin) or 50 mg/m² days 1-5 and days 29-33 (in combination with cisplatin and radiation therapy)

-Ovarian cancer, refractory: Oral: 50 mg/m² once daily for 21 days every 4 weeks until disease progression or unacceptable toxicity (Rose, 1998)

-Small cell lung cancer, limited stage (combination chemotherapy): I.V.: 120 mg/m²/day on days 1, 2, and 3 every 3 weeks for 4 courses or 100 mg/m²/day on days 1, 2, and 3 for induction therapy, followed by consolidation chemotherapy (Saito, 2006) or 100 mg/m²/day on days 1, 2, and 3 every 3 weeks up to a maximum of 6 cycles or 100 mg/m²/day I.V. on day 1, followed by 200 mg/m²/day orally on days 2 through 4 every 3 weeks for a maximum of 5 courses

-Small cell lung cancer, extensive stage (combination chemotherapy): 100 mg/m²/day I.V. on days 1, 2, and 3 every 3 weeks for 4 cycles (Lara, 2009) **or** 100 mg/m²/day I.V. on day 1, followed by 200 mg/m²/day **orally** on days 2 through 4 every 3 weeks for a maximum of 5 courses **or** I.V.: 80 mg/m²/day on days 1, 2, and 3 every 3 weeks up to 8 cycles

-Testicular cancer (combination chemotherapy):

-Nonseminoma: I.V.: 100 mg/m²/day on days 1 through 5 every 21 days for 3-4 courses

-Nonseminoma, metastatic (high-dose regimens): I.V.: 750 mg/m²/day administered 5, 4, and 3 days before peripheral blood stem cell infusion, repeat for a second cycle after recovery of granulocyte and platelet counts **or** 400 mg/m²/day (beginning on cycle 3) on days 1, 2, and 3, with peripheral blood stem cell support, administered at 14- to 21-day intervals for 3 cycles

-Thymoma, locally advanced or metastatic: I.V.: 120 mg/m² days 1, 2, and 3 every 3 weeks (in combination with cisplatin) for up to 8 cycles

-Unknown primary adenocarcinoma: Oral: 50 mg once daily on days 1, 3, 5, 7, and 9 alternating with 100 mg once daily on days 2, 4, 6, 8, and 10 every 3 weeks (in combination with paclitaxel and

Geriatric

Refer to adult dosing

Renal Impairment:

Oral, I.V.:

U.S. labeling recommends the following adjustments:

- Cl_{cr} >50 mL/minute: No adjustment required.
- Cl_{cr} 15-50 mL/minute: Administer 75% of dose
- Cl_{cr} <15 mL minute: Data not available; consider further dose reductions

The following adjustments have been recommended:

**Aronoff, 2007:

- Cl_{cr} 10-50 mL/minute: Administer 75% of dose.
- Cl_{cr} <10 mL minute: Administer 50% of dose.
- Hemodialysis: Administer 50% of dose; supplemental posthemodialysis dose is not necessary.
- Peritoneal dialysis: Administer 50% of dose; supplemental dose is not necessary.
- Continuous renal replacement therapy (CRRT): Administer 75% of dose.

**Janus, 2010: Hemodialysis: Reduce dose by 50%; not removed by hemodialysis so may be administered before or after dialysis

**Kintzel, 1995:

- Cl_{cr} 46-60 mL/minute: Administer 85% of dose
- Cl_{cr} 31-45 mL/minute: Administer 80% of dose
- Cl_{cr} ≤30 mL/minute: Administer 75% of dose

Hepatic Impairment:

*U.S. labeling: No dosage adjustment provided in manufacturer's labeling.

*Canadian labeling:

- Mild-to-moderate impairment: No dosage adjustment provided in manufacturer's labeling.
- Severe impairment: Use is contraindicated.

The following adjustments have also been recommended:

-Donelli, 1998: Liver dysfunction may reduce the metabolism and increase the toxicity of etoposide. Normal doses of I.V. etoposide should be given to patients with liver dysfunction (dose reductions may result in subtherapeutic concentrations); however, use caution with concomitant liver dysfunction (severe) and renal dysfunction as the decreased metabolic clearance cannot be compensated by increased renal clearance.

-Floyd, 2006: Bilirubin 1.5-3 mg/dL or AST >3 times ULN: Administer 50% of dose

-King, 2001; Koren, 1992: Bilirubin 1.5-3 mg/dL or AST >180 units/L: Administer 50% of dose

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer (**Note:** Excludes HSCT dosing): Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosing: Adjustment for Toxicity

Oral, I.V.:

- Infusion (hypersensitivity) reactions: Interrupt infusion.
- ANC $<500/\text{mm}^3$ or platelets $<50,000/\text{mm}^3$: Withhold treatment until recovery.
- Severe adverse reactions (nonhematologic): Reduce dose or discontinue treatment.
- WBC $2000\text{-}3000/\text{mm}^3$ or platelets $75,000\text{-}100,000/\text{mm}^3$: Canadian labeling (not in U.S. labeling): Reduce dose by 50%

Common side effect:

Dermatologic: Alopecia (8% to 66%)

Gastrointestinal: Nausea/vomiting (31% to 43%), anorexia (10% to 13%), diarrhea (1% to 13%), Stomatitis (1% to 6%), abdominal pain (up to 2%)

Hematologic: Leukopenia (60% to 91%; grade 4: 3% to 17%; nadir: 7-14 days; recovery: by day 20), thrombocytopenia (22% to 41%; grades 3/4: 1% to 20%; nadir 9-16 days; recovery: by day 20), anemia ($\leq 33\%$)

Cardiovascular: Hypotension (1% to 2%; due to rapid infusion)

Hepatic: Hepatic toxicity (up to 3%)

Neuromuscular & skeletal: Peripheral neuropathy (1% to 2%)

Miscellaneous: Anaphylactic-like reaction

Pregnancy Risk Factor: D