POSITION ONLY

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Toposar™

etoposide injection, USP

Pharmacia
&Upjohn

WARNINGS

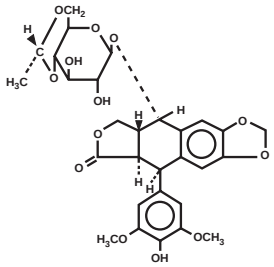
TOPOSAR (etoposide injection, USP) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe myelosuppression with resulting infection or bleeding may occur.

DESCRIPTION

TOPOSAR (etoposide injection, USP) (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is 4′-demethylepipodophyllotoxin 9-[4,6-0-(R)-ethylidene-β-D-glucopyranoside]. It is very soluble in methanol and chloroform, slightly soluble in ethanol and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents. It has a molecular weight of 588.58 and a molecular formula of $C_{29}H_{32}O_{13}$.

TOPOSAR is available for intravenous use as a 20 mg/mL solution in 100 mg (5mL), 200 mg (10mL) and 500 mg (25mL) sterile, multiple dose vials. The pH of the clear yellow solution is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5% (v/v) alcohol.

The structural formula is:



CLINICAL PHARMACOLOGY

Etoposide has been shown to cause metaphase arrest in chick fibroblasts. Its main effect, however, appears to be at the G_2 portion of the cell cycle in mammalian cells. Two different dose-dependent responses are seen. At high concentrations (10 μg/mL or more), lysis of cells entering mitosis is observed. At low concentrations (0.3 to 10 μg/mL), cells are inhibited from entering prophase. It does not interfere with microtubular assembly. The predominant macromolecular effect of etoposide appears to be DNA synthesis inhibition.

Pharmacokinetics: On intravenous administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. Total body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min/m^2 and, like the terminal elimination half-life, are independent of dose over a range 100 to 600 mg/m^2. Over the same dose range, the areas under the plasma concentration vs. time curves (AUC) and the maximum plasma concentration (C_{max}) values increase linearly with dose. Etoposide does not accumulate in the plasma following daily administration of 100 mg/m^2 for 4 to 5 days.

The mean volumes of distribution at steady state fall in the range of 18 to 29 liters or 7 to 17 L/m^2. Etoposide enters the CSF poorly. Although it is detectable in CSF and intracerebral tumors, the concentrations are lower than in extracerebral tumors and in plasma. Etoposide concentrations are higher in normal lung than in lung metastases and are similar in primary tumors and normal tissues of the myometrium. *In vitro*, etoposide is highly protein bound (97%) to human plasma proteins. An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children. In a study determining the effect of other therapeutic agents on the *in vitro* binding of carbon-14 labeled etoposide to human serum proteins, only phenylbutazone, sodium salicylate and aspirin displaced protein-bound etoposide at concentrations achieved *in vivo*[1].

Etoposide binding ratio correlates directly with serum albumin in patients with cancer and in normal volunteers. The unbound fraction of etoposide significantly correlated with bilirubin in a population of cancer patients.[2,3]

After intravenous administration of ^{3}H-etoposide (70 to 290 mg/m^2), mean recoveries of radioactivity in the urine range from 42% to 67%, and fecal recoveries range from 0% to 16% of the dose. Less than 50% of an intravenous dose is excreted in the urine as etoposide with mean recoveries of 8% to 35% within 24 hours.

In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m^2 or about 35% of the total body clearance over a dose range of 80 to 600 mg/m^2. Etoposide, therefore, is cleared by both renal and nonrenal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known.

Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the nonrenal clearance of etoposide. The major urinary metabolite of etoposide in adults and children is the hydroxy acid [4′-demethylepipodophyllic acid-9-(4,6-0-(R)-ethylidene-β-D-glucopyranoside)], formed by opening of the lactone ring. It is also present in human plasma, presumably as the **trans** isomer. Glucuronide and/or sulfate conjugates of etoposide are excreted in human urine and represent 5% to 22% of the dose.

After either intravenous infusion or oral capsule administration, the C_{max} and AUC values exhibit marked intrasubject and intersubject variability.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration, and nonrenal clearance. In children, elevated serum SGPT levels are associated with reduced drug total body clearance. Prior to use of cisplatin may also result in a decrease of etoposide total body clearance in children.

INDICATIONS AND USAGE

TOPOSAR is indicated in the management of the following neoplasms:

Refractory Testicular Tumors — TOPOSAR in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic and radiotherapeutic therapy.

Small cell lung cancer — Etoposide injection and/or capsules in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.

CONTRAINDICATIONS

TOPOSAR is contraindicated in patients who have demonstrated a previous hypersensitivity to it.

WARNINGS

Patients being treated with TOPOSAR must be frequently observed for myelosuppression both during and after therapy. Dose-limiting bone marrow suppression is the most significant toxicity associated with etoposide therapy. Therefore, the following studies should be obtained at the start of therapy and prior to each subsequent dose of TOPOSAR: platelet count, hemoglobin, white blood cell count and differential. The occurrence of a platelet count below 50,000/mm^3 or an absolute neutrophil count below 500/mm^3 is an indication to withhold further therapy until the blood counts have sufficiently recovered.

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea and hypotension. (See **ADVERSE REACTIONS** section.) Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

TOPOSAR should be given only by slow intravenous infusion (usually over a 30- to 60-minute period) since hypotension has been reported as a possible side effect of rapid intravenous injection.

Pregnancy: Pregnancy "Category D". Etoposide can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Etoposide is teratogenic and embryocidal in rats and mice at doses of 1% to 3% of the recommended clinical dose based on body surface area.

In a teratology study in SPF rats, etoposide was administered intravenously at doses of 0.13, 0.4, 1.2, and 3.6 mg/kg/day on days 6 to 15 of gestation. Etoposide caused dose-related maternal toxicity, embryotoxicity, and teratogenicity at dose levels of 0.4 mg/kg/day and higher. Embryonic resorptions were 90% and 100% at the two highest dosages. At 0.4 and 1.2 mg/kg, fetal weights were decreased and fetal abnormalities including decreased weight, major skeletal abnormalities, exencephaly, encephalocele and anophthalmia occurred. Even at the lowest dose tested, 0.13 mg/kg, a significant increase in retarded ossification was observed.

Etoposide administered as a single intraperitoneal injection in Swiss-Albino mice at dosages of 1, 1.5, and 2 mg/kg on days 6, 7 or 8 of gestation caused dose-related embryotoxicity, cranial abnormalities and major skeletal malformations.

PRECAUTIONS

General: In all instances where the use of TOPOSAR is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most such adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of TOPOSAR therapy should be carried out with caution, and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.

Laboratory Tests: Periodic complete blood counts should be done during the course of TOPOSAR treatment. They should be performed prior to therapy and at appropriate intervals during and after therapy. At least one determination should be done prior to each dose of TOPOSAR.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity tests with etoposide have not been conducted in laboratory animals. Etoposide should be considered a potential carcinogen in humans. The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents.

The mutagenic and genotoxic potential of etoposide has been established in mammalian cells. Etoposide caused aberrations in chromosome number and structure in embryonic murine cells and human hematopoietic cells; gene mutations in Chinese hamster ovary cells; and DNA damage by strand breakage and DNA-protein cross-links in mouse leukemic cells. Etoposide also caused a dose-related increase in sister chromatid exchanges in Chinese hamster ovary cells.

Treatment of Swiss-Albino mice with 1.5 mg/kg IP of etoposide on day 7 of gestation increased the

incidence of intrauterine death and fetal malformations as well as significantly decreased the average fetal body weight. Maternal weight gain was not affected.

Treatment of pregnant SPF rats with 1.2 mg/kg/day IV of etoposide for 10 days led to a prenatal mortality of 92%, and 50% of the implanting fetuses were abnormal.

Pregnancy: Pregnancy "Category D" (See **WARNINGS** section).

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etoposide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

TOPOSAR contains polysorbate 80. In premature infants, a life-threatening syndrome consisting of liver and renal failure, pulmonary deterioration, thrombocytopenia and ascites has been associated with an injectable vitamin E product containing polysorbate 80.

ADVERSE REACTIONS

The following data on adverse reactions are based on both oral and intravenous administration of etoposide as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Hematologic Toxicity: Myelosuppression is dose related and dose limiting with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported.

The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents.

Gastrointestinal Toxicity: Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion.

Hypotension: Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare occurrence, it is recommended that etoposide be administered by slow intravenous infusion over a 30- to 60-minute period. If hypotension occurs, it usually responds to cessation of the infusion and administration of fluids or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

Allergic Reactions: Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea and hypotension have been reported to occur in 0.7% to 2% of patients receiving intravenous etoposide and in less than 1% of the patients treated with oral capsules. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate; however the reactions can be fatal. Hypertension and flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of etoposide.

Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported rarely.

Rash, urticaria, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.

Alopecia: Reversible alopecia, sometimes progressing to total baldness was observed in up to 66% of patients.

Other Toxicities: The following adverse reactions have been infrequently reported: aftertaste, fever, pigmentation, abdominal pain, constipation, dysphagia, transient cortical blindness and a single report of radiation recall dermatitis.

Hepatic toxicity, generally in patients receiving higher doses of the drug than those recommended, has been reported with etoposide. Metabolic acidosis also has been reported in patients receiving these higher doses.

The incidences of adverse reactions in the table that follows are derived from multiple databases from studies in 2,081 patients when etoposide was used either orally or by injection as a single agent.

ADVERSE DRUG EFFECT	PERCENT RANGE OF REPORTED INCIDENCE
Hematologic toxicity	
Leukopenia (less than 1,000 WBC/mm^3)	3–17
Leukopenia (less than 4,000 WBC/mm^3)	60–91
Thrombocytopenia (less than 50,000 platelets/mm^3)	1–20
Thrombocytopenia (less than 100,000 platelets/mm^3)	22–41
Anemia	0–33
Gastrointestinal toxicity	
Nausea and vomiting	31–43
Abdominal pain	0–2
Anorexia	10–13
Diarrhea	1–13
Stomatitis	1–6
Hepatic	0–3
Alopecia	8–66
Peripheral neurotoxicity	1–2
Hypotension	1–2
Allergic reaction	1–2

OVERDOSAGE

No proven antidotes have been established for etoposide overdosage.

DOSAGE AND ADMINISTRATION

Note: Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene and styrene) have been reported to crack and leak when used with *undiluted* etoposide injection.

The usual dose of TOPOSAR in testicular cancer in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m^2/day on days 1 through 5 to 100 mg/m^2/day on days 1, 3 and 5.

In small cell lung cancer, the TOPOSAR dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m^2/day for 4 days to 50 mg/m^2/day for 5 days.

Chemotherapy courses are repeated at 3- to 4-week intervals after adequate recovery from any toxicity.

The dosage should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior x-ray therapy or chemotherapy which may have compromised bone marrow reserve.

Administration Precautions: As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of TOPOSAR. Skin reactions associated with accidental exposure to TOPOSAR may occur. The use of gloves is recommended. If TOPOSAR solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Preparation for Intravenous Administration: TOPOSAR must be diluted prior to use with either 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur. Hypotension following rapid intravenous administration has been reported, hence, it is recommended that the TOPOSAR solution be administered over a 30- to 60- minute period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. **TOPOSAR should not be given by rapid intravenous injection.**

Parenteral drug products should be inspected visually for particulate matter and discoloration (see **DESCRIPTION** section) prior to administration whenever solution and container permit.

Stability: Unopened vials of TOPOSAR are stable for 24 months at room temperature (25°C). Vials diluted as recommended to a concentration of 0.2 or 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25°C) under normal room fluorescent lights in both glass and plastic containers.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[4-10] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

TOPOSAR™ (etoposide injection, USP) (20 mg/mL)

NDC 0013-7336-91	100 mg/5mL Sterile, Multiple Dose Vial, 10 vial packs
NDC 0013-7346-94	200 mg/10mL Sterile, Multiple Dose Vial, 5 vial packs
NDC 0013-7356-88	500 mg/25mL Sterile, Multiple Dose Vial, single vial packs

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

℞ only

References

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