

Toposar

Etoposide USP

Composition:

Toposar : Each 5 ml injectable solution contains Etoposide USP 100mg.

Description:

Pharmacodynamics: Pharmacotherapeutic classification: podophyllotoxin derivatives. Etoposide is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. Podophyllotoxins inhibit mitosis by blocking microtubular assembly. Etoposide inhibits cell cycle progression at a premitotic phase (late S and G2). It does not interfere with the synthesis of nucleic acids

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/m² and, like the terminal elimination half-life, are independent of dose over a range 100-600 mg/m². 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/m² 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/m².

Therapeutic indications: Etoposide is indicated in the management of the following neoplasms: **Small Cell Lung Cancer:** Etoposide is indicated in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer. **Refractory Testicular Tumors:** Etoposide is also indicated in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic, and radio therapeutic therapy.

Dosage and administrations:

Small cell lung cancer: The dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m²/day for 4 days to 50 mg/m²/day for 5 days. **Refractory Testicular Tumors:** The usual dose of Etoposide in testicular cancer in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m²/day on days 1 through 5 to 100 mg/m²/day on days 1, 3, and 5. For recommended dosing adjustments in patients with renal impairment chemotherapy courses are repeated at 3- to 4-week intervals after adequate recovery from any toxicity. Or, as directed by the registered physicians.

Contraindication: Etoposide is contraindicated in patients who have demonstrated a previous hypersensitivity to Etoposide or any component of the formulation.

Preparation for Intravenous Administration:

Etoposide must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, 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 Etoposide 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.

Precaution:

Patients being treated with Etoposide must be frequently observed for myelosuppression both during and after therapy. Myelosuppression resulting in death has been reported. 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 cycle of Etoposide: platelet count, hemoglobin, white blood cell count, and differential. The occurrence of a platelet count below 50,000/mm³ or an absolute neutrophil count below 500/mm³ 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. Higher rates of anaphylactic-like reactions have been reported in children who received infusions at concentrations higher than those recommended. The role that concentration of infusion (or rate of infusion) plays in the development of anaphylactic-like reactions is uncertain. 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. For parenteral administration, Etoposide 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. In all instances where the use of Etoposide 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 Etoposide 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. Patients with low serum albumin may be at an increased risk for Etoposide associated toxicities.

Drug interactions

High-dose cyclosporine resulting in concentrations above 2000 ng/ml administered with oral Etoposide has led to an 80% increase in Etoposide exposure with a 38% decrease in total body clearance of etoposide compared to Etoposide alone. **Laboratory Tests:** Periodic complete blood counts should be done during the course of Etoposide treatment. They should be performed prior to each cycle of therapy and at appropriate intervals during and after therapy. At least one determination should be done prior to each dose of Etoposide. **Renal Impairment:** In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance:

Measured Creatinine Clearance	>50 mL/min	15-50 mL/min
Etoposide	100% of dose	75% of dose

Subsequent Etoposide dosing should be based on patient tolerance and clinical effect. Data are not available in patients with creatinine clearances <15 ml/min and further dose reduction should be considered in these patients.

Side effects:

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. Fever and infection have also been reported in patients with neutropenia. Death associated with myelosuppression 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. Mild to severe mucositis/esophagitis may occur. 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/or 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 the 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/or 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: abdominal pain, aftertaste, constipation, dysphagia, asthenia, fatigue, malaise, somnolence, transient cortical blindness, optic neuritis, interstitial pneumonitis/pulmonary fibrosis, fever, seizure (occasionally associated with allergic reactions), Stevens-Johnson syndrome, and toxic epidermal necrolysis, pigmentation, and a single report of radiation recall dermatitis.

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 to 0.4 mg/ml are stable for 96 and 24 hours, respectively, at room temperature (25° C) under normal room fluorescent light in both glass and plastic containers. **Procedures for proper handling and disposal:** Procedure for proper handling and disposal of anticancer drugs should be considered.

Overdose:

No proven antidote has been established for Etoposide over dosage.

Pregnancy and lactation:

Pregnancy category D. There are no adequate and well controlled studies in pregnant woman Etoposide has been reported to be found in human milk. Patient receives Etoposide should not be breast feed.

Storage:

Store below 25° C in a dry place. Keep all medicines out of reach of children. Protect from light.

Packaging:

Toposar: Each box contains one vial of 5ml solution.