

Topoxin

Etoposide

COMPOSITION

Topoxin Injection: Each vial contains 5 ml solution containing Etoposide USP 100 mg.

Topoxin Capsule: Each capsule contains Etoposide USP 50 mg.

DESCRIPTION

Etoposide is a semi-synthetic derivative of podophyllotoxin. Empirical formula: $C_{29}H_{32}O_{13}$ and MW: = 588.58 Chemical name: 4'-demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-b-d-glucopyranoside.

CLINICAL PHARMACOLOGY

Etoposide has been shown to cause metaphase arrest in chick fibroblasts. Its main effect, however, appears to be at the G2 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

Absorption: Absorption from the oral route of administration is variable and incomplete. Peak blood levels occur about one hour after oral administration.

Distribution: Following intravenous administration of 100 mg Etoposide the peak plasma concentration ranged from 2.2-6.1 microgram/mL with an average of 4.7, and time to peak ranged from 0.5-2.0 hours (average 1 hour). The elimination half-life based on a model-dependent method averaged 5.8±3.2 hours.

Metabolism: Etoposide is approximately 66% metabolised. One metabolite has been identified but its activity not studied. However, it appears to be extensively distributed and retained. After 72 hours, 44% of the administered dose of Etoposide was recovered in the urine; 29% as unchanged drug and 15% as metabolite. Recovery in the faeces ranged from less than 2% to 16% over three days.

Excretion: Renal clearance 13.6±4.5 mL/min: total body clearance 47±22 mL/min. The one metabolite identified has a renal clearance of 31.3 mL/min and total clearance of 111.7 mL/min.

INDICATIONS

Etoposide is indicated for use in the treatment of:

- Small cell carcinoma of the lung
- Acute monocytic and myelomonocytic leukaemia
- Hodgkin's disease
- Non-Hodgkin's lymphoma
- Testicular Cancer
- Malignant lymphoma

Use in Pregnancy

Pregnancy Category D

Etoposide can cause foetal harm when administered to pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be appraised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

DOSAGE AND ADMINISTRATION

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. Equivalent doses of Etoposide should be used.

In small cell lung cancer, the Etoposide 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. Equivalent doses of Etoposide should be used.

Preparation for Intravenous Administration: Topoxin Injection 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 Topoxin 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. Topoxin should not be given by rapid intravenous injection.

Stability

Stability: Unopened vials of Topoxin 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.

CONTRAINDICATIONS

Patients with severe hepatic dysfunction. Patients who have a demonstrated hypersensitivity to any of the ingredients. Severe bone marrow failure (WBC less than 2000 cells/mm³ or platelet count less than 75 000 cells/mm³) not due to malignant disease.

PRECAUTIONS

Patients being treated with Etoposide must be observed for myelosuppression carefully and frequently both during and after therapy. Dose limiting bone marrow suppression is the most significant toxicity associated with Etoposide therapy. Therefore the following counts should be obtained at the start of therapy and prior to each subsequent course of Etoposide: platelet count, haemoglobin, white blood cell count and differential. The occurrence of a platelet count below 50,000/mm³ indicates that the patient is at risk of bleeding; the occurrence of a total white cell count below 3,000/mm³ or an absolute neutrophil count below 500/mm³ indicates that the patient is at risk of infection. Therapy should not be commenced if there is a risk of the platelet count, the white cell count or the neutrophil count falling

below these levels. Furthermore, if the counts drop below these levels during therapy, further therapy should be withheld until the blood counts have sufficiently recovered.

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifest by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension. Treatment is symptomatic. Administration of Etoposide should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician. There have been reports of cardiac arrest secondary to allergic reactions during infusion with Etoposide. 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 infusion.

Infections must be brought under control before using Etoposide due to bone marrow suppression following use of the drug and the risk of septicæmia.

Combined chemotherapy may cause increased bone marrow suppression and should be used with caution.

Laboratory Tests: Periodic complete blood counts, hepatic and renal function tests and serum urate should be done during the course of Etoposide treatment. They should be performed prior to therapy and at appropriate periods during therapy. At least one determination should be done to each course of Etoposide.

Patients with Impaired Liver or Renal Function: Etoposide should be given cautiously to individuals with any degree of hepatic or renal dysfunction

OVERDOSE

No information is available relating to Etoposide poisoning in humans

ADVERSE EFFECTS

The incidences of adverse reactions, given below as mean percent, are derived from studies that used single agent Etoposide therapy.

More Common Reactions:

Haematological Toxicity: The principal toxicity of Etoposide is dose-related bone marrow suppression, with granulocyte nadirs occurring 7 to 14 days, and platelet nadirs 9 to 16 days, after drug administration.

Thrombocytopenia (less than 100,000 platelets/mm³) and severe thrombocytopenia (less than 50,000 platelets/mm³) were seen in 28 to 41 percent and 4 to 20 percent of this same group of patients.

Pancytopenia was found in 7% of 340 patients treated with 50-60 mg/m² Etoposide Injection I.V for 5 days.

Alopecia: Reversible alopecia, sometimes progressing to total baldness, has been observed in up to 66 percent of patients.

Gastrointestinal Toxicity: Nausea and vomiting the major gastrointestinal toxicities.

Hypotension: Temporary hypotension following rapid intravenous administration has been reported.

Less Common Reactions:

Allergic Reactions: Anaphylactic-like reactions characterised by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension have also been reported to occur in 0.7 to 2 percent of patients, occurring during or immediately after intravenous Etoposide administration. Anaphylactic-like reactions have occurred very rarely in 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. One fatal acute reaction associated with bronchospasm has been reported. Hypertension and flushing have also been reported. Blood pressure usually normalises with a few hours after cessation of the infusion. Anaphylactic-like reactions can occur with the initial dose of Etoposide. Apnoea has occurred in patients receiving Etoposide infusion.

Solutions more concentrated than those recommended should not be given intravenously. If such solutions are justifiable, higher rates of anaphylactic-like reactions may occur.

Neuropathy: The use of Etoposide has been reported to cause peripheral neuropathy in 0.7 percent of patients. The associated use of Vincristine sulphate can possibly enhance this neuropathy. Caution should be taken when giving Etoposide and Vincristine combined to older individuals whose performance status is impaired and to patients with pre-existing neurological disease and poor nutritional status.

Other Toxicities: The following reactions have been rarely reported:

Central nervous system toxicity (somnolence and fatigue), liver toxicity (transient jaundice and elevated alkaline phosphatase), renal toxicity (elevated urea; hyperuricaemia), septicæmia during high dose regimens, aftertaste; fever, rash, pigmentation, pruritus, abdominal pain, urticaria, constipation, dysphagia, transient cortical blindness, mucositis, esophagitis and a single report of radiation recall dermatitis.

DRUG INTERACTIONS

Etoposide should not be mixed with other anti neoplastic agents in the infusion solution.

PHARMACEUTICAL INFORMATION

Storage condition

Topoxin Injection: Store the vial in original carton at 15°C to 25°C. Protect from light. Keep out of the reach of children.

Topoxin Capsule: Store in original carton at 2°C to 8°C. Protect from light. Keep out of the reach of children.

Presentation & Packaging

Topoxin Injection: Each commercial box contains 1 vial containing Etoposide USP 100 mg/5ml.

Topoxin Capsule: Each commercial box contains 30 Capsules in Alu-Alu blister pack.