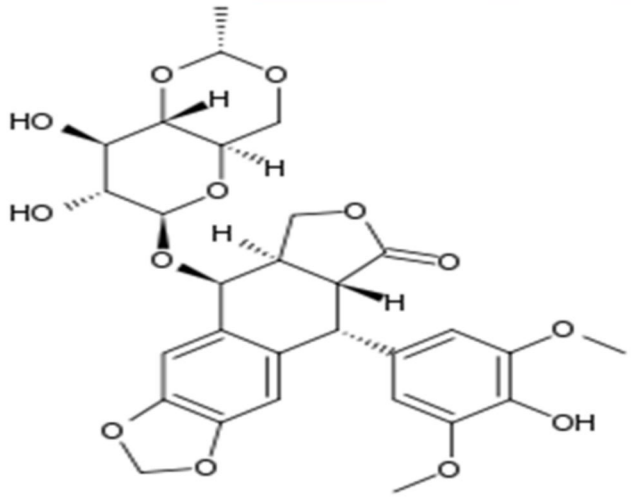
Zuvitop-100 (Etoposide Injection IP)

Composition:
Each ml contains:
Etoposide IP 20 mg
Citric Acid IP 2 mg
Polysorbate 80 IP 80 mg
Polyethylene glycol 300 IP 650 mg
Benzoyl alcohol IP 30 mg
Ethyl alcohol IP 30.5% v/v

DESCRIPTION :
Zuvitop-100 (etoposide Injection, IP) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is 4'-demethylepipodophyllotoxin 9-[4,6-0-(R)- ethylidence - B-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 C29 H32 O13.

The Structural formula is :



Pharmacodynamics

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 mcg/mL or more), lysis of cells entering mitosis is observed. At low concentrations (0.3 to 10 mcg/mL), cells are inhibited from entering prophase. It does not interfere with microtubular assembly. The predominant macromolecular effect of etoposide appears to be the induction of DNA stand breaks by an interaction with DNA topoisomerase II or the formation of freeradicals.

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 bodyclearance values range from 33 to 48 mL/min or 16 to 36 mL/min/m2 and, like the terminal elimination halflife, are independent of dose over a range of 100 to 600 mg/m2. Over the same dose range, the areas under the plasma concentration vs. time curves (AUC) and the maximum plasma concentration (Cmax) values increase linearly with dose. Etoposide does not accumulate in the plasma following daily administration of 100 mg/m2 for 4 or 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. Etoposideenters the CSF poorly. Although it is detectable in CSF and intracerebral tumors, the concentrations are lowerthan in extracerebral tumors and in plasma. Etoposide concentrations are higher in normal lung than in lungmetastases and are similar in primary tumors and normal tissues of the myometrium. In vitro, etoposide ishighly protein bound (97%) to human plasma proteins. An inverse relationship between plasma albumin levelsand etoposide renal clearance is found in children. In a study determining the effect of other therapeutic agentson the in vitro binding of carbon-14 labeled etoposide to human serum proteins, only phenylbutazone, sodiumsalicylate, and aspirin displaced protein-bound etoposide at concentrations achieved in vivo.

- 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. Data have suggested a significant Inverse correlation between serum albumin concentration and free fraction of etoposide.

- After intravenous administration of 14C-etoposide (100 to 124 mg/m2), mean recovery of radioactivity in the urine was 56% of the dose at 120 hours, 45% of which was excreted as etoposide: fecal recovery of radioactivity was 44% of the dose at 120 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/m2 or about 35% of the total body clearance over a dose range of 80 to 600 mg/m2. 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 of unchanged drug and/or metabolites is an important route of etoposide elimination as fecal recovery of radioactivity is 44% of the intravenous dose. The hydroxy acid metabolite [4'-demethylepipodophyllic acid-9-(4,6-O-(R)-ethylidene-β-D-glucopyranoside)], formed by opening of the lactone ring, is found in the urine of adults and children. It is also present in human plasma, presumably as the trans isomer. Glucuronide and/or sulfate conjugates of etoposide are also excreted in human urine. Only 8% or less of an intravenous dose is excreted in the urine as radiolabeled metabolites of 14C-etoposide. In addition, Odemethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

- After intravenous infusion, the Cmax and AUC values exhibit marked intra- and inter-subject variability.

- There is no evidence of a first-pass effect for etoposide. For example, no correlation exists between the absolute oral bioavailability of etoposide capsules and nonrenal clearance. No evidence exists for any other differences in etoposide metabolism and excretion after administration of oral capsules as compared to intravenous infusion.

- In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration, and nonrenal clearance. Patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and a lower volume of distribution at steady state. Use of cisplatin therapy is associated with reduced total body clearance. In children, elevated serum SGPT levels are associated with reduced drug total body clearance. Prior use of cisplatin may also result in a decrease of etoposide total body clearance in children.

- Although some minor differences in pharmacokinetic parameters between age and gender have been observed, these differences were not considered clinically significant.

INDICATIONS:

- Etoposide Injection is indicated in the management of the following neoplasms.
- Small cell lung cancer, malignant lymphomas
- Acute leukemia's... Testicular tumors.
- Bladder Cancer. Trophoblastic diseases
- Etoposide Injection are indicated in the management of the following neoplasms.
- Small cell lung cancer. Malignant lymphomas.

DOSAGE AND ADMINISTRATION:
Preparation for intravenous administration:
Zuvitop-100 may be diluted with either 5 percent dextrose injection or 0.9% sodium chloride injection to give a final concentration of 0.2 or 0.4 mg/ml. thus 100 mg of Etoposide should be dissolved in at least 250 ml of the diluent. The solution be administered over 30 to 60 minutes or longer.
The usual dose of Etoposide in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m2/day on day 1 through 5 to 100 mg/m2/ day 1,3 and 5. Chemotherapy courses are repeated at 3 to 4 week intervals after adequate recovery from any toxicity. Not to be used in newly born or premature infants.
The dosage by either route, should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects or prior radiation therapy or chemotherapy.

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

WARNING:
Patients being treated with Etoposide 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 Etoposide: platelet count, haemoglobin, white blood cell count and
differential count. 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, dyspnoea and hypotension.

Pregnancy: Etoposide can cause fetal harm when administered to a pregnant women. 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 pregnatn. 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/daay on days 6 to 15 of gestation. Etoposide caused does - related matemal toxicity, embryo toxicity and teratogenicity at dose levels of 0.4 mg/kg/day and higher. Embryonic reabsorptions were 90 and 100% at the 2 highest dosages, At 0.4 and 1.2 mg/kg, 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 dossification was observed.
Etoposide administered as a single intraperitoneal Injection in swiss-Albino mice at dosage of 1,1.5 and 2 mg/kg on days 6,7 or 8 of gestation, caused dose-related embryotoxicity, cranial abnormality and major skeletal malformations.
Nursing Mothers: It is knows whether the 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 the drug, taking into account the importance of the drug to the mother.

Paediatric use: Safety and effectiveness in children has not been established.

PRECAUTIONS:
General : 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 doage or discontinued and appropriate corrective measures should be taken according to the clinical judgement of the physician. Reinstitution of Etoposide therapy should be carried out with caution and adequate consideration of the further need for the drug alertness as to possible recurrence of toxicity.

Laboratory tests: periodic complete blood counts should be done during the course of Etoposide 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.

Carcinogenesis, mutagenesis, Impairment of fertility: Carcinogenicity tests with Etoposide have not been conducted in laboratory animals. Given its mechanism of action it should be considered as a possible carcinogen in humans. The mutagenic and genotoxic potential of Etoposide has been established in mammalian cells. Etoposide caused aberration in chromosome number and structure in embryonic murine cells and human hematopoietic cells, gene mutations in Chinese hamster ovary cell, and DNA damage by stand breakage and DNA-protein crosslinks in mouse leukemia cells. Etoposide also caused a dose-related increase in sister chromatid exchange in Chinese hamster ovary cells.

Treatment of Swiss-albino mice with 1.5 mg/kg 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 I.V. of Etoposide for 10 days led to prenatal mortality of 92% and 50% of the implanting fetuses were abnormal.

ADVERSE REACTIONS:
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.

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.

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, 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. These reactions have usually responded promptly to the cessation of the infusion and administration of presser 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 normalizes within a few hours after cessation of the infusion.

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

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

Drug Interactions:
Studies in animals and clinical trials in humans indicate that the anti-neoplastic activity of Etoposide and cisplatin may be synergistic against some tumors. Response rates in humans receiving combination chemotherapy with Etoposide and cisplatin suggest that the combination has a synergistic antineoplastic activity against testicular carcinomas, small cell carcinoma of the lung or non-small cell carcinoma, small cell carcinoma of the lung or non-small cell carcinoma of the lung. Limited data indicates that patients previously treated with cisplatin may have impaired elimination of Etoposide.

OVER DOSAGE:
No proven antidotes have been established for Etoposide overdosage.

CONTRAINDICATIONS:
Etoposide is contraindicated in patients who have demonstrated a previous Hypersensitivity to it.

Storage:
Store below 25°C . Protect from light. Do not freeze.
Keep out of the reach of children.

PRESENTATION :
Zuvitop-100 Injection - vial of 5 ml individually packed.

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
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