PRESCRIBING INFORMATION

PrETOPOSIDE INJECTION USP

20 mg/mL
(100 mg/5 mL, 200 mg/10 mL, 1 g/50 mL)

Antineoplastic Agent

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Control # 114553

PACKAGE INSERT

[Pr]Etoposide Injection, USP

20 mg/mL

(100 mg/5 mL, 200 mg/10 mL, 1g/ 50 mL)

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CAUTION

ETOPOSIDE IS A POTENT DRUG AND SHOULD BE USED ONLY BY QUALIFIED PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE TAKEN REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW OR ABNORMAL RENAL OR HEPATIC FUNCTION IS SEEN. ETOPOSIDE INJECTION CONTAINS POLYSORBATE 80. IN PREMATURE INFANTS A LIFE THREATENING SYNDROME OF LIVER AND RENAL FAILURE, PULMONARY DETERIORATION, THROMBOCYTOPENIA AND ASCITES HAS BEEN ASSOCIATED WITH INJECTABLE VITAMIN E PRODUCT CONTAINING POLYSORBATE 80. ETOPOSIDE INJECTION CONTAINS BENZYL ALCOHOL. BENZYL ALCOHOL HAS BEEN ASSOCIATED WITH AN INCREASED INCIDENCE OF NEUROLOGICAL AND OTHER COMPLICATIONS IN NEWBORN INFANTS WHICH ARE SOMETIMES FATAL.

ACTIONS AND CLINICAL PHARMACOLOGY

Etoposide is a semi-synthetic derivative of podophyllotoxin.

In vitro, etoposide has cytostatic action, which prevents the cells from entering mitosis or destroys them in the pre-mitotic phase. Etoposide interferes with the synthesis of DNA and has a secondary effect on arresting cells in resting (G_2) phase in experiments with human lymphoblastic cell lines.

Etoposide has a marked action on human hemopoietic cells causing leukopenia and thrombocytopenia. Animal experiments have shown evidence of teratogenicity.

An intravenous dose (259 mg/m^2) of tritium-labelled etoposide given over one hour in man, showed the mean volume of distribution to be 32% of body weight. The plasma decay was biphasic with a beta half-life of 11.5 hours. Urinary recovery was 44%, of which 67% was unchanged drug. Recovery in feces was variable (1.5 - 16%) over a three day period.

In a limited number of children, etoposide administered in a dose of 200 - 250 mg/m^2 produced a peak serum concentration between 17 and 88 μg/mL and showed a terminal half-life ($t_{½\beta}$) of 5.7 ± 1.3 hours. Mean plasma clearance was 21.5 mL/min/m^2 and CSF concentrations 24 hours post-infusion ranged from less than 10 ng/mL to 45 μg/mL.

After intravenous infusion of etoposide, the C_{max} and AUC values exhibit marked intra- and inter-subject variability.

Etoposide crosses the blood brain barrier in low concentrations.

Etoposide is cleared by both renal and non-renal processes (i.e. metabolism and biliary excretion). Biliary excretion, however, appears to be a minor route of etoposide elimination.

INDICATIONS AND CLINICAL USE

Etoposide is indicated as follows:

Small Cell Carcinoma of the Lung

- first-line therapy in combination with other established antineoplastic agents.
- second-line combination or single agent therapy in patients who have not responded or relapsed on other chemotherapeutic regimens.

Malignant Lymphoma (histiocytic type)

- first-line therapy in combination with other established antineoplastic agents.

Non-small Cell Carcinoma of the Lung

- for patients considered ineligible for surgery, etoposide has been shown to be effective alone or in combination with cisplatin.
- for patients who require chemotherapy following surgery.

Testicular Malignancies (germ cell tumors including seminomas)

- in combination with other effective chemotherapeutic agents in patients who have already received appropriate therapy.
- in first-line combination chemotherapeutic regimens with appropriate surgical and/or radiotherapeutic procedures.

CONTRAINDICATIONS

Etoposide should not be given to individuals who have demonstrated a previous hypersensitivity to it or any component of the formulation. Also, it is contraindicated in patients having severe leukopenia, thrombocytopenia and severe hepatic and/or renal impairment.

WARNINGS

ETOPOSIDE IS A POTENT DRUG AND SHOULD BE USED ONLY BY QUALIFIED PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE TAKEN REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW OR ABNORMAL RENAL OR HEPATIC FUNCTION IS SEEN. ETOPOSIDE INJECTION CONTAINS POLYSORBATE 80. IN PREMATURE INFANTS A LIFE THREATENING SYNDROME OF LIVER AND RENAL FAILURE, PULMONARY DETERIORATION, THROMBOCYTOPENIA AND ASCITES HAS BEEN ASSOCIATED WITH INJECTABLE VITAMIN E PRODUCT CONTAINING POLYSORBATE 80. ETOPOSIDE INJECTION CONTAINS BENZYL ALCOHOL. BENZYL ALCOHOL HAS BEEN ASSOCIATED WITH AN INCREASED INCIDENCE OF NEUROLOGICAL AND OTHER COMPLICATIONS IN NEWBORN INFANTS WHICH ARE SOMETIMES FATAL.

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, 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.

Bacterial infection must be brought under control before the administration of etoposide therapy because of the risk of septicemia.

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea and/or hypotension (see **ADVERSE REACTIONS**). Treatment is symptomatic. The 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.

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.

Pregnancy

Etoposide can cause fetal harm when administered to pregnant women.

Etoposide has been shown to be embryotoxic in rats and teratogenic in mice and rats. There are no adequate and well-controlled studies in pregnant women. If the 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 and should exercise adequate contraceptive control.

Etoposide has caused reduced or absent spermatogenesis and reduced testes weights at autopsy in rats and dogs, as well as reduced weight of ovaries in female rats. Chronic toxicity studies in rats have shown etoposide to have an oncogenic potential (see **ADVERSE REACTIONS, Hematologic Toxicity**).

Nursing Mothers

There has been evidence of etoposide being excreted in breast milk.

Because of the potential for serious adverse reactions in nursing infants from etoposide, breast feeding should be discontinued.

As with any potent antineoplastic drug, the benefit to patient versus the risk of toxicity must be carefully weighed.

PRECAUTIONS

General

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 judgement of the physician. Re-institution of etoposide therapy should be carried out with caution and with adequate consideration of the further need for the drug and alertness to the possible recurrence of toxicity.

Etoposide should be administered by individuals experienced in the use of antineoplastic therapy.

Neutropenia is at its lowest level seven to fourteen days after initial therapy. Thrombocytopenia is at its lowest level nine to sixteen days after initial therapy. Bone marrow recovery requires 20 days.

Liver and renal function should be regularly monitored.

Professional staff administering Etoposide Injection should exercise particular care to prevent spillage and self contact with the drug. Skin reactions, at times severe, associated with accidental exposure to etoposide may occur. Gloves should be worn by anyone handling the drug. If etoposide solution contacts the skin, immediately wash thoroughly with soap and water. If etoposide solution contacts mucous membranes, flush thoroughly with water. Materials used for cleaning accidental spills should be disposed of by incineration.

Carcinogenesis

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 occurrence of acute leukemia, which can occur with or without a pre-leukemic phase, has been reported rarely in patients treated with etoposide in association with other antineoplastic drugs. Neither the cumulative risk nor the predisposing factors related to the development of secondary leukemia are known. The roles of both administration schedules and cumulative doses of etoposide have been suggested, but have not been clearly defined.

An 11q23 chromosome abnormality has been observed in some cases of secondary leukemia in patients who have received epipodophyllotoxins. This abnormality has also been seen in patients developing secondary leukemia after being treated with chemotherapy regimens not containing epipodophyllotoxins and in leukemia occurring *de novo*. Another characteristic that has been associated with secondary leukemia in patients who have received epipodophyllotoxins appears to be a short latency period, with average median time to development of leukemia being approximately 32 months.

Drug Interactions

Severe cases of neuropathy have been reported in 0.7% of patients possibly due to an interaction of vincristine and etoposide.

Pediatric Use

Clinical experience in childhood malignancies is very limited (see **WARNINGS**).

ADVERSE REACTIONS

The following data on adverse reactions are based on 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: Since leukopenia and thrombocytopenia have been reported in patients on etoposide therapy, platelets and white blood cell counts should be performed prior to each cycle. A white blood cell count of between 2000 - 3000 cells/mm^3 suggests that the dose of etoposide should be reduced by 50%. Platelet counts between 75,000 - 100,000 cells/mm^3 require a dosage reduction of 50%. Should the neutrophil count fall below 500 cells/mm^3 or the platelet count fall below 50,000 cells/mm^3, etoposide should be discontinued and should not be resumed until counts have returned to normal (see **WARNINGS**). Myelosuppression is dose related and dose limiting, with granulocyte nadirs occurring 7 to 14 days 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 pre-leukemic phase has been reported 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/eosophagitis may occur.

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 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 during or immediately after etoposide administration. Higher rates of anaphylactic-like reactions have been reported in children who received etoposide 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. Anaphylactic-like reactions have usually responded promptly to etoposide cessation and subsequent administration of pressor agents, corticosteroids, antihistamines or volume expanders, as appropriate. Acute fatal reactions associated with bronchospasm have been reported. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions can occur with the initial dose of etoposide. Apnea with spontaneous resumption of breathing following discontinuation has been described in patients receiving etoposide infusion.

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

Neuropathy: The use of etoposide has been reported to cause peripheral neuropathy in 0.7% of patients. The associated use of vincristine sulfate can possibly enhance this neuropathy.

Other Toxicities: Weakness (3%), mouth ulceration (2%). The following have been reported in less than 1% : hyperuricemia, sepsis, numbness and tingling, dizziness, depression, nail pigmentation and moniliasis. The following adverse reactions have been infrequently reported: somnolence and fatigue, liver toxicity, fever, aftertaste, rash, pigmentation, pruritus, urticaria, constipation, dysphagia, transient cortical blindness and a single report of radiation recall dermatitis.
Occasionally following extravasation, soft tissue irritation and inflammation has occurred; ulceration is generally not seen.

The incidences of adverse reactions in Table 1 are derived from multiple databases from studies in patients when etoposide was used as a single agent.

TABLE 1

Etoposide - Adverse Reactions

ADVERSE DRUG EFFECT	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
Other	8 - 66
Alopecia	1 - 2
Peripheral neurotoxicity	1 - 2
Hypotension	1 - 2
Allergic reaction	0 - 3
Hepatic	

Legend: WBC = white blood cell

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The anticipated acute complications would be related to etoposide's hematotoxicity.

Total doses of 2.4 g/m^2 to 3.5 g/m^2 administered IV over three days resulted in severe mucositis and myelotoxicity.

Metabolic acidosis and cases of serious hepatic toxicity have been reported in patients receiving higher than recommended intravenous doses of etoposide.

There is no known antidote and therefore symptomatic measures should be taken to sustain the patient through any period of toxicity that might occur. Patients' renal and hepatic functions should be monitored for 3-4 weeks in case of delayed toxicity.

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. This effect has not been reported with diluted Etoposide Injection.**

Intravenous: 50 - 100 mg/m^2 daily for 5 days.

Hypotension following rapid intravenous administration has been reported, hence, it is recommended that the etoposide solution be administered over a period of not less than 30 minutes (usually over 30 to 60 minutes). Longer infusion times may be required based on patient tolerance. **Etoposide should not be given by rapid intravenous injection.**

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

PHARMACEUTICAL INFORMATION

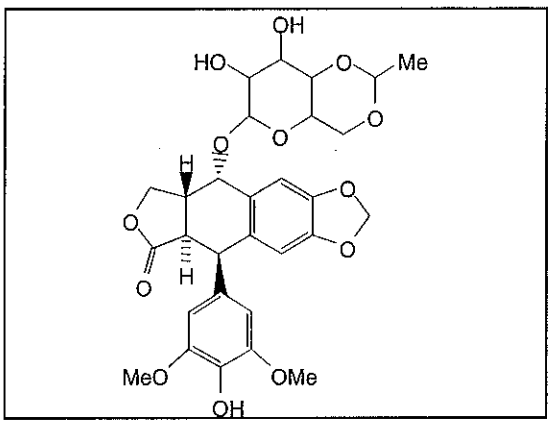
Drug Substance

Common Name: Etoposide

Chemical Name: (1)Furo[3',4':6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one,9-[(4,6-*0*-ethylidene-β-D-glucopyranosyl)oxyl]5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5*R*-[5α,5aβ,-8aα,9β(R*)]]-;

(2)4'-Demethylepipodophyllotoxin 9-[4-6-*O*-(R)-ethylidene-β-D-glucopyranoside].

Chemical Structure:



Molecular Formula: $C_{29}H_{32}O_{13}$

Molecular Weight: 588.58

Melting Point: 236-251°C (crystals from methanol)

pka: 9.8

Description: Etoposide is a white to yellowish or brown-tinged yellowish, fine, crystalline powder. Etoposide is a semi-synthetic derivative of podophyllotoxin. It is slightly soluble in ethanol and chloroform, sparingly soluble in methanol and practically insoluble in water.

Composition: Each mL contains 20 mg etoposide, 30 mg benzyl alcohol, 2 mg citric acid, 650 mg polyethylene glycol, and 80 mg polysorbate 80 with dehydrated

alcohol qs.

Stability and Storage Recommendations:

Etoposide Injection, USP should be stored at room temperature (15-30°C). Protect from light. Once punctured, Etoposide Injection, USP should be stored at 15-30°C and used within 28 days.

Compatibility and Admixtures

Etoposide Injection, USP **must be diluted prior to use** with 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP to give a concentration of 0.2 mg/mL or 0.4 mg/mL.

MORE CONCENTRATED SOLUTIONS SHOW CRYSTAL FORMATION UPON STIRRING OR SEEDING WITHIN 5 MINUTES AND SHOULD NOT BE GIVEN INTRAVENOUSLY.

Etoposide diluted to 0.4 mg/mL and administered through tubing connected to a pump with a peristaltic mechanism may precipitate out of solution in the tubing. Contact with buffered aqueous solutions above pH 8 should be avoided. Reconstitution results in a clear, colourless solution.

Etoposide diluted with 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP to a concentration of 0.2 or 0.4 mg/mL is stable for 24 hours at 15-30°C under fluorescent light in polyvinyl chloride (PVC) bags.

Etoposide should not be mixed with other antineoplastic drugs. Care should be taken to prevent spillage and self contact with the drug. **If Etoposide Injection solution contacts the skin, immediately wash thoroughly with soap and water. If Etoposide Injection solution contacts mucous membranes, flush thoroughly with water.**

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

SPECIAL INSTRUCTIONS FOR HANDLING OF CYTOTOXIC DRUGS

Handling and Disposal

1. Preparation of Etoposide Injection, USP should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II)

2. Personnel preparing Etoposide Injection, USP should wear PVC gloves, safety glasses, disposable gowns and masks.

3. All needles, syringes, vials and other materials which have come in contact with Etoposide Injection, USP should be segregated and incinerated at 1000°C or more. Sealed containers may explode if a tight seal exists. Intact vials should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

4. Personnel regularly involved in the preparation and handling of Etoposide should have bi-annual blood examinations.

AVAILABILITY OF DOSAGE FORM

Etoposide Injection 20 mg/mL is available in multidose vials of 100 mg/5 mL, 200 mg/10 mL and 1g/50 mL; single packs.

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