patients. It has been associated with cardiac toxicity of ECG changes. To prevent it, Etoposide should be administered by slow intravenous infusion over 30-60 min. period. If hypotension does occur, 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: Anaphylactic like symptoms characterised by chills, fever, tachycardia, bronchospasm and dyspnoea may occur in approximately 0.7-2% of patients. These reactions are usually observed during or immediately after administration of Etoposide and often respond, promptly to the cessation of the infusion and administration of pressor agents, corticosteroids &anti histamines.

Dermatologic: Reversible alopecia, sometimes progressing to total baldness, occurs in at least 66% of patients. Increased pigmentation pruritis & rarely radiation recall dermatitis have been observed.

Hepatic: Mild and transient hyperbilirubinaemia and increased transaminase levels, may be observed but are more common in high dose protocols.

Other Toxicities: Peripheral neuropathy, fever, muscle cramps, metabolic acidosis, hypercuricaemia etc. have been rarely reported.

DRUG INTERACTIONS

Studies in animals and clinical trial in humans indicate that the antineoplastic activity of Etoposide and Cisplatin may be synergistic against some tumors. Limited data, however Indicates that patients previously treated with Cisplatin may have impaired elimination of Etoposide. Etoposide and ldarubicin are not compatible in solution.

OVERDOSAGE

No proven antidotes have been established for ETOPA™ overdosage.

STORAGE

Store at controlled room temperature 20° to 25°C (68° to 77°F). Protect from light. Do not Freeze.

PRESENTATION

ETOPA™ is available as 5 ml injection containing 100 mg of Etoposide.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

Manufactured by:
Getwell Pharmaceuticals
474, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

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GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Etoposide Concentrate IP for Etoposide Injection IP

ETOPA™

FOR I.V INFUSION AFTER DILUTION

Rx only

WARNING

1. Since ETOPA™ (Etoposide) is a cytotoxic anticancer drug, procedures for proper handling and disposal of such drugs should be followed.
ETOPA™ (Etoposide) is a vesicant and care should be taken to avoid extravasation. It may cause skin rashes after contact, gloves for medical personnel are recommended during handling. In the event of skin or mucosal contact, the affected areas should be washed immediately with soap and water.

2. Bone marrow suppression is the dose limiting toxicity of ETOPA™ (Etoposide) therapy. Therefore. patients being treated with ETOPA™ (Etoposide) must be frequently observed for myelosuppression both during and after therapy. Regular, monitoring of blood counts should be done at the start of therapy and prior to each subsequent course of ETOPA™ (Etoposide). If the platelet count is below 50,000/mm^3 or an absolute neutrophil count below 500/mm^3, therapy should either be with held or the dosage be reduced, as the case may be.

3. Anaphylactic like symptoms characterized by chills, fever. Tachycardia, bronchospasm and dyspnoea may occur with ETOPA™ (Etoposide) therapy. The infusion should be terminated and treatment initiated with corticosteroids and antihistamines, in such events.

4. Caution should be exercised while administering the drug to patients with hepatic and renal dysfunction.

DESCRIPTION

ETOPA™ (Etoposide) is a semisynthetic derivative of podophyllotoxin used in the treatment of wide variety of Neoplasms.

Etoposide is a white crystalline powder. It is sparingly soluble in methanol and chloroform slightly soluble in ethanol and very slightly soluble in water or ethyl ether.

COMPOSITION

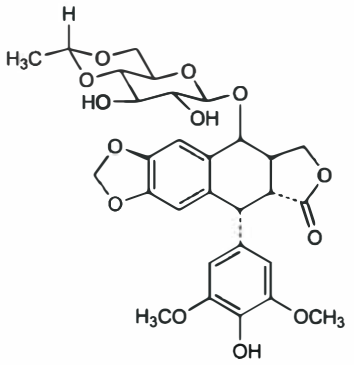
Each ml contains:

Etoposide IP	20 mg
Benzyl Alcohol IP	30 mg
Dehydrated Alcohol IP	30.5% v/v

Volume is adjusted with polyethylene Glycol 300 IP

CHEMICAL STRUCTURE

Chemical name is 4-demethylepipodophyllotoxin 9-(4, 6-0-(R)-ethylidene-B-D-glucopyranoside) Chemical formula is $C_{29}H_{32}O_{13}$ Molecular Weight -588.6.



INDICATIONS

Etoposide has demonstrated highly significant clinical activity against several neoplasms including small cell lung cancer, testicular cancers and bladder cancer. Etoposide is also active in malignant lymphomas of both Hodgkins and non Hodgkins type and acute leukaemias. In addition, it is extremely active in gestational trophoblastic tumours and paediatric sarcomas especially Ewing's sarcoma when used in combination.

CONTRAINDICATIONS

Etoposide is contraindicated in patients with severe myelosuppression and those with prior history of hypersensitivity to this preparation.

USE IN PREGNANCY

Etoposide can cause foetal harm when administered to pregnant women. It has been shown to be teratogenic in mice and rats. If the drug is used during pregnancy, the patients should be apprised of the potential hazard to the foetus. Women of child bearing potential should be advised to avoid pregnancy during Etoposide therapy.

USE IN LACTATION

It is not known whether the drug is excreted in human milk or not. To avoid any harmful effect to the infants, nursing should be discontinued while the patient is on Etoposide therapy.

USE IN CHILDREN

Safety and effectiveness in children has not been established.

DOSAGE AND ADMINISTRATION

The dosage schedule of ETOPA™ (Etoposide) used most commonly in combination with other approved chemotherapeutic agent, is 50-100 mg/m^2/day 1-5 to be repeated every 3-4 weeks. Alternate day schedule of 100-125 mg/m^2 on day1,3 & 5 is also commonly employed. The dosage should lake into account the myelosuppressive effects of other drugs in the combination or the effects of prior radiation therapy & chemotherapy.

Prior to infusion, the dose should be diluted to a final concentration of 0.2-0.4 mg/ml with 0.9% Sodium Chloride Injection IP or 5% Dextrose Injection IP ETOPA™ (Etoposide) should be infused intravenously over 30-60 min. to avoid hypotension. ETOPA™

(Etoposide) is a vesicant and care should be taken to avoid extravasation. Blood counts should be checked prior to drug administration and dose should be reduced for patients with severe renal dysfunction.

MECHANISM OF ACTION

Etoposide induces an irreversible blockade of cells in the premitotic phases of cell cycle leading to accumulation of cells in the late S or G2 phase. Although its precise mechanism of action is not clear, cytotoxic effect appears to result from single and double strand breaks in DNA and DNA protein cross links. Etoposide exerts its cytotoxic effects by interfering with the scission-reunion reaction of the enzyme topoisomerase II. The enzyme then covalently binds to DNA forming single strand, protein associated breaks. Etoposide also inhibits the transport of nucleosides across the plasma membrane Hence it exerts its cytotoxic effect by interfering with DNA synthesis and repair.

PHARMACOKINETICS

After I.V. administration, peak plasma concentration of 30 g/ml is achieved. There is biphasic pattern of clearance with a distribution half life of approximately 1.5 hours and a terminal half life ranging from 3-11 hours. Maximum plama levels and areas under the plasma concentration versus time curve (AUC) increase linearly with dose over 100-600 mg/m^2 doses range.

Etoposide does not accumulate in plasma following daily administration of 100 mg/m^2 for 5 consecutive days.

Plasma and renal clearance are independent of dose. it is largely protein bound with approximately 94% of total drug bound to serum proteins.

Etoposide does not penetrate effectively into the cerebrospinal fluid. Urinary clearance of Etoposide ranges from 5.1 to 14.6 ml/min/m^2 and accounts for approximately 36% of total drug disposition.

ADVERSE REACTION

Heamatologic: Myelosuppression is dose related and the major limiting toxicity of Etoposide. Granulocytopenia is common with nadir granulocyte counts occurring 7-14 day after drug administration. Thrombocytopenia occurs less frequently and nadir platelet counts are observed 9-16 days after Etoposide administration. Haematologic recovery is usually complete by day 20 after administration of standard dosage. Cumulative haematologic toxicity is unusual.

Gastrointestinal: Nausea and vomiting occurs in approximately 30-40% of patients and is more frequently observed with oral than intravenous administration. It is generally mild to moderate and discontinuation of treatment due to adverse gastrointestinal effects is rarely required. In addition, diarrhoea, abdominal pain, stomatitis, anorexia have been reported. Mucositis in a prominent toxicity at very high doses and appears to be non haematologic dose limiting toxicity Etoposide.

Cardiovascular: Transient hypotension following rapid intravenous administration has been reported in 1-2% of