GETWELL

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

Etoposide Capsules IP

ETOPA™

Rx only

WARNING

General, patients being treated with ETOPA™ must be frequently observed for myelosuppression, both during and after therapy. Dose limiting bone marrow suppression is the most significant toxicity associated with ETOPA™ therapy. Therefore, the following studies should be obtained at the start of therapy and prior to each subsequent does of ETOPA™ platelet count, haemogolobin, white blood cell count and differential white blood cell counts. 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.

Physician should be aware of the possible occurrence of anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea and hypotension .

DESCRIPTION

Etoposide, the active ingredient of ETOPA™ is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is available as capsules of 50 mg and 100 mg.

COMPOSITION

Each hard gelatin capsule **ETOPA™ 50 mg** contains	
Etoposide IP	50 mg
Excipients	q.s
Approved colour used in capsule shell.	
Each hard gelatin capsule **ETOPA™ 100 mg** contains	
Etoposide IP	100 mg
Excipients	q.s
Approved colour used in capsule shell.	

PROPERTIES

Etoposide has been shown to induce inhibition of DNA synthesis. In the chick fibroblasts Etoposide has been demonstrated to cause metaphase arrest. In mammalian cells, however its main effect appears to be at the G2 portion of the cell cycle.
Two different dose-dependent responses are seen. At high concentrations (10mcg/ml or more), lysis of cells entering mitosis is observed. At low concentrations (0.3-10 mcg/ml) cells are inhibited from entering prophase. It does not interfere with microtubular assembly.

After either intravenous infusion or oral capsule administration of Etoposide as a capsule, the maximum plasma concentration (C_{max}) and area under the plasma concentration vs. time curve (AUC) values exhibit marked intra and inter subject variability, thus resulting in variability in the estimates of the absolute oral bioavailability of Etoposide oral capsules. The C_{max} and AUC values for orally administered Etoposide capsules consitently fall in the same range as the values for an intravenous dose of one half the size of the oral. The overall mean values of oral capsules bioavailability is approximately 50 % (range 25 -75 %). The bioavailability of Etoposide capsules appear to be linear up to a dose of atleast 250 mg/m^2.

There is no evidence of a first pass effect of 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 capsules as compared to intravenous infusion.

INDICATIONS

Etopa capsules are indicated in the management of the following neoplasms
Small cell lung cancer
Malignant lymphomas

CONTRAINDICATIONS

Capsules are contraindicated in patients with previous history of hypersensitivity to it.

Pregnancy
Etoposide can cause fatal harm when administered to pregnant women, as it 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. Woman of childbearing potential should be advised to avoid becoming pregnant.
Etosopide 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, the drug was administered intravenously at doses of 0.13, 0.4, 1.2 and 3.6mg/kg/day on days 6 to 15 of gestation. The drug caused dose related maternal toxicity, embryotoxicity and teratogenicity at dose levels of 0.4mg/kg/day and higher. Embryonic resorptions were 90 % and 100 % at the two highest dosage at 0.4 and 1.2mg/kg fatal abnormalities including decreased weight, major seletal abnormalities, exencephaly, encephalocele and anophthalmia occurred. Even at the lowest dose tested 0.13 mg/kg, a significant increase in retarded ossitication was observed. The drug administered as a single intraperitoneal injection in swiss-albino mice at dosage of 1, 1.5 and 2mg/kg on days 6, 7 or 8 of gestation, caused dose related embryotoxicity, cranial abnormality and major skeletal malformation.

Nursing mothers
It is not known 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 of Etoposide, a decision should be made whether to discontinue the drug , taking into account the important of the drug to the mother.

Peadiatric use
Safety and effectiveness in children have 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 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.

Laboratory tests
Periodic complete blood count 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
Carcinogenesis test with Etoposide have not been conducted in laboratory animals. Given its mechanism of action it should be considered as possible carcinogen in humans. The mutagenic and genotoxic potential of Etoposide caused aberration in chromosome number and structure in embryonic murine cells, and human hematopoetic cells; gene mutations in chinese hamster ovary cell, and DNA damage by strand breakage and DNA protein crosslinks in mouse leukaemia cells. Etoposide also caused a dose-related increase in sister chromatid exchanges in chinese hamster ovary cells.
Treatment of swiss albino mice with 1.5 mg/kg IP of Etoposide on day 7 of gestation increased the incidence of intrauterine death and fetal body weight. Maternal weight gain was not effected. Treatment of pregnant SPF rats with 1.2 mg/kg/day IV of Etoposide for 10 days led to prenatal mortality of 92 % and 50 % of implanting fetuses were abnormal.
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 tumours. Response rates in humans receiving combination chemotherapy with Etoposide and cisplatin suggest that the combination has a synergistic antineoplastic activity against testicular carcinomas of the lung. Limited data indicates that patients previously treated with cisplatin may have impaired elimination of Etoposide.

ADVERSE REACTIONS:

Hematologic toxicity: Myelosuppression is dose related with granulocyte occurring 7 to 14 days after drug administration. Bone marrow recovery is usually complete by day 20 and no cumulative toxicity has been reported.
Gastroinestinal toxicity: Nausea and vomiting are the major gastro-intestinal side effects. The serverity of such nausea and vomiting is generally mild to moderate and discontinuation of treatment is required in about 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 electocardiographic changes.
No delayed hypotension has been noted.
If hypotension occurs, it usually responds to administration of fluids or other 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 hypotension have been reported to occur following intravenous infusion of etoposide. 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 normalizes within a few hours after cessation of the therapy.

Alopecia
Reversible alopecia sometimes progressing to total baldness was observed in about 66 % of patients
Other toxicities
Other infrequently reported adverse effects are rash, fever, pigmentation, pruritus, abdominal pain, constipation, dysphagia, transient cortical blindness and a single report of radiation recall dermatitis.
There are reports of hepatic toxicity in patients receiving higher than recommended dosage of ETOPA™ Metabolic acidosis has been reported in such patients.

DOSAGE AND ADMINISTRATION

In small cell lung cancer the recommended dose of ETOPA™ capsules is two cancer the IV dose rounded to the nearest 50 mg. For one course of therapy, the normal adult dose is 175-200 mg of etoposide ETOPA™ daily for 5 consecutive days orally, followed by a recession (withdrawal) interval of 3 weeks. Therapy can be repeated if necessary. The dose can be increased or reduced.
The dosage by either route, should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior radiation therapy or chemotherapy.

OVERDOSAGE

No proven antidotes is available for ETOPA™ overdosage, hence management of overdose is by symptomatic treatment.

STORAGE

Store protected from moisture at a temperature not exceeding 30°C. Do not refrigerate.

PRESENTATION

ETOPA™ 50 mg container of 8 capsules.
ETOPA™ 100 mg container of 4 capsules.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase -V, Gurgaon -122 016, Haryana, India.

Manufactured by:
Getwell Pharmaceuticals
Vastrapur, Ahmedabad - 380015, Gujarat, INDIA.
At: 357, GIDC, Sachin, Surat, Gujarat, INDIA

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