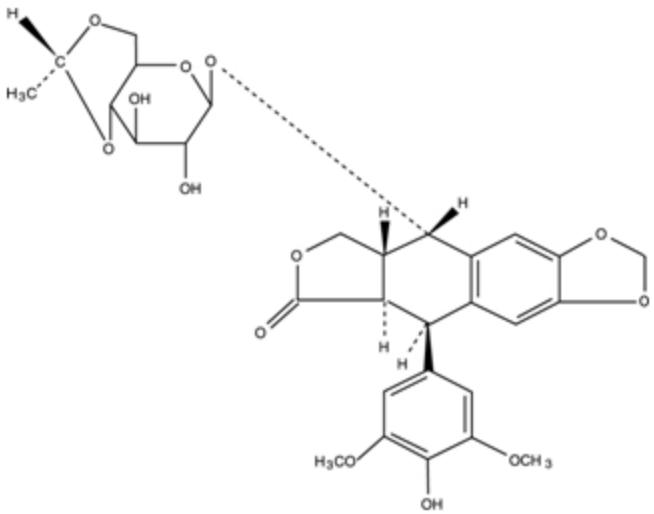
ZUVITOP (ETOPOSIDE CAPSULES I P)

COMPOSITION

Zuvitop 50mg
Each hard gelatin capsules contains:
Etoposide IP 50mg
Excipients .....q.s

Zuvitop 100mg
Each hard gelatin capsules contains:
Etoposide IP 100mg
Excipients .....q.s

DESCRIPTION
Etoposide, the active ingredient of Zuvitop-50 is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases,. It is available as capsules of 50mg and 100mg.
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 strand breaks by an interaction with DNA topoisomerase II or the formation of free radicals.

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 body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min/m2 and, like the terminal elimination half-life, are independent of dose over a range 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 to 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. Etoposide enters the CSF poorly. Although it is detectable in CSF and intracerebral tumors, the concentrations are lower than in extra cerebral tumors and in plasma. Etoposide concentrations are higher in normal lung than in lung metastases and are similar in primary tumors and normal tissues of the myometrium. In vitro, etoposide is highly protein bound (97%) to human plasma proteins. An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children. In a study determining the effect of other therapeutic agents on the in vitro binding of 14C-etoposide to human serum proteins, only phenylbutazone, sodium salicylate 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 (see PRECAUTIONS).

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-(4,6-0-(R)-ethylidene-ß-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. Glucoronide 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, 0-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

After either intravenous infusion or oral capsule administration, the Cmax and AUC values exhibit marked intra- and inter-subject variability. This results in variability in the estimates of the absolute oral bioavailability of etoposide oral capsules.

Cmax and AUC values for orally administered etoposide capsules consistently fall in the same range as the Cmax and AUC values for an intravenous dose of one-half the size of the oral dose. The overall mean value of oral capsule

bioavailability is approximately 50% (range 25% to 75%). The bioavailability of etoposide capsules appears to be linear up to a dose of at least 250 mg/m2.

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 (see PRECAUTIONS). 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

Zuvitop-50 capsules are indicated in the management of the following neoplasms:
Small Cell Lung Cancer
Malignant Lymphomas

DOSAGE AND ADMINISTRATION

Etoposide Capsules
In small cell lung cancer, the recommended dose of Zuvitop-50 capsules is two times the IV dose rounded to the nearest 50 mg. For one courses of therapy, the normal adult dose in 175-200mg of Zuvitop-50 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.

WARNINGS

General, Patients being treated with Zuvitop-50 must be frequently observed from myelosuppression, both during and after therapy. Dose limiting bone marrow suppression is the most significant toxicity associated with Zuvitop-50 therapy. Therefore, the following studies should be obtained at the start of therapy and prior to each subsequent does of Zuvitop-50 platelet count, hemoglobin, white blood cell count and differential white blood cell counts. The occurrence of a platelet 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 Zuvitop-50 metabolic acidosis has been reported in such patients.

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.
Patients with low serum albumin may be at an increased risk for etoposide associated toxicities.

ADVERSE REACTIONS

The following data on adverse reactions are based on both 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

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. Fever and infection have also been reported in patients with neutropenia. Death associated with myelosuppression has been reported.

The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents (see WARNINGS).

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/esophagitis may occur. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion.

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, 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 receiving intravenous etoposide and in less than 1% of the patients treated with the oral capsules. These reactions have usually responded promptly to the cessation of the infusion and administration of presser agents, corticosteroids, antihistamines or volume expanders as appropriate; however, the reactions can be fatal. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of etoposide.

Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported rarely.

Rash, urticarial, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with per vasculitis, has been reported.

Drug Interactions

High-dose cyclosporine A resulting in concentrations above 2000 ng/mL administered with oral etoposide has led to an 80% increase in etoposide exposure with a 38% decrease in total body clearance of etoposide compared to etoposide alone.

Laboratory Tests

Periodic complete blood counts should be done during the course of etoposide treatment. They should be performed prior to each cycle of therapy and at appropriate intervals during and after therapy. At least one

Carcinogenesis, Mutagenesis, Impairment of Fertility

Etoposide has been shown to be mutagenic in Ames assay.

Treatment of Swiss-Albino mice with 1.5 mg/kg I.P. 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.

Irreversible testicular atrophy was present in rats treated with etoposide intravenously for 30 days at 0.5 mg/kg/day (about 1/16th of the human dose on a mg/m2 basis).

Pregnancy

Pregnancy Category D

Nursing Mothers

It is not known whether this 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 nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of more than 600 patients in four clinical studies in the NDA databases who received etoposide or etoposide phosphate in combination with other chemotherapeutic agents for the treatment of small cell lung cancer (SCLC), about one-third were older than 65 years. When advanced age was determined to be a prognostic factor for response or survival in these studies, comparisons between treatment groups were performed for the elderly subset. In the one study (etoposide in combination with cyclophosphamide and vincristine compared with cyclophosphamide and vincristine or cyclophosphamide, vincristine and doxorubicin) where age was a significant prognostic factor for survival, a survival benefit for elderly patients was observed for the etoposide regimen compared with the control regimens. No differences in myelosuppression were seen between elderly and younger patients in these studies except for an increased frequency of WHO Grade III or IV leukopenia among elderly patients in a study of etoposide phosphate or etoposide in combination with cisplatin. Elderly patients in this study also had more anorexia, mucositis, dehydration, somnolence and elevated BUN levels than younger patients.

In five single-agent studies of etoposide phosphate in patients with a variety of tumor types, 34% of patients were age 65 years or more. WHO Grade III or IV leukopenia, granulocytopenia and asthenia were more frequent among elderly patients.

Post-marketing experience also suggests that elderly patients may be more sensitive to some of the known adverse effects of etoposide, including myelosuppression, gastrointestinal effects, infectious complications and alopecia.

Although some minor differences in pharmacokinetic parameters between elderly and nonelderly patients have been observed, these differences were not considered clinically significant.

Etoposide and its metabolites are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS: RENAL IMPAIRMENT for recommended dosing adjustments in patients with renal impairment).

OVERDOSAGE

No proven antidotes is available to Zuvitop-50 overdosage, hence management of overdosage is by symptomatic treatment.

CONTRAINDICATIONS

Zuvitop-50 capsules are contraindicated in patients with previous history of hypersensitivity to it.

STORAGE:

Store in a cool, dry place.

Keep all medicine out of reach of children.

PRESENTATION:

Zuvitop 50 – Container of 8 capsules

Zuvitop 100 – Container of 4 capsules

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
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