PRODUCT MONOGRAPH

VEPESID*

(etoposide)

Injection, 20 mg/mL

Capsule, 50 mg

Antineoplastic Agent

Bristol Laboratories of Canada
Division of Bristol-Myers Squibb Canada Inc.
2365 Côte de Liesse
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DATE OF PREPARATION:
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DATE OF REVISION:
December 2, 1994

PRODUCT MONOGRAPH

NAME OF DRUG

VEPESID*

(etoposide)

Injection, 20 mg/mL

Capsule, 50 mg

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CAUTION: VEPESID (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. VEPESID 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.

CLINICAL PHARMACOLOGY

VEPESID (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 premitotic 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.

A plasma decay with a beta half-life of 6.8 hours was observed following oral administration of etoposide. The $T_{1/2}$ for oral absorption was 0.44 hour and peak plasma concentrations were noted 0.5 to 3 hours after oral administration.

In a limited number of children, VEPESID 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 1/2 β) of 5.7 $\pm$ 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 either intravenous infusion or oral capsule administration of etoposide, the C_{max} and AUC values exhibit marked intra- and inter-subject variability. The overall mean value of oral capsule bioavailability is approximately 50% (range 25-75%).

Etoposide crosses the blood brain barrier in low concentrations.

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

INDICATIONS AND CLINICAL USE

VEPESID (etoposide) is indicated as follows:

For oral and intravenous formulations:

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 effective alone or in combination with PLATINOL (cisplatin).
- for patients who require chemotherapy following surgery.

Testicular Malignancies (germ cell tumours including seminomas)

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

CONTRAINDICATIONS

VEPESID (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

VEPESID (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. VEPESID 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.

Patients being treated with VEPESID (etoposide) must be frequently observed for myelosuppression both during and after therapy. Dose-limiting bone marrow suppression is the most significant toxicity associated with VEPESID therapy. Therefore, the following studies should be obtained at the start of therapy and prior to each subsequent dose of VEPESID: 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 VEPESID 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 VEPESID 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, VEPESID 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

VEPESID can cause fetal harm when administered to pregnant women.

VEPESID 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.

VEPESID 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 VEPESID being excreted in human 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. Reinstitution of VEPESID (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.

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

Since leukopenia and thrombocytopenia have been reported in patients on VEPESID 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 VEPESID 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, VEPESID should be discontinued and should not be resumed until counts have returned to normal (See WARNINGS).

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 VEPESID Injection should exercise particular care to prevent spillage and self contact with the drug. Skin reactions, at times severe,

associated with accidental exposure to VEPESID may occur. Gloves should be worn by anyone handling the drug. If VEPESID solution contacts the skin, immediately wash thoroughly with soap and water. If VEPESID solution contacts mucous membranes, flush thoroughly with water. Materials used for cleaning accidental spills should be disposed of by incineration.

Drug Interactions

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

Pediatric Use

Clinical experience in childhood malignances is very limited (See WARNINGS).

ADVERSE REACTIONS

The following data on adverse reactions are based on both oral and intravenous administration of VEPESID (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 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 preleukemic phase has been reported in patients treated with VEPESID 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. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion. 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 VEPESID 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 VEPESID administration. These reactions have usually responded promptly to VEPESID 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 VEPESID.

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

Other Toxicities: Weakness (3%), mouth ulceration (2%). The following have been reported in less than 1 percent: hyperuricemia, sepsis, numbness and tingling, dizziness, depression, nail pigmentation and moniliasis. The following adverse reactions have been infrequently reported: somnolence and fatigue, 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 the table that follows are derived from multiple data bases from studies in patients when VEPESID was used either orally or by injection as a single agent.

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
Alopecia	8 - 66
Peripheral neurotoxicity	1 - 2
Hypotension	1 - 2
Allergic reaction	1 - 2
Hepatic	0 - 3

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The anticipated acute complications would be related to VEPESID's hematoxicity.

Total doses of 2.4 g/m^2 to 3.5 g/m^2 administered I.V. 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 VEPESID (etoposide) Injection. This effect has not been reported with diluted VEPESID.

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

Hypotension following rapid intravenous administration has been reported, hence, it is recommended that the VEPESID 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. **VEPESID should not be given by rapid intravenous injection.**

Oral: 100 - 200 mg/m^2 daily for 5 days.

Due to limited bioavailability, the effective oral dose is approximately twice the effective intravenous dose, rounded to the nearest 50 mg. In view of significant intra-patient variability, dose adjustment may be required to achieve the desired therapeutic effect.

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

Preparation of Intravenous Solutions

VEPESID injection must be diluted prior to use with either 5 percent dextrose injection U.S.P. or 0.9% sodium chloride injection U.S.P. to give a final concentration of 0.2 or 0.4 mg/mL. **MORE CONCENTRATED SOLUTIONS SHOW CRYSTAL FORMATION**

UPON STIRRING OR SEEDING WITHIN 5 MINUTES AND SHOULD NOT BE GIVEN INTRAVENOUSLY. VEPESID diluted to 0.4 mg/mL and administered through tubing connected to a pump with 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. VEPESID diluted with 0.9% sodium chloride injection U.S.P. or 5% dextrose injection U.S.P. to a concentration of 0.2 or 0.4 mg/mL is stable for 96 and 24 hours respectively, at room temperature under room light in polyvinyl chloride (PVC) bag. VEPESID should not be mixed with other antineoplastic drugs. Care should be taken to prevent spillage and self contact with the drug. **If VEPESID solution contacts the skin, immediately wash thoroughly with soap and water. If VEPESID solution contacts mucous membranes, flush thoroughly with water.**

PHARMACEUTICAL INFORMATION

Drug Substance

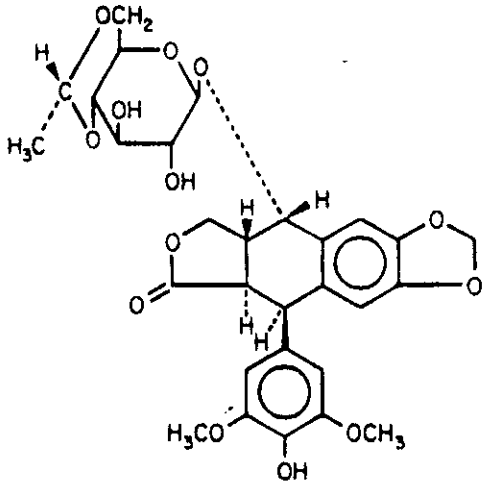
Trade Name: VEPESID

Proper Name: Etoposide

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

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

Structural Formula:



Molecular Weight: 588.58

Description: Etoposide is a white to yellowish or brown-tinged yellowish, fine, crystalline powder. Etoposide is a semi-synthetic derivative of podophyllotoxin. It is very soluble in methanol and chloroform, slightly soluble in ethanol and very slightly soluble in water and ether. It is made water soluble by means of organic solvents.

Composition: VEPESID Injection 20 mg/mL is available in 100 mg (5 mL) vials and ampules, and 150 mg (7.5mL), 500 mg (25mL) and 1 g (50 mL) vials. The pH of the clear yellow solution is 3 to 4. Each mL contains 20 mg etoposide, alcohol, benzyl alcohol, citric acid, polyethylene glycol 300, and polysorbate 80.

VEPESID Capsules are available as 50 mg pink capsules. Each liquid-filled, soft gelatin capsule contains 50 mg of etoposide in a vehicle containing citric acid, glycerol, polyethylene glycol 400 and water. The shell of the capsule contains gelatin, glycerol, parabens (ethyl and propyl), purified water, sorbitol with the following dye system: red iron oxide and titanium dioxide. The capsules are printed with edible ink.

Preparation for Intravenous Administration

VEPESID Injection must be diluted with 5% dextrose injection U.S.P. or 0.9% sodium chloride injection U.S.P. to give a concentration of 0.2 mg/mL or 0.4 mg/mL.

As with all parenteral drug products, intravenous drug admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit.

Stability and Storage Recommendations

INJECTION

VEPESID Injection should be stored at room temperature (15°-30°C).

When diluted with 0.9% sodium chloride injection U.S.P. or 5% dextrose injection U.S.P. to a concentration of 0.2 or 0.4 mg/mL, VEPESID solutions are stable for 96 and 24 hours respectively, at room temperature (25°C) under room light in polyvinyl chloride (PVC) bag.

CAPSULES

VEPESID capsules should be stored at room temperature (15°-30°C).

SPECIAL INSTRUCTIONS

Handling and Disposal

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

2. Personnel preparing VEPESID should wear PVC gloves, safety glasses, disposable gowns and masks.

3. All needles, syringes, vials and other materials which have come in contact with VEPESID should be segregated and incinerated at 1000°C or more. Sealed containers may explode. 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 VEPESID should have bi-annual blood examinations.

AVAILABILITY OF DOSAGE FORMS

VEPESID (etoposide) injection is available in multi-dose vials containing 100 mg, 150 mg, 500 mg and 1 g of etoposide at a concentration of 20 mg/mL.

VEPESID is available in a 5 mL ampoule containing 100 mg at a concentration of 20 mg/mL.

VEPESID 50 mg capsules are available in bottles of 20.

HUMAN PHARMACOLOGY

Pharmacokinetics

On intravenous administration, the disposition of VEPESID (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/m^2 and, like the terminal elimination half-life, are independent of dose over a range 100-600 mg/m^2. 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/m^2 for 4 to 5 days.

The mean volumes of distribution at steady state fall in the range of 18 to 29 litres or 7 to 17 L/m^2. Etoposide enters the CSF poorly. Although it is detectable in CSF and intracerebral tumours, the concentrations are lower than in extracerebral tumours and in plasma. Etoposide concentrations are higher in normal lung than in lung metastases and are similar in primary tumours and normal tissues of the myometrium.

In vitro, etoposide is highly protein bound (97%) to human plasma proteins. Phenylbutazone, sodium salicylate, and aspirin at concentrations achieved *in vivo* displace protein-bound etoposide.

After intravenous administration of ^{3}H-etoposide (70-290 mg/m^2), mean recoveries of radioactivity in the urine range from 42 to 67%, and fecal recoveries range from 0 to 16% of the dose. Less than 50% of an intravenous dose is excreted in the urine as etoposide with mean recoveries of 8 to 35% within 24 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/m^2 or about 35% of

the total body clearance over a dose range of 80 to 600 mg/m^2. An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children.

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 appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the nonrenal clearance of etoposide. The major urinary metabolite of etoposide in adults and children is the hydroxy acid [4′-demethyl epipodophyllic acid-9-(4, 6-0-(R)-ethylidene-β-D-glucopyranoside)], formed by opening of the lactone ring. It is also present in human plasma, presumable as the trans isomer. Glucuronide and/or sulfate conjugates of etoposide are excreted in human urine and represent 5 to 22% of the dose.

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 25-75%). The bioavailability of etoposide capsules appears to be linear up to a dose of at least 250 mg/m^2. Dose proportionality in absorption following oral capsule administration has not been established.

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 non-renal clearance. No evidence exists for any other differences in etoposide metabolism and

excretion after administration of oral capsules as compared to intravenous infusion.

The effective oral dose is approximately twice the effective intravenous dose.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, low serum albumin concentration, and nonrenal clearance. In adult cancer patients with liver dysfunction, total body clearance of etoposide is not reduced. In children, elevated 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. Further study is required to determine if dosage modification is required in patients with decreased body clearance.

ANIMAL PHARMACOLOGY

In vitro:

Etoposide interferes with the synthesis of DNA. *In vitro* experiments with radiolabelled thymidine have demonstrated that etoposide has a concentration dependent inhibition of thymidine uptake.

It has been shown that etoposide, *in vitro* tests on chick connective tissue (fibroblasts) arrested mitosis at metaphase. These effects appeared to be concentration dependent.

Etoposide will inhibit tissue culture *in vitro* as shown in studies with cell line of P-815, HeLa and L types.

Human hemopoietic cell lines treated with etoposide showed a high incidence of multiple chromosomal abnormalities.

The drug has shown activity in rodent transplantable tumors of the sarcomas 37 and 180 and the Walker carcinosarcoma, as well as leukemias P-1534 and L-1210.

Etoposide has been shown to cause metaphase arrest in chick fibroblasts. Its main effect, however, appears to be at the late S or early G_2 portion of the cell cycle in mammalian cells. Two different dose-dependent responses are seen. At high concentrations (10 μg/mL or more), lysis of cells entering mitosis is observed. At low concentrations (0.3 to 10 μg/mL), cells are inhibited from entering prophase. It does not interfere with microtubular assembly. The predominant macromolecular effect of VEPESID (etoposide) appears to be the induction of DNA strand breaks by an interaction with DNA-topoisomerase II or the formation of free radicals.

Pharmacokinetics:

In rats, etoposide was distributed in highest concentrations in liver, kidney and small intestine thirty minutes after intravenous injection of radio-labelled etoposide. Etoposide accumulated to a significant degree after 24 hours in liver, kidney, bile and thyroid, and its major route of excretion was shown to be the bile.

In monkeys, following oral administration, a maximum blood level of etoposide was achieved after 45 minutes and following an intravenous bolus administration, a maximum level was seen after 15 minutes.

In monkeys, the oral half life was 1.7 hours, and the intravenous half life was 1.3 hours. Nineteen percent of the etoposide oral dose was excreted in the urine after 80 hours, and 63% of etoposide oral dose was found in the feces.

TOXICOLOGY

Acute Toxicity

The LD_{50} was determined in mice, rats and rabbits (see following Table).

TABLE 1

LD_{50} of etoposide I.V.

	Etoposide solution		Ampoule solvent
	mg/kg	mL/kg	mL/kg
Mouse	118 ± 9.5	5.9	6.6 ± 0.3
Rat	68 ± 3.5	3.4	4.2 ± 0.4
Rabbit	80	4.0	ca 4.0

The exact estimate of the toxicity of etoposide is limited by the toxicity of the solvent, so acute intravenous toxicity of etoposide cannot be given with certainty.

Subacute Toxicity

Etoposide was administered intraperitoneally at doses of 0.6, 1.8 and 6.0 mg/kg/day to three groups of 20 rats (10 males and 10 females) for four weeks.

A dose of 0.6 mg/kg produced no significant effects. No deaths occurred.

1.8 mg/kg/day produced anemia and transient lymphopenia with significant thymus involution and reduced splenic lymphoid tissue in some animals. No deaths occurred. 6.0 mg/kg/day had significant effects on the hemopoietic and lymphopoietic systems, characterized by fairly severe anemia and marked leukopenia with agranulocytosis in one case. Spermiogenesis in the males was diminished or absent. Non-specific effects (weight loss, diarrhea, pulmonary lesions, hepatocyte degeneration) were

reported. Mortality was 2/20 in this group.

0.6 mg/kg/day at necropsy showed slight evidence of thymus involution in 11/20 rats. There were marked areas of retroperitoneal hemorrhage and small petechial hemorrhages in the pleura and renal capsule.

1.8 mg/kg/day at necropsy showed moderate thymus involution in 18/20 rats. There was a small quantity of serosanguinous ascitic fluid in 7/20 rats. Also seen were small petechial hemorrhages in pleura and renal capsule as in other dosage groups.

6.0 mg/kg/day at necropsy resulted in two spontaneous deaths, one with no postmortem changes, the other with hemorrhagic peritonitis due to perforation. At necropsy significant thymus involution was seen in three, with obvious involution in the remainder. The liver appeared swollen and edematous in 10/18 rats.

Petechial hemorrhages in lungs and renal capsule were observed.

Etoposide was administered intravenously at dosage levels of 0.4, 1.2 and 3.6 mg/kg/day to three groups of four rhesus monkeys (two males and two females) for four weeks.

0.4 mg/kg/day was without any significant effect. 1.2 mg/kg/day produced non-significant anemia and leukopenia and diminished lymphoid tissue. 3.6 mg/kg/day produced progressive anemia and severe leukopenia and agranulocytosis and impaired platelet function (plasma clot retraction). There was diminished lymphoid tissue and reaction centres in the spleen and lymph nodes in all four monkeys and evidence of focal hepatocyte degeneration. Non-specific effects at this dosage included weight loss, reduced serum albumin, mild enteritis and increased hemosiderin deposition in one or two animals. Mortality was zero in all groups.

0.4 mg/kg/day at necropsy showed small grey/yellow nodules in the lungs of two

monkeys. 1.2 mg/kg/day showed small grey/yellow nodules in the lungs of one monkey, and in another the liver was congested with small surface scars.

3.6 mg/kg/day at necropsy showed findings of enlarged submandibular glands, small lung abscesses, grey nodules, small hemorrhagic foci, enlarged mesenteric lymph nodes and fatty bone marrow.

The veins showed no evidence of poor local tolerance.

Chronic Toxicity

Three groups of 80 rats (40 males and 40 females) were given etoposide ampoule solution orally for 26 weeks at 3, 10 and 30 mg/kg daily. Following the completion of the 26 week study, 40 rats at the mid and high dose level received no drug orally for an additional eight weeks to detect possible reversibility of effects.

At 3 mg/kg

Females had a decrease in leukocytes. Both females and males had decreases in RBC, erythropoiesis, leukopoiesis and increased serum cholesterol.

At 10 mg/kg

Decreased total leukocytes, lymphocytes and monocytes, plasma cell increase, bone marrow changes showing moderate disturbance of erythropoiesis and leukopoiesis.

At 30 mg/kg

Females had increased platelet counts. Males had diarrhea. Both females and males had impaired food intake and weight gain, decreased leukocytes, lymphocytes, monocytes, neutrophils and anemia due to changes in the bone marrow. Serum

cholesterol was increased. Urine volume was increased with enhanced electrolyte excretion.

At necropsy, the following changes were noted - reduced weight of testes, ovary and spleen; increased liver weights; thymus involution; a mammary adenocarcinoma and nephroblastoma; degenerative changes in seminal epithelium. These immunosuppressive effects on the hemopoietic and lymphatic system were reversible following treatment, however, histological lung changes were more pronounced after the recovery phase. The tumor findings can be related to the cytostatic mechanism.

Three groups of six beagle dogs (three males and three females) were given etoposide ampoule solution for 26 weeks orally at 0.5, 1.5 and 5-6 mg/kg once daily. Following the completion of the 26 week study, two dogs each of the mid and high dose level were kept for a further five weeks without drug administration to demonstrate reversibility of effects. The following toxicity was reported:

0.5 mg/kg

Changes in bone marrow, slight disturbances of erythropoiesis, sporadic occurrence of micronuclei in normoblasts and leukocytes, increased urinary excretion of potassium.

1.5 mg/kg

Increased platelet counts, disturbed erythropoiesis and leukopoiesis, ECG changes.

Three males showed decreased testicular weights and reduced spermiogenesis.

5-6 mg/kg

Reduction in body weight gain, food intake impaired, loss of weight, black

pigmentation of ear skin due to melanin deposition in basal cells of epidermis. Hematological findings showed a decrease in total leukocyte counts, neutrophils, lymphocytes and monocytes and a slight decrease in erythrocytes, hematocrit and hemoglobin. Also macrocytosis, hypochromic anemia and micronuclei in the erythrocytes and leukocytes, bone marrow changes, and increased platelet count were noted. Also a marked transient increase of SGPT values and a slight trend to increased BUN and creatinine values together with a decrease in blood protein were observed.

The immunosuppressive effects on the hematopoietic and lymphatic system were reversible following withdrawal of treatment.

In summary, the results of the two oral 26-week toxicity studies revealed clear-cut toxic effects after oral administration of high doses of the ampoule solution of etoposide in rats and dogs. The main evidence of toxicity was seen in the erythro and leukopoietic organs, thymus and testes.

Hemolysis Studies

Etoposide given in a four-week intravenous study in monkeys produced no evidence of intravascular hemolysis. Plasma protein precipitation studies *in vivo* and *in vitro* indicate that intravenous administration of etoposide ampoule solution should have no untoward effects on human blood and plasma at the doses likely to be used.

Teratology

Etoposide was subjected to a teratology study in SPF rats at doses of 0.13, 0.4, 1.2 and 3.6 mg/kg/day administered intravenously on days 6 to 15 of gestation. Etoposide caused dose-related maternal toxicity, embryotoxicity and teratogenicity at dose levels of 0.4 mg/kg/day and higher. Embryonic resorptions were 90 and 100 percent at the two highest dosages. At 0.4 and 1.2 mg/kg, fetal weights were

decreased and fetal abnormalities occurred including major skeletal abnormalities, exencephaly, encephalocele and anophthalmia. At the dose of 1.2 mg/kg, a prenatal mortality of 92 percent was observed with 50 percent of the implanting fetuses abnormal. Even at the lowest dose tested, 0.13 mg/kg, a significant increase in retarded ossification was observed.

A study of Swiss-Albino mice given a single intraperitoneal injection of etoposide at dosages of 1.0, 1.5 and 2 mg/kg on days 6, 7 and 8 of gestation disclosed dose-related embryotoxicity, various cranial abnormalities, major skeletal malformations, an increased incidence of intrauterine death and significantly decreased average fetal body weights. Maternal weight gain was not affected.

Etoposide induced aberrations in chromosome number and structure in embryonic murine cells.

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