PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PR VEPESID®

etoposide

capsules, 50 mg, for oral use

Antineoplastic Agent

Manufacturer:

CHEPLAPHARM Arzneimittel GmbH

Ziegelhof 24

17489 Greifswald

Germany

Date of Initial Authorization:

December 31, 1984

Importer / Distributor:

XEDITON Pharmaceuticals Inc.

2020 Winston Park Drive, Suite 402,

Oakville, Ontario L6H 6X7

Tel: 1-888-XEDITON (933-4866)

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, Endocrine and Metabolism	07/2024
7 Warnings and Precautions, Driving and Operating Machinery	07/2024
8 Adverse Reactions	07/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VEPESID (etoposide) is indicated for:

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.

1.1 Pediatrics

Pediatrics(<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

VEPESID (etoposide) is contraindicated

- in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- in patients having severe leukopenia, thrombocytopenia and severe hepatic and/or renal impairment.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Vepesid (etoposide) is a potent drug and should be used only by qualified physicians experienced with cancer chemotherapeutic drugs (see 7 WARNINGS AND PRECAUTIONS).

Severe myelosuppression with resulting infection or bleeding may occur.

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.

Tumour lysis syndrome (sometimes fatal) has been reported following the use of etoposide in association with other chemotherapeutic drugs.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The bioavailability varies from patient to patient following any oral dose. This should be taken into consideration when prescribing this medication.

4.2 Recommended Dose and Dosage Adjustment

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

Daily doses greater than 200 mg should be divided and given twice daily.

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.

Renal Impairment:

In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance.

Table1: Dosage in Patients with Renal Impairment

Measured Creatinine Clearance	Dose of Etoposide
> 50 mL/min	100 % of dose
15 – 50 mL/min	75 % of dose

Subsequent dosing should be based on patient tolerance and clinical effect. Data are not available in patients with creatinine clearance <15 mL/min and further dose reduction should be considered in those patients.

Health Canada has not authorized an indication for pediatric use.

4.3 Administration

Capsules should be taken on an empty stomach.

4.4 Missed dose

Missed doses should not be replaced by double doses and medication should be resumed at the usual time.

5 OVERDOSAGE

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

Total doses of 2.4 g/m^2 to 3.5 g/m^2 administered intravenously 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules, 50 mg, etoposide	Capsule filling: Citric acid, glycerol, polyethylene glycol 400, purified water. Capsule shell: gelatin, glycerol, parabens (ethyl and propyl), purified water, red iron oxide, sorbitol, titanium dioxide

Each liquid-filled, soft gelatin pink capsule contains 50 mg of etoposide.

VEPESID 50 mg capsules are available in bottles of 20.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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.

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

Carcinogenesis and Mutagenesis

Carcinogenicity tests with VEPESID have not been conducted in laboratory animals. Given its mechanism of action, it should be considered a possible carcinogen in humans.

The occurrence of acute leukemia, which can occur with or without a preleukemic phase, has been reported rarely in patients treated with VEPESID 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.

Endocrine and Metabolism

Tumour lysis syndrome (sometimes fatal) has been reported following the use of etoposide in association with other chemotherapeutic drugs. Close monitoring of patients is needed to detect early signs of tumour lysis syndrome, especially in patients with risk factors such as bulky treatment-sensitive tumours, and renal insufficiency. Appropriate preventive measures should also be considered in patients at risk of this complication of therapy.

Contamination

Professional staff administering VEPESID 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.

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. Etoposide may cause adverse reactions that affect the ability to drive and use machines such as fatigue, somnolence, nausea, vomiting, cortical blindness, hypersensitivity reactions with hypotension. Patients who experience such adverse reactions should be advised to avoid driving or using machines.

Hematologic

Fatal myelosuppression has been reported following etoposide administration. 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. 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. A white blood cell count of between 2,000 – 3,000 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%.

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.

Hepatic/Biliary/Pancreatic

Liver function should be regularly monitored.

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

Immune

Concomitant use of VEPESID with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reaction of the vaccine virus because normal defense mechanisms may be suppressed by VEPESID. Vaccination with a live vaccine in a patient taking VEPESID may result in severe infection. Patient's antibody response to vaccines may be decreased. The use of live vaccines should be avoided and individual specialist advice sought (see 9.1 Serious Drug Interactions).

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea and/or hypotension (see 8 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.

Renal

Renal function should be regularly monitored.

Reproductive Health: Female and Male Potential

- **Fertility**

  Given the mutagenic potential of VEPESID, an effective contraception is required for both male and female patients during treatment and up to 6 months after ending treatment. Genetic consultation is recommended if the patient wishes to have children after ending the treatment. VEPESID may decrease fertility. As VEPESID may decrease male fertility,

preservation of sperm may be considered for the purpose of later fatherhood.

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 16 NON-CLINICAL TOXICOLOGY **Error! Reference source not found.Error! Reference source not found.**).

- **Teratogenic Risk**

  VEPESID can cause fetal harm when administered to pregnant women. (See 7.1.1 Pregnant Women).

7.1 Special Populations

7.1.1 Pregnant Women

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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Safety and effectiveness in pediatric patients have not been systematically studied. Clinical experience in childhood malignancies is very limited.

7.1.4 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most commonly reported adverse reactions are leukopenia, thrombocytopenia, nausea and vomiting, anorexia and alopecia.

The following data on adverse events 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.

The incidences of adverse reactions are derived from multiple data bases from studies in patients when VEPESID was used either orally or by injection as a single agent.

Blood and lymphatic system disorders:

Leukopenia (less than 4,000 cells/mm^3) and severe leukopenia (less than 1,000 cells/mm^3) were observed in 60% to 91% and 3% to 17%, respectively, of patients treated with single agent VEPESID. Thrombocytopenia (less than 100,000 platelets/mm^3) and severe thrombocytopenia (less than 50,000 platelets/mm^3) were seen in 22% to 41% and 1% to 20 %, respectively, of this same group of patients. Anemia was observed in 0% to 33% of patients.

Since leukopenia (including neutropenia) and thrombocytopenia have been reported in patients on VEPESID therapy, platelets and white blood cell counts should be performed prior to each cycle (see 7 WARNINGS AND PRECAUTIONS).

Myelosuppression with fatal outcome has been reported following etoposide administration (see 7 WARNINGS AND PRECAUTIONS).

Cardiac disorders:

Myocardial infarction (some with a fatal outcome) and arrhythmia have been reported.

Gastrointestinal disorders:

Nausea and vomiting are the major gastrointestinal toxicities. They have been noted in 31% to 43% of patients given intravenous VEPESID. 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. Anorexia was seen in 10% to 13% and stomatitis in 1% to 6%. of those patients given intravenous VEPSID. Abdominal pain and diarrhea were noted in 0% to 2% and in 1% to 13%, respectively. Mild to severe mucositis/esophagitis may occur. Mouth ulceration has been

reported in 2% of the patients. Constipation, dysgeusia and dysphagia have been reported rarely.

General disorders and administration site conditions:

Asthenia has been reported in 3% of the patients. Fatigue, malaise and pyrexia have been reported rarely.

Hepatobiliary disorders:

Hepatotoxicity has been reported rarely.

Immune system disorders:

Anaphylactic-like reactions have occurred very rarely in patients treated with oral capsules. During or immediately after intravenous VEPESID administration, anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea and/or hypotension have been reported to occur in 0.7% - 2% of patients. Higher rates of anaphylactic- like reactions have been reported in children who received VEPESID 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 the cessation of the infusion of VEPESID, 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 and/or seizures 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. Apnea with spontaneous resumption of breathing following discontinuation has been described in patients receiving etoposide infusion.

There have been case reports where angioedema has been reported in hypersensitivity reactions following etoposide administration.

Infections and infestations:

Infection, including opportunistic infections like *pneumocystis jirovecii* pneumonia, has been reported. Candida infections (including moniliasis) have been reported in less than 1% of patients.

Sepsis has been reported in less than 1% of patients.

Investigations:

Alanine aminotransferase increased, alkaline phosphatase increased, aspartate amino transferase increased, and bilirubin increased have been reported with unknown frequency.

Metabolism and nutrition disorders:

Tumour lysis syndrome (sometimes fatal) has been reported following the use of VEPESID in association with other chemotherapeutic drugs.

Hyperuricemia has been reported in less than 1% of patients.

Neoplasms benign and Malignant (including cysts and polyps)

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.

Nervous system disorders:

Peripheral neuropathy has been reported in 0.7% of patients. The occurrence of Posterior Reversible Encephalopathy Syndrome (PRES) has been reported in patients treated with VEPESID in association with other antineoplastic agents.

Neurotoxicity has been reported in 1% to 2% of the patients. Dizziness, hypoesthesia and paresthesia have been reported in less than 1% of the patients. Somnolence, transient cortical blindness and optic neuritis have been rarely reported.

Psychiatric disorders:

Depression has been reported in less than 1% of patients.

Reproductive system and breast disorders:

VEPESID may lead to infertility.

Respiratory, thoracic and mediastinal disorders:

Interstitial pneumonitis and pulmonary fibrosis have been rarely reported.

Skin and subcutaneous tissue disorders:

Alopecia, sometimes progressing to total baldness, has been observed in up to 66% of patients.

Nail pigmentation has been reported in less than 1% of patients.

Stevens-Johnson syndrome, toxic epidermal necrolysis (one fatal case), rash, pigmentation, pruritus, urticaria, and radiation recall dermatitis have been reported rarely.

Vascular disorders:

Events of haemorrhage have been observed.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
There is increased risk of fatal systemic vaccine disease with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients. See 9.4 Drug-Drug Interactions

9.2 Drug interactions Overview

Effects of other drugs on VEPESID

Cyclosporine: High dose cyclosporine, resulting in concentrations above 2,000 ng/mL, administered with oral etoposide has led to an 80% increase in etoposide exposure (AUC) with a 38% decrease in total body clearance of etoposide compared to etoposide alone.

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

Cisplatin: Concomitant cisplatin therapy is associated with reduced total body clearance of etoposide.

Phenytoin and other antiepileptic drugs: Concomitant phenytoin therapy is associated with increased VEPESID clearance and reduced efficacy. Other antiepileptic therapy may also be associated with increased VEPESID clearance and reduced efficacy.

Effects of VEPESID on other drugs

Co-administration of antiepileptic drugs and VEPESID can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.

Warfarin: Concomitant warfarin therapy may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.

Other interactions

Cross resistance between anthracyclines and etoposide has been reported in preclinical experiments.

9.3 Drug-Behavioural Interactions

Drug-Behavioural interactions have not been established.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4: Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Anthracyclines	PCE	Cross resistance with etoposide	Close monitoring of therapeutic effects.
Antiepileptic drugs, e.g. phenytoin	PM	Increase of etoposide clearance; pharmacokinetic interaction	Reduced efficacy of VEPESID. Decreased seizure control. Close monitoring of the patient for therapeutic effects.
Cyclosporine (high dose)	CT	Decrease in total body clearance of etoposide	Increase in etoposide exposure when used with high dose cyclosporine (>2,000 ng/mL) Monitor the patient closely for adverse reactions of etoposide.
Cisplatin	PM	Decrease in total body clearance of etoposide	Increase in etoposide exposure when used with cisplatin. Monitor the patient closely for adverse reactions of etoposide.
Live vaccines	PM	Suppression of normal defense mechanisms against viruses by VEPESID.	Increased risk of fatal systemic vaccine disease. Live vaccines are not recommended in immunosuppressed patients.
Vincristine	T	Interaction of unknown mechanism	Close monitoring of the patient for neuropathy.
Warfarin	PM	Elevated international normalized ratio (INR)	Close monitoring of INR is recommended.

Legend: C = Case Study; CT = Clinical Trial; PCE = Preclinical Experiments; PM = Post Marketing Information (safety database and literature); T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

VEPESID (etoposide) is a semi-synthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases.

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. Its main effect 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. Etoposide has been shown to cause metaphase arrest in chick fibroblasts.

In vitro experiments with radiolabelled thymidine have demonstrated that etoposide has a concentration dependent inhibition of thymidine uptake. Etoposide has demonstrated *in vitro* sensitivity as shown in studies with cell line of P-815, HeLa and L types.

In vivo, etoposide has shown activity in rodent transplantable tumours of the sarcomas 37 and 180 and the Walker carcinosarcoma, as well as leukemias P-1534 and L-1210.

10.2 Pharmacodynamics

This information is not available for the product.

10.3 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 (C_{max}) values increase linearly with dose.

Etoposide does not accumulate in the plasma following daily administration of 100 mg/m^2 for 4 to 6 days.

Absorption

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.

C_{max} and AUC values for orally administered etoposide capsules for doses up to approximately 250 mg consistently fall in the same range as the C_{max} 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 25-76%). A recent study concluded that the mean bioavailability of a 100 mg oral dose was 76 ± 22%. A 400 mg dose of VEPESID capsule proved to be 48 ± 18% bioavailable.

Distribution:

An intravenous dose (259 mg/m²) 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.

After either intravenous infusion or oral capsule administration of etoposide, the C_{max} 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. The overall mean value of oral capsule bioavailability is approximately 50% (range 25-75%).

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 crosses the blood brain barrier in low concentrations. 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. In a study of the effects of other therapeutic agents on in vitro binding of ^{14}C etoposide to human serum proteins, only phenylbutazone, sodium salicylate, and aspirin displace protein-bound etoposide at concentrations generally achieved *in vivo*.

Etoposide binding ratio correlates directly with serum albumin in cancer patients and normal volunteers. Unbound fraction of etoposide correlates significantly with bilirubin in cancer patients. There appears to be a significant inverse correlation between serum albumin concentration and free etoposide fraction.

Metabolism:

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.

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 hydroxyacid metabolite [4'-dimethyl- epipodophyllic acid-9-(4,6-0-ethylidene-β-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. Glucuronide 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 ^{14}C-etoposide. In addition, O-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

Elimination

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.

After intravenous administration of ^{14}C-etoposide (100-124 mg/m^2), 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 adults, the total body clearance of etoposide is correlated with creatinine clearance, low serum albumin concentration, and nonrenal clearance.

Special Populations and Conditions

- **Pediatrics**

  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 ± 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.

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 in children.

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.

- **Geriatrics**

  Although minor differences in pharmacokinetic parameters between patients ≤ 65 years and > 65 years of age have been observed, these are not considered clinically significant.

- **Sex**

  Although minor differences in pharmacokinetic parameters between gender have been observed, these are not considered clinically significant.

- **Hepatic Insufficiency**

  In adult cancer patients with liver dysfunction, total body clearance of etoposide is not reduced.

- **Renal Insufficiency**

  Patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and higher steady state volume of distribution (see 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

Keep out of reach and sight of children.

To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing VEPESID capsules. This includes handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

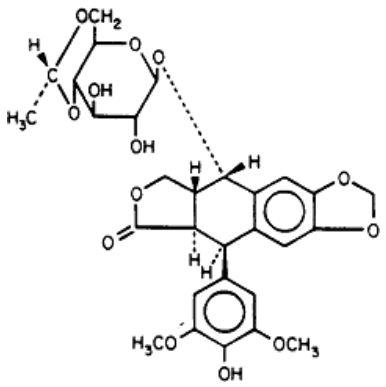
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

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-*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]
Molecular formula:	$C_{29}H_{32}0_{13}$
Molecular mass:	588.58

Structural formula:



Physicochemical properties: 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.

14 CLINICAL TRIALS

This information is not available for this drug product.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

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

Table 5: 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 hemorrhage 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 tumour 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.

Carcinogenicity:

Carcinogenicity tests with VEPESID have not been conducted in laboratory animals. Given its mechanism of action, it should be considered a possible carcinogen in humans.

Genotoxicity:

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

Reproductive and Developmental Toxicology:

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.

Special Toxicology:

<u>Hemolysis Studies</u>

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]VEPESID®

etoposide capsules

Read this carefully before you start taking **VEPESID** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VEPESID**.

Serious Warnings and Precautions

- VEPESID should only be prescribed and managed by healthcare professionals who are experienced in anticancer medicines.
- VEPESID can cause serious side effects, including:
  - **Myelosuppression** (a large decrease in the production of blood cells and platelets by the bone marrow), which may result in infection, bleeding or even death.
  - **Tumour lysis syndrome** (the sudden, rapid death of cancer cells due to the treatment) when taken with other anticancer medicines. This condition can also lead to death. Your healthcare professional will closely monitor you during your treatment for early signs, especially if you are at risk. They may also put in place preventive measures to reduce the risk.

  See the **Serious side effects and what to do about them** table for more information on this and other serious side effects
- You will regularly have blood tests during your treatment with VEPESID, and after you stop taking it. These tests will check:
  - The amount of blood cells in your body.
  - That your liver or kidneys are working properly.

  Depending on your blood test results, your healthcare professional may adjust your dose, stop or discontinue your treatment with VEPESID.

What is VEPESID used for?

VEPISID is used in adults to treat:

- a type of lung cancer known as small cell carcinoma of the lung:
  - as a first-line treatment in combination with other anticancer medicines.

  - as a second-line treatment alone or in combination with other anticancer medicines in patients who have not responded well or relapsed on other anticancer medicines.

- another type of lung cancer known as non-small cell carcinoma of the lung:
  - in patients considered ineligible for surgery. VEPESID can be taken alone or with cisplatin in these patients.
  - in patients who require chemotherapy following surgery.
- a type of cancer of the lymphatic system known as malignant lymphoma (histiocytic type):
  - as a first-line treatment in combination with other anticancer medicines.
- cancer of the testicles:
  - in combination with other anticancer medicines in patients who have already received appropriate therapy.

How does VEPESID work?

Etoposide, the active ingredient in VEPESID, destroys quickly dividing cells such as cancer cells. It works by blocking the action of an enzyme called topoisomerase. This enzyme helps with cell division and tumour growth by keeping the genetic material (DNA) in the proper shape when cells are dividing. Blocking this enzyme damages the cells' DNA, which prevents them from dividing and results in cell death. This helps to treat cancer.

What are the ingredients in VEPESID?

Medicinal ingredients: etoposide

Non-medicinal ingredients: citric acid, glycerol, polyethylene glycol 400, and purified water. The capsule shell also contains gelatin, glycerol, parabens (ethyl and propyl), purified water, red iron oxide, sorbitol and titanium dioxide.

VEPESID comes in the following dosage forms:

Capsules: 50 mg.

Do not use VEPESID if:

- you are allergic to etoposide or to any of the other ingredients in VEPESID.
- you have the **severe** form of the following conditions:
  - leukopenia (low levels of white blood cells in your blood);

- thrombocytopenia (low levels of platelets in your blood); or
- liver or kidney problems.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VEPESID. Talk about any health conditions or problems you may have, including if you:

- have been told that you have:
  - low albumin levels in your blood.
  - low levels of white blood cells in your blood.
  - low levels of platelets in your blood.
  - risk factors for developing leukemia (cancer of the blood) such as a blood disorder or a genetic abnormality.
- have liver or kidney problems.
- have an infection.
- have recently received, or are planning to receive, a live vaccine.
- have a large tumour that responds to treatment (also known as a bulky treatment-sensitive tumour).
- are pregnant, think you are pregnant, plan to become pregnant or could become pregnant.
- plan to father a child.
- are breastfeeding or planning to breastfeed.

Other warnings you should know about:

Your healthcare professional will weigh the benefits of VEPESID against the possible side effects of the medicine. Most of them are reversible if they are detected early. If you experience a side effect during your treatment with VEPESID:

- you should tell your healthcare professional **right away**.
- your healthcare professional may reduce your dose or stop your treatment with VEPESID and treat your side effect first. They will then decide if you should continue your treatment with VEPESID.

Secondary acute leukemia (new cancer of the blood): It was rarely reported in patients taking VEPESID with other anticancer medicines. It occurred in patients with or without risk factors for

leukemia. The condition can develop rapidly after the start of treatment (i.e., average median time of 32 months approximately).

Infection: If you have an infection, tell your healthcare professional. It should be treated before you start your treatment. Taking VEPESID while you have an infection may increase your risk of sepsis. It is a serious condition that happens when your body's immune system has an extreme response to an infection.

Driving and using machines: VEPESID may cause drowsiness, nausea, vomiting, lack of energy, loss of vision or allergic reactions with a drop in blood pressure. Do not drive, use machinery, or do activities that require you to be alert until you know how VEPESID affects you.

Vaccinations: VEPESID decreases a patient's ability to fight infections. Therefore, you should avoid receiving live vaccines while taking VEPESID as it may result in severe infection.

Fertility: VEPESID may affect your ability to become pregnant or father a child. Talk to your healthcare professional if you wish to have children in the future.

Pregnancy and birth control:

- **Male and female patients**: Use a highly effective birth control method during your treatment with VEPESID and for at least 6 months after your last dose.
- VEPESID can harm an unborn baby.
- If you become pregnant during your treatment or it is recommended that you take VEPESID during pregnancy, your healthcare professional will discuss the potential risks with you.
- You should avoid becoming pregnant while taking VEPESID. Tell your healthcare professional **right away** if you discover that you are pregnant during your treatment.

Breastfeeding: VEPESID can pass into breastmilk and could harm a breastfed baby. Do **not** breastfeed while you are taking VEPESID. Talk to your healthcare professional about the best way to feed your baby during your treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Receiving live vaccines during your treatment with VEPESID **is not recommended**. It may increase your risk of severe infection, and can even lead to death.

The following may also interact with VEPESID:

- certain medicines used to treat cancer (e.g., vincristine, cisplatin and anthracyclines)
- medicines used to treat seizures (e.g., phenytoin)
- cyclosporine, used to prevent the rejection of organ transplants
- warfarin, used to treat and prevent blood clots

How to take VEPESID:

- Take VEPESID exactly as your healthcare professional tells you.
- Take VEPESID on an empty stomach.
- It is advisable to wear gloves when handling VEPESID capsules as they may cause skin reactions which may be serious.

Usual dose:

- Your healthcare professional will determine the right dose for you based on your body surface area. It is the external surface area of your body given in square meters (i.e., m^2). It takes into account both your weight and height.
- **Usual adult dose:** 100 – 200 mg per m^2 (body surface area) per day for 5 days.

Overdose:

If you think you, or a person you are caring for, have taken too much VEPESID, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten or missed a dose, skip the missed dose and take the next dose as scheduled. Do not double the dose to make up for the missed dose.

What are possible side effects from using VEPESID?

These are not all the possible side effects you may have when taking **VEPESID**. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- nausea or vomiting
- feeling weak, dizzy or sleepy
- lack of energy
- bad aftertaste
- change in the way things taste
- difficulty swallowing
- loss of appetite
- hair loss
- abnormal nail or skin pigmentation
- itching, rash
- constipation, diarrhea
- general feeling of discomfort

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		✓	
Leukopenia (low white blood cells): aches, fatigue, fever, infections, mouth ulcers, pains and flu-like symptoms, sweating		✓	
Myelosuppression (a large decrease in the production of blood cells and platelets by the bone marrow): bleeding, bruising, chills, fatigue, fever, infections, weakness, shortness of breath or other signs of infection		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Anemia (decreased number of red blood cells): fatigue, loss of energy, looking pale, shortness of breath, weakness		✓	
COMMON			
Mucositis (inflammation and ulceration of the mucous membranes lining the digestive tract): painful, red, shiny or swollen gums, tongue, mouth or throat sores, blood in the mouth, difficult or painful swallowing or talking, dry mouth, mild burning, or pain when eating food		✓	
UNCOMMON			
Sepsis: confusion, fever, low body temperature, rapid breathing, rapid heart rate, swelling			✓
Infections: chills, fatigue, feeling unwell, fever, sore throat		✓	
Peripheral neuropathy (problem with the nerves in your limbs): gradual weakness, numbness, pain or other sensations in the hands and feet, lack of coordination, falling, inability to move		✓	
Hyperuricemia (increased levels of uric acid in the blood): swelling, redness in the joints, sudden and intense attacks of joint pain (gout attack)		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Allergic Reaction / Angioedema: chills, fever, fast heartbeat, difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, flushing, swelling of the face, lips, tongue or throat			✓
Hepatotoxicity (damage to your liver): jaundice (yellowing of the skin or whites of eyes), urine turns dark, light-colored stool, loss of appetite for several days or longer, nausea, lower stomach pain		✓	
Bronchospasm (when there is a sudden narrowing of the airway): difficulty breathing with wheezing or coughing		✓	
Pneumonia (infection in the lungs): chest pain when you breath or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, nausea, vomiting or diarrhea, shortness of breath		✓	
Seizures (fits)**:** uncontrollable shaking with or without loss of consciousness		✓	
Stevens-Johnson syndrome / toxic epidermal necrolysis (severe skin reactions): rash,			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
red skin, red or purple skin patches possibly with blister or crust in the center, pus-filled rash, peeling skin, blisters on the lips, eyes, skin or in the mouth, itching, burning, flu-like feeling, fever			
Optic neuritis (eye pain or changes in vision)		✓	
Radiation recall dermatitis (skin reaction at site of radiation): skin rash, flaking and/or itchy skin, swelling, blistering, peeling or discolouration of the skin		✓	
Interstitial lung disease/ pulmonary fibrosis (diseases that inflame or scar lung tissue): shortness of breath when rest that gets worse with exertion, dry painful cough			✓
UNKNOWN FREQUENCY			
Secondary acute leukemia (new cancer of the blood): feeling tired, pale skin, trouble breathing, bruising or bleeding easily (e.g., nosebleeds or bleeding gums), fever, chills, excessive sweating or other signs of infection		✓	
Tumour lysis syndrome (the sudden, rapid death of cancer cells due to the treatment): nausea, shortness of breath, irregular heartbeat, heart rhythm disturbances, lack of urination, clouding of urine,			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
muscle spasms or twitching, tiredness and/or joint pain, severe muscle weakness, and seizures. Metabolic disorders (kidney failure, abnormal heartbeat) and abnormal blood tests due to rapid breakdown of cancer cells			
Posterior Reversible Encephalopathy Syndrome (PRES) (a nervous system disorder): change in mental state, coma, confusion, numbness and tingling, headache, seizures, vision changes		✓	
Myocardial infarction (heart attack): pressure or squeezing pain in the chest, jaw, left arm, between the shoulder blades or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			✓
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat		✓	
Bleeding problems: coughing up blood, blood in the urine, black tarry stools, pinpoint red spots on skin, extensive bruising		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store capsules at room temperature (15°C - 30°C).
- Keep out of reach and sight of children.

If you want more information about VEPESID:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the Xediton Pharmaceuticals Inc. website: www.xediton.com, or by calling Xediton Pharmaceuticals Inc. at 1-888-XEDITON (933-4866).

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