

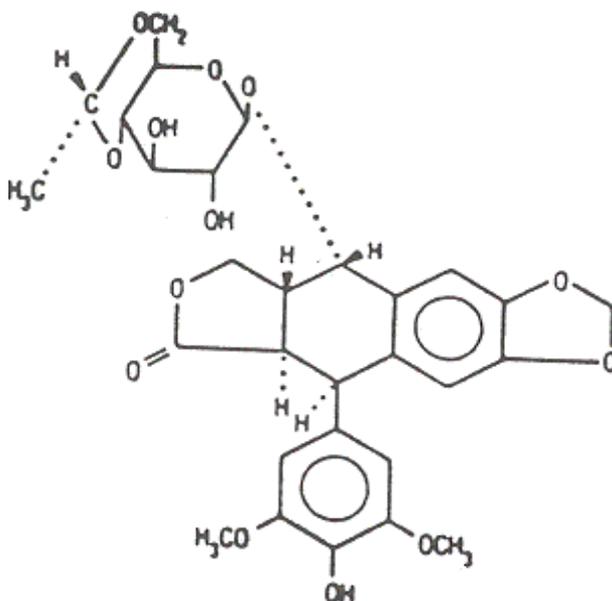
## PRODUCT INFORMATION

**VEPESID™**

**(etoposide)**

### DESCRIPTION

Vepesid (etoposide; commonly known as VP-16-213 or VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is 4'-demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-β-D- glucopyranoside]. It is very soluble in methanol and chloroform, slightly soluble in ethanol and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents.



Molecular weight 588.58

Molecular formula  $C_{29}H_{32}O_{13}$

Vepesid Capsules are soft gelatin capsules containing 50 or 100mg etoposide. The inactive ingredients are: citric acid, glycerol, purified water, macrogol 400, gelatin, parabens, titanium dioxide and iron oxide pigment.

## PHARMACOLOGY

In vitro studies suggest that etoposide initially causes metaphase arrest, however this effect appears to be superseded by interference with cell cycle progression before the cell enters mitosis. Cytofluorometric studies using human lymphoblast cell lines have shown that the major delay in cell cycle progression and the maximum cell killing occurs in the S and G<sub>2</sub> phases of the cell cycle.

This has been confirmed in several cell lines. The mechanism by which this occurs is unknown but may be related to an inhibition of nucleoside transport demonstrated in HeLa cells. Etoposide does not interfere with microtubule assembly. It is particularly active in human leukaemia cells and a high response rate is also seen in small cell carcinoma of the lung.

Etoposide acts indirectly on cultured HeLa cells and induces single-stranded breaks in DNA. This effect was not demonstrated on DNA in vitro.

## PHARMACOKINETICS

### Absorption

Absorption from the oral route of administration is variable and incomplete. Peak blood levels occur about one hour after oral administration.

### Bioavailability

While the absolute bioavailability averaged approximately 55% there were considerable variations between subjects (17-74%) and in one study within individual subjects.

### Distribution

Following intravenous administration of 100mg etoposide the peak plasma concentration ranged from 2.2-6.1 micrograms/mL with an average of 4.7, and time to peak ranged from 0.5-2.0 hours (average 1 hour). Only small levels are found in the cerebrospinal fluid, compared with plasma levels.

In a limited number of children, etoposide administered in a dose of 200-250mg/ square metre produced a mean plasma clearance of  $17.8 \pm 11.2$  (SD) mL/min/m<sup>2</sup> based on a model-independent method. The elimination half-life based on a model-dependent method averaged  $5.8 \pm 3.2$  hours.

Etoposide is stored extensively in the tissues and has a volume of distribution during terminal phase of excretion of 28 L.

### Protein binding

In vitro, etoposide is highly protein bound (97%) to human plasma proteins.

### **Metabolism**

Etoposide is approximately 66% metabolised. One metabolite has been identified but its activity not studied. However, it appears to be extensively distributed and retained. After intravenous administration of <sup>14</sup>C-etoposide (100-124 mg/m<sup>2</sup>), 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.

### **Excretion**

Renal clearance 13.6 ± 4.5 mL/min: total body clearance 47 ± 22 mL/min. The one metabolite identified has a renal clearance of 31.3 mL/min. and total clearance of 111.7 mL/min. Patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and lower steady state volume of distribution. In one study, clearance was reduced by 30% in patients with serum creatinine > 130 µmole/L compared with patients with serum creatinine < 100µmole/L.

Biliary excretion of unchanged drug and/or metabolites is an important route of etoposide elimination as fecal recovery of radioactivity is 44% of the intravenous dose. The hydroxy acid metabolite [4'-demethylepipodophyllic acid-9-(4,6-O-(R)-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 <sup>14</sup>C-etoposide. In addition, O-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

### **Half-life**

Etoposide shows a biexponential plasma decay curve. The beta phase half-life is 11.5 hours.

## **CLINICAL IMPLICATIONS OF PHARMACOKINETIC DATA**

Etoposide and its metabolite are widely distributed within the body and bound to tissue protein. Only about 60% of the administered drug can be accounted for by unchanged or metabolised drug excreted in the urine or faeces, indicating prolonged tissue storage. The fact that approximately 30% of the administered dose is excreted unchanged by the kidneys indicates that the dosage may need to be adjusted in patients with renal impairment.

## **INDICATIONS**

Vepesid (etoposide) is indicated for use in the treatment of:

1. Small cell carcinoma of the lung.
2. Acute monocytic and myelomonocytic leukaemia.
3. Hodgkin's disease.
4. Non-Hodgkin's lymphoma.

## **CONTRAINDICATIONS**

1. Patients with severe hepatic dysfunction.
2. Patients who have a demonstrated hypersensitivity to any of the ingredients.
3. Severe bone marrow failure (WBC less than 2000 cells/mm<sup>3</sup> or platelet count less than 75000 cells/mm<sup>3</sup>) not due to malignant disease.

## **PRECAUTIONS**

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Vepesid (etoposide) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe myelosuppression with resulting infection or bleeding may occur.

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### **General**

In all instances where the use of Vepesid is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most such adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgement of the physician. Reinstitution of Vepesid therapy should be carried out with caution, and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity. Patients with low serum albumin may be at increased risk for etoposide – associated toxicities.

### **Laboratory Tests**

Periodic complete blood counts, hepatic and renal function tests and serum urate should be done during the course of Vepesid treatment. They should be performed prior to therapy and at appropriate periods during therapy. AT least one determination should be done prior to each course of Vepesid.

### **Myelosuppression**

Fatal myelosuppression has been reported following etoposide administration.

Patients being treated with Vepesid must be observed for myelosuppression carefully and frequently 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 course of Vepesid: platelet count, haemoglobin, white blood cell count and differential. The occurrence of a platelet count below 50,000/mm<sup>3</sup> indicates that the patient is at risk of bleeding; the occurrence of a total white cell count below 3,000/mm<sup>3</sup> or an absolute neutrophil count below 500/mm<sup>3</sup> indicates that the patient is at risk of infection. Therapy should not be commenced if there is a risk of the platelet count, the white cell count or the neutrophil count falling below these levels. Furthermore, if the counts drop below these levels during therapy, further therapy should be withheld until the blood counts have sufficiently recovered.

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 reserves.

Infections must be brought under control before using etoposide due to bone marrow suppression following use of the drug and the risk of septicaemia.

Combined chemotherapy may cause increased bone marrow suppression and should be used with caution.

### **Anaphylactic Reactions**

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension. Treatment is symptomatic. 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.

### **Patients with Impaired Liver or Renal Function**

Vepesid should be given cautiously in individuals with a degree of hepatic and renal dysfunction (see DOSAGE AND ADMINISTRATION With Impaired Liver Function and With Impaired Renal Function).

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Six-month chronic toxicity studies in rats have shown Vepesid to have oncogenetic potential but two-year 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.

Vepesid induced aberrations in chromosome number and structure in embryonic murine cells. (See also ADVERSE REACTIONS, Haematological)

### **Use in Pregnancy**

#### **Pregnancy Category (Category D)**

Vepesid can cause fetal harm when administered to pregnant women. Vepesid has been shown to be teratogenic in mice and rats. There are no adequate and well- controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Vepesid was subjected to a teratology study in SPF rats at doses of 0.13, 0.4, 1.2 and 3.6mg/kg/day administered intravenously on Days 6 to 15 of gestation. Vepesid caused a dose-related maternal toxicity, embryotoxicity and teratogenicity at dose levels of 0.13mg/kg/day and higher administered intravenously. 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 and encephalocele and anophthalmia. Even at the lowest dose tested, 0.13mg/kg, a significant increase in retarded ossification was observed.

A study in Swiss-Albino mice given a single intraperitoneal injection of Vepesid at dosages of 1.0, 1.5 and 2.0 mg/kg on Days 6, 7 and 8 of gestation showed dose-related embryotoxicity, various cranial abnormalities and major skeletal malformation.

### **Use In Lactation**

It is not known whether this drug is excreted in human milk.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Vepesid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **Pediatric Use**

Safety and effectiveness in children has not been systematically studied

### **Geriatric Use**

Clinical studies of Vepesid (etoposide) for the treatment of refractory testicular tumors did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Of more than 600 patients in four clinical studies in the NDA databases who received Vepesid or etoposide phosphate in combination with other chemotherapeutic agents for the treatment of small cell lung cancer (SCLC), about one third were older than 65 years. When advanced age was determined to be a prognostic factor for response or survival in these studies, comparisons between treatment groups were performed for the elderly subset. In the one study (etoposide in combination with cyclophosphamide and vincristine and doxorubicin) where age was a significant prognostic factor for survival, a survival benefit for elderly patients was observed for the etoposide regimen compared with the control regimens. No differences in myelosuppression were seen between elderly and younger patients in these studies except for an increased frequency of WHO grade III or IV leukopenia among elderly patients in a study of etoposide phosphate or etoposide in combination with cisplatin. Elderly patients in this study also had more anorexia, mucositis, dehydration, somnolence, and elevated BUN levels than younger patients.

In five single-agent studies of etoposide phosphate in patients with a variety of tumor types, 34% of patients were age 65 years or more. WHO Grade III or IV leukopenia, granulocytopenia, and asthenia were more frequent among elderly patients, post marketing experience also suggests that elderly patients may be more sensitive to some of the known adverse effects of etoposide, including myelosuppression, gastrointestinal effects, infectious complication and alopecia.

Although some minor differences in pharmacokinetic parameters between elderly and nonelderly patients have been observed, these differences were not considered clinically significant. Etoposide and its metabolites are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **PRECAUTIONS, Renal Impairment** for recommended dosing adjustments in patients with

renal impairment.

### **Interactions**

Single case reports exist of increased bone marrow depression and possible increased risk of anthracycline-induced cardiomyopathy. Vepesid may need to be used with caution in combination chemotherapy.

High dose cyclosporin, resulting in concentrations above 2000ng/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.

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

### **ADVERSE REACTIONS**

The incidences of adverse reactions, given below as mean percent, are derived from studies that used single agent Vepesid therapy.

#### **More Common Reactions**

*Haematological:* Myelosuppression with fatal outcome has been reported following etoposide administration (see PRECAUTIONS) The principal toxicity of etoposide is dose-related bone marrow suppression, with granulocyte nadirs occurring 7 to 14 days, and platelet nadirs 9 to 16 days, after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. Leucopenia (less than 4,000 cells/mm<sup>3</sup>) and severe leucopenia (less than 1,000 cells/mm<sup>3</sup>) were observed in 60 to 91 percent and 7 to 17 percent, respectively, of patients treated with single agent Vepesid. Thrombocytopenia (less than 100,000 platelets/mm<sup>3</sup>) and severe thrombocytopenia (less than 50,000 platelets/mm<sup>3</sup>) were seen in 28 to 41 percent and 4 to 20 percent of this group of patients. Pancytopenia was found in 7% of 340 patients treated with 50-60mg/square metre Vepesid I.V. for 5 days.

The occurrence of acute nonlymphocytic leukaemia with or without a preleukaemic phase has been reported in patients treated with Vepesid in association with other antineoplastic agents, in particular, cisplatin.

*Alopecia:* Reversible alopecia, sometimes progressing to total baldness, has been observed in up to 66 percent of patients.

*Gastrointestinal:* Nausea and vomiting are the major gastrointestinal toxicities and can usually be controlled by antiemetic therapy. Anorexia, stomatitis and diarrhoea have also been reported.

#### *Cardiovascular:*

Cardiac arrest and heart failure, some with fatal outcomes have been reported. Patients with cardiac arrest secondary to acute allergic reactions recovered fully from their episodes

### **Less Common Reactions**

*Allergic:* Anaphylactic-like reactions manifested by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension, have occurred very rarely in patients treated with oral capsules. These reactions have usually responded promptly to the administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate.

*Neuropathy:* The use of Vepesid has been reported to cause peripheral neuropathy in 0.7 percent of patients. The associated use of vincristine sulphate can possibly enhance this neuropathy.

Caution should be taken when given etoposide and vincristine combined to older individuals whose performance status is impaired and to patients with pre-existing neurological disease and poor nutritional status.

*Other:* The following reactions have been rarely reported:

Interstitial pneumonitis/pulmonary fibrosis, seizures (occasionally associated with allergic reactions) central nervous system toxicity (somnolence and fatigue), liver toxicity (transient jaundice and elevated alkaline phosphatase), renal toxicity (elevated urea; hyperuricaemia), septicaemia during high dose regimens, aftertaste, mucositis, stomatitis, esophagitis, fever, Stevens-Johnson syndrome, toxic epidermal necrolysis (one fatal case has been reported) rash, pigmentation, pruritus, urticaria, abdominal pain, constipation, dysphagia, asthenia, malaise transient cortical blindness, a single report of radiation recall dermatitis and optic neuritis. One case of myocardial infarction has been reported in a patient also treated with mediastinal radiation. There is one case report of a possible drug-related life-threatening cardiotoxicity. Bronchospasm and apnea have been reported.

### **DOSAGE AND ADMINISTRATION**

Biological activity appears to be schedule dependent with multiple dosage over 3-5 days showing superiority over single dose administration.

#### **Adult**

Oral Absorption from the oral route is variable (range 17-74% of intravenous dose in one trial, 25-80% in another, the corresponding means being 50 and 53%).

Dosages should be titrated to achieve maximum therapeutic effect and to minimise toxicity. The suggested starting dose is approximately 100-200mg/m<sup>2</sup>/day on days 1 to 5.

Total dose should not exceed 650mg/m<sup>2</sup> per course.

Capsules should be taken on an empty stomach.

### **Paediatric**

Specific paediatric dosages have not been evaluated.

### **Use in the Elderly**

As for Adults. However see "DOSAGE: Impaired Liver Function" and "- Impaired Renal Function."

### **Impaired Liver Function**

There are indications that patients with severely impaired liver function (as expressed by an elevation of serum bilirubin above 85 micromoles/L and clinical jaundice) may develop more profound myelotoxicity during etoposide treatment. Its use is contraindicated in patients with severe hepatic dysfunction, and it should be used with caution in patients with mild to moderate hepatic impairment.

### **Impaired Renal Function**

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

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

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

### **Instructions to be given to Patients**

Patients should be warned that nausea and reversible alopecia may occur as a result of Vepesid therapy.

Patients would be advised to use adequate contraceptive measures during treatment with Vepesid (see WARNINGS).

Capsules should be taken with water, preferably on an empty stomach.

## **OVERDOSAGE**

Mucositis, myelotoxicity and metabolic acidosis and in cases of serious hepatic toxicity have been reported in patients receiving higher than recommended doses of etoposide.

### **Procedures for Handling and Disposal of Anticancer Drugs**

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published and should be used appropriately.

## **PRESENTATION**

Vepesid Capsules. Oblong, pink, soft gelatin capsules containing 50 or 100mg etoposide. Vepesid 50mg capsule supplied in blister packs of 10 and 20 capsules, 100mg capsule supplied in blister packs of 10 capsules.

## **STORAGE**

Vepesid Capsules. Store below 25°C. Shelf-life is 3 years.

## **DATE OF APPROVAL**

Approved by the Therapeutic Goods Administration : May 1991

Safety amendments approved : September 1993

Safety amendments approved : September 1996

Safety amendments approved : 26 August 1997

Safety amendments approved : 27 January 2000

Safety amendments approved : 5 October 2000

Approved by the Therapeutic Goods Administration: May 2004

Safety-related notification: 16 July 2010

Safety-related notification: 27 August 2010

Date of amendment: 27 September 2010

## **SPONSOR**

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