DATA SHEET

1 PRODUCT NAME

VEPESID® 50mg and 100mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pale pink, soft gelatin capsules containing 50 mg or 100 mg etoposide.

Excipients with known effect:

Each 50mg capsule contains 0.47 mg of parahydroxybenzoate.

Each 100mg capsule contains 0.61 mg of parahydroxybenzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft gelatin capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VEPESID is indicated in the treatment of:

Small Cell Lung Cancer - VEPESID Capsules in combination with other approved chemotherapeutic agents as first-line treatment in patients with small cell lung cancer.

Hodgkin's Disease.

Malignant (non-Hodgkin's) lymphomas, especially of the histiocytic variety.

Acute non-lymphocytic leukaemia.

Testicular tumours in combination regimens for the treatment of refractory testicular tumours

4.2 Dose and method of administration

The dose of **VEPESID** capsules is based on the recommended dose with consideration given to the bioavailability of **VEPESID** capsules appearing to be dependent upon the dose administered. In view of significant intra-patient variability, dose adjustment may be required to achieve the desired therapeutic effect.

The usual dose of **VEPESID** capsules is 100-200mg/m^2 (body surface area)/day, days 1 to 5 or 200 mg/m^2/day, days 1, 3 and 5 every 3 to 4 weeks in combination with other agents approved for use in the disease to be treated. Dosage should be modified to take into account the myelosuppressive effects of other medications in the combination or the effects of prior X-ray therapy or chemotherapy which may have compromised bone marrow reserve.

Capsules should be taken on an empty stomach.

Elderly: No dosage adjustment is necessary; however, total dosage per course should not exceed 650mg/m^2.

The usual number of treatment cycles (duration of treatment plus treatment-free interval) is 3 or 4. Doses may be increased or decreased and treatment cycles repeated, according to the individual's bone marrow reserve and tumour response. The optimum use of **Vepesid** is in combination with other chemotherapeutic agents.

Renal Impairment:

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.

4.3 Contraindications

Vepesid is contraindicated in patients with severe hepatic dysfunction or in those patients who have demonstrated a previous hypersensitivity to etoposide or any component of the formulation.

4.4 Special warnings and precautions for use

Vepesid 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.

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 dose of **VEPESID**: platelet count, haemoglobin, 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.

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.

General

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

Carcinogenesis

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 (see **Adverse Effects** - Haematological toxicity).

Vepesid has been shown to be mutagenic in *in vitro* test systems.

The occurrence of acute leukaemia, which can occur with or without a preleukaemic phase, has been reported rarely in patients treated with **VEPESID** in association with other antineoplastic drugs.

Paediatric Use

Safety and effectiveness in paediatric patients have not been systematically studied.

Vaccinations

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 defence 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.

4.5 Interaction with other medicines and other forms of interaction

Phenylbutazone, sodium salicylate and aspirin at concentrations achieved in vivo displace protein-bound etoposide.

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.

Concomitant phenytoin therapy is associated with increased **VEPESID** clearance and reduced efficacy, and other antiepileptic therapy may be associated with increased **VEPESID** clearance and reduced efficacy.

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

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

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

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 **4.4 Special warnings and precautions for use**).

4.6 Fertility, pregnancy and lactation

Pregnancy
VEPESID can cause foetal 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 medicine is used during pregnancy, or if the patient becomes pregnant while receiving this medicine, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

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. As **VEPESID** may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.

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 0.4mg/kg/day and higher. Embryonic resorptions were 90 and 100 percent at the two highest dosages. At 0.4 and 1.2mg/kg, foetal weights were decreased and foetal 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 of Swiss-Albino mice given a single intraperitoneal injection of **VEPESID** at dosages of 1.0, 1.5 and 2mg/kg on Days 6, 7 and 8 of gestation disclosed dose-related embryotoxicity, various cranial abnormalities and major skeletal malformations.

Breast feeding
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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In the paragraphs below the incidences of adverse reactions, given as the mean percent, are derived from studies that utilised single agent **VEPESID** therapy.

Haematological Toxicity
Myelosuppression with fatal outcome has been reported following etoposide administration Myelosuppression is most often dose-limiting, with granulocyte nadirs occurring 7 to 14 days, and platelet nadirs occurring 9 to 16 days, after administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported.

Leukopenia and severe leukopenia (less than 1,000 cell/mm^3) were observed in 60 to 91 percent and 7 to 17 percent, respectively, of patients treated with single agent **VEPESID**. Thrombocytopenia and severe thrombocytopenia (less than 50,000 platelets/mm^3) were seen in 28 to 41 percent and 4 to 20 percent, respectively, of this same group of patients. The occurrence of acute leukaemia with or without

a preleukaemic 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 and can usually be controlled by antiemetic therapy. Anorexia, stomatitis and diarrhoea have also been reported. Mild to severe mucositis/esophagitis may occur.

Alopecia
Reversible alopecia, sometimes progressing to total baldness, has been observed in up to 66 per cent of patients.

Allergic Reactions
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.

Other Toxicities
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, aftertaste, 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.

Metabolic Complications

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

Myocardial infarction and arrhythmia have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytostatics, plant alkaloids and other natural products, podophyllotoxin derivatives, ATC code: L01CB01.

VEPESID, a ready-to-use dosage form of etoposide (VP-16-213), a semi-synthetic derivative of podophyllotoxin, is an anti-neoplastic drug for oral use, which can be used alone or in combination with other oncolytic drugs.

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

5.2 Pharmacokinetic properties

On intravenous administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. Total body clearance values range from 33 to 48mL/min or 16 to 36mL/min/m^2 and, like the terminal elimination half-life, are independent of dose over a range 100-600mg/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 100mg/m^2 for 4 to 6 days.

The mean volumes of distribution at steady state fall in the range of 18 to 29 litres or 7 to 17/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.

After intravenous administration of 3H-etoposide (70-290mg/m^2), mean recoveries of radioactivity in the urine range from 42 to 67%, and faecal 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 10mL/min/m2 or about 35% of the total body clearance over a dose range of 80 to 600mg/m2. Etoposide, therefore, is cleared by both renal and non-renal 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 non-renal 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-ethylidene-ß-D-glucopyranoside)], formed by opening of the lactone ring. It is also present in human plasma, presumably as the trans isomer. Glucuronide and/or sulphate conjugates of etoposide are excreted in human urine and represent 5 to 22% of the dose.

After oral capsule administration, 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%).

A recent study concluded that the mean bioavailability of a 100mg oral dose was 76 ± 22%. A 400mg dose of **VEPESID** capsules proved to be 48 ±18% bioavailable.

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.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, low serum albumin concentration, and non-renal clearance. In adult cancer patients with liver dysfunction, total body clearance of etoposide is not reduced. Patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and lower steady state volume of distribution (See **4.2 Dose and method of administration**). 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 etoposide body clearance

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Other ingredients: citric acid, glycerin, purified water and polyethylene glycol 400. The soft gelatin capsules contain gelatin, glycerin, sorbitol, purified water and parabens (ethyl and propyl) with the following dye system: iron oxide (red) and titanium dioxide, the capsules are printed with edible ink.

6.2 Incompatibilities

None Stated.

6.3 Shelf life

VEPESID Capsules: 36 months.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

VEPESID 100mg capsules are packed in blisters of 10 capsules, each capsule containing 100mg etoposide.

VEPESID 50mg capsules are packed in blisters of 20 capsules, each capsule containing 50mg etoposide.

6.6 Special precautions for disposal

Procedures for proper handling and disposal of anti-cancer agents 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.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Link Pharmaceuticals Ltd.
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Auckland 1010
NEW ZEALAND

9 DATE OF FIRST APPROVAL

21/10/1982.

10 DATE OF REVISION OF THE TEXT

30/08/2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Updated to SmPC format
8 Sponsor	Updated to sponsor details due to change in product sponsor.