DATA SHEET

1 PRODUCT NAME

ETOPOPHOS® 100 mg powder for injection.

ETOPOPHOS® 500 mg powder for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ETOPOPHOS 100 mg

Each single use vial contains 113.6 mg of etoposide phosphate (equivalent to 100 mg etoposide) as a lyophilised powder for injection.

Excipients with known effect:

Each 100 mg vial of ETOPOPHOS contains 7.7 mg of sodium.

ETOPOPHOS 500 mg

Each pharmacy bulk vial contains 568 mg of etoposide phosphate (equivalent to 500mg etoposide) as a lyophilised powder for injection

Excipients with known effect:

Each 500 mg vial of ETOPOPHOS contains 38.3 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lyophilised powder for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ETOPOPHOS is indicated in the treatment of:

Small cell lung cancer - ETOPOPHOS Injection 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 both as first-line combination regimens and for the treatment of refractory testicular tumours.

4.2 Dose and method of administration

ETOPOPHOS is administered by slow intravenous infusion. **ETOPOPHOS SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION.** The usual dose for etoposide is 50 to 100 mg/m^2 /day, days 1 to 5 or 100 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.

ETOPOPHOS may be infused over 5-210 minutes.

Prior to use, the contents of each vial must be reconstituted with Sterile Water for Injection, 5% Dextrose Injection, 0.9% Sodium Chloride Injection, Bacteriostatic Water for Injection with Benzyl Alcohol, or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol to a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide (22.7 mg/mL or 11.4 mg/mL etoposide phosphate), respectively. Use the following quantity of diluent:

Vial Strength	Volume of Diluent	Final Concentration (Etoposide Equivalent)
113.6 mg	5 mL	22.7 mg/mL (20 mg/mL)
	10 mL	11.4 mg/mL (10 mg/mL)
568 mg	25 mL	22.7 mg/mL (20 mg/mL)
	50 mL	11.4 mg/mL (10 mg/mL)

Following reconstitution the solution may be administered without further dilution or it can be further diluted to concentrations as low as 0.1 mg/mL etoposide (0.11 mg/mL etoposide phosphate) with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection.

The 500 mg pharmacy bulk vial is intended for use in a pharmacy admixture service only under a laminar flow hood. The closure should be penetrated only once with a sterile transfer set or other sterile dispensing device, which allows measured distribution of the contents, and the contents dispensed in aliquots using aseptic technique. Following closure puncture, container should be maintained at controlled room temperature, 20°C - 25°C, under a laminar flow hood until contents are dispensed. Contents should be used as soon as possible following initial closure puncture. Unused portion should be discarded within 24 hours of closure puncture.

Renal Impairment

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

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

Subsequent etoposide dosing should be based on patient tolerance and clinical effect. Equivalent dose adjustments of ETOPOPHOS should be used.

Data are not available in patients with creatinine clearances <15 mL/min and further dose reduction should be considered in these patients.

Liver Impairment

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.

4.3 Contraindications

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

ETOPOPHOS must not be given by intra-cavity injection.

4.4 Special warnings and precautions for use

ETOPOPHOS 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.

Since etoposide phosphate is rapidly and completely converted to etoposide, the WARNINGS and PRECAUTIONS that are considered when prescribing etoposide should be considered when prescribing ETOPOPHOS® (etoposide phosphate).

General

In all instances where the use of ETOPOPHOS 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 ETOPOPHOS 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.

Myelosuppression

Fatal myelosuppression has been reported following etoposide administration. Patients being treated with ETOPOPHOS 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 ETOPOPHOS therapy. Therefore, the following studies should be obtained at the start of therapy and prior to each subsequent dose of ETOPOPHOS: 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.

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.

Secondary leukaemia

The occurrence of acute leukaemia, which can occur with or without a myelodysplastic syndrome, has been described in patients that were treated with etoposide in association with other antineoplastic drugs.

Neither the cumulative risk, nor the predisposing factors related to the development of secondary leukaemia 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 leukaemia in patients who have received epipodophyllotoxins. This abnormality has also been seen in patients developing secondary leukaemia after being treated with chemotherapy regimens not containing epipodophyllotoxins and in leukaemia occurring *de novo*. Another characteristic that has been associated with secondary leukaemia in patients who have received epipodophyllotoxins appears to be a short latency period, with average median time to development of leukaemia being approximately 32 months.

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. The infusion should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician; however, the reactions can be fatal.

Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with anaphylactic-type reactions.

Injection site reactions may occur during the administration of ETOPOPHOS (see Section 4.8 Undesirable effects). Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

Tumour lysis syndrome

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.

Patients with Impaired Liver or Renal Function

ETOPOPHOS should be given cautiously in individuals with a degree of hepatic and renal dysfunction (see Section 4.2 Dose and method of administration).

Reversible cases of acute renal failure have been reported with administration of high dose (2220 mg/m^2) ETOPOPHOS with total body irradiation used for hematopoietic stem cell transplantation. The ETOPOPHOS formulation contains dextran 40, which has been associated with acute renal failure when administered in high doses. Renal function should be evaluated prior to and after etoposide phosphate administration until complete renal function recovery. (see Section 4.8 Undesirable effects, Other toxicities).

Paediatric Use

Safety and effectiveness in children have not been systematically studied.

Vaccinations

Concomitant use of ETOPOPHOS 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 ETOPOPHOS. Vaccination with a live vaccine in a patient taking ETOPOPHOS 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 Section 4.5 Interactions with other medicines and other forms of Interaction).

Mutagenic potential

Given the mutagenic potential of etoposide, 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 etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.

4.5 Interaction with other medicines and other forms of interaction

ETOPOPHOS should not be physically mixed with any other drug.

Prior or concurrent use of other drugs with similar myelosuppressive action as etoposide may be expected to have additive or synergetic effects.

In vitro plasma protein binding is 97%. Phenylbutazone, sodium salicylate, and acetylsalicylic acid may displace etoposide from plasma protein binding (see Section 5.2 Pharmacokinetic Properties).

Caution should be exercised when administering ETOPOPHOS with drugs that are known to inhibit of phosphatase activities (e.g., levamisole hydrochloride). High dose ciclosporin, (concentrations >2000 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.

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

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

Co-administration of antiepileptic drugs and ETOPOPHOS 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 Section 4.4 Warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Pregnancy

ETOPOPHOS can cause foetal harm when administered to pregnant women. Etoposide has been shown to be teratogenic in mice and rats, and it is therefore assumed the ETOPOPHOS is also teratogenic. 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.

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 ETOPOPHOS, 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.

Fertility

Given the mutagenic potential of etoposide, 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 etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.

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. Etoposide phosphate may cause adverse reactions that affect the ability to drive or 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.

4.8 Undesirable effects

ETOPOPHOS has been found to be well tolerated as a single agent in clinical studies involving 206 patients with a wide variety of malignancies, and in combination with cisplatin in 60 patients with small cell lung cancer. The most frequent clinically significant adverse experiences were leukopenia and neutropenia.

Unless otherwise stated, the following safety data relate to 98 patients administered single agent ETOPOPHOS therapy at or above 450 mg/m^2 on a 5 consecutive day or day 1, 3 and 5 schedule. Adverse events reported were those occurring during or following the first course of therapy.

Acute fatal reactions associated with bronchospasm have been reported.

The most frequent undesirable effect of ETOPOPHOS was leukopenia, occurring in 91% of patients (<4000 cells/mm^3). Severe leukopenia (<1000 cells/mm^3) in 17% of patients.

Neutropenia (<2000 cells/mm^3) occurred in 88% of patients and was severe (<500 cells/mm^3) in 37% of patients. Fever and infection have also been reported in patients with neutropenia.

Thrombocytopenia (<100,000 thrombocytes/mm^3) was reported in 23% of patients. Nine percent of patients had a platelet count nadir 50,000 thrombocytes/mm^3.

Anaemia (Hb <11g/dL) was observed in 72% of patients and was severe (Hb <8g/dL) in 19% of patients.

Gastrointestinal adverse events were usually mild to moderate: Nausea and/or vomiting (37% of patients), anorexia (16%), mucositis (11%), constipation (8%), abdominal pain (7%), diarrhoea (6%) and taste alteration (6%) were reported. Treatment discontinuation was required in 1% of patients.

Asthenia or malaise affected 39% of patients and was severe in 3% of patients.

Alopecia was observed in 23% of patients.

In clinical studies involving ETOPOPHOS, 151 patients were treated with infusion times ranging from 30 minutes to 3.5 hours, and 63 patients received a 5-minute bolus injection. Four patients experienced one or more episodes of hypertension and 8 patients' one or more episodes of hypotension, which may or may not be drug related. Only one of the episodes of hypotension was reported among the patients receiving the 5-minute bolus injection. If clinically significant hyper or hypotension occurs in patients receiving ETOPOPHOS, appropriate supportive therapy should be initiated.

Other events reported were: chills and/or fever (24% of patients), dizziness (5%) and extravasation/phlebitis (5%).

Since etoposide phosphate is converted to etoposide**,** the adverse experiences reported below that are associated with etoposide can be expected to occur with ETOPOPHOS.

The following data on adverse reactions are based on both oral and intravenous administration of etoposide as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Haematological Toxicity

Myelosuppression with fatal outcome has been reported following etoposide administration (see Section 4.4 Warnings and precautions for use). Myelosuppression is most often dose-limiting, with leukocyte nadirs occurring 15 to 22 days, granulocyte nadirs occurring 12 to 19 days, and platelet nadirs occurring 10 to 15 days, after administration. Bone marrow recovery is usually complete by day 21, and no cumulative toxicity has been reported. Fever and infection have also been reported in patients with neutropenia.

Leukopenia and severe leukopenia (less than 1,000 cells/mm^3) were observed from 60 to 91% and 7 to 17%, respectively, in patients treated with single agent etoposide. Thrombocytopenia and severe thrombocytopenia (less than 50,000 platelets/mm^3) were seen in 28 to 41% and 4 to 20%, respectively, with this same group of patients. The occurrence of acute leukaemia with or without a preleukaemic phase has been reported in patients treated with etoposide in association with other antineoplastic agents.

Infection, including opportunistic infections like pneumocystis jirovecii pneumonia, and haemorrhage have been reported.

Gastrointestinal Toxicity

Nausea and vomiting are the major gastrointestinal toxicities. They have been noted in 31-43% of patients given intravenous etoposide. The nausea and vomiting can usually be controlled by antiemetic therapy. Anorexia was seen in 10 to 13% of patients and stomatitis in 1-6% of those patients given intravenous etoposide. Mild to severe mucositis/esophagitis may occur. Diarrhoea was noted in 1 to 13% of these patients.

Alopecia

Reversible alopecia, sometimes progressing to total baldness, has been observed in up to 44% of patients.

Hypotension

Temporary hypotension following rapid intravenous administration has been reported. The incidence has been reported between 1 and 2% of patients and has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. If hypotension occurred with etoposide, it usually responded to stopping the infusion and administering fluid or other supportive therapy as appropriate.

Allergic Reactions

Anaphylactic-like reactions characterized by chills, rigors, fever, tachycardia, bronchospasm, dyspnoea, diaphoresis, fever, pruritis, hypertension or hypotension, loss of consciousness, nausea, and vomiting have also been reported to occur in 3% of patients. These have occurred during or immediately after etoposide administration. Higher rates of anaphylactic-like reactions have been reported in children who received 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 and administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate. However, the reactions can be fatal.

Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions can occur with the initial dose of etoposide. Apnoea with spontaneous resumption of breathing following discontinuation of the infusion has been described.

Rash, urticaria, and/or pruritis have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.

Neuropathy

The use of etoposide has been reported to cause peripheral neuropathy in 0.7% of patients. The associated use of vincristine sulphate can possibly enhance this neuropathy.

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, alanine aminotransferase increased, alkaline phosphatase increased,

aspartate amino transferase increased, bilirubin increased, aftertaste, fever, oesophagitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (one fatal case has been reported), rash, pigmentation, pruritis, urticaria, abdominal pain, constipation, dysphagia, asthenia, malaise, transient cortical blindness, a single report of radiation recall dermatitis, and optic neuritis. Rarely, hepatic toxicity may be seen.

Hepatic toxicity, generally in patients receiving higher doses of etoposide than those recommended, has been reported. Metabolic acidosis has also been reported in patients receiving higher doses.

Local soft tissue toxicity has been reported following extravasation of ETOPOPHOS. Infiltration of ETOPOPHOS may result in swelling, pain, cellulitis and necrosis including skin necrosis.

Reversible acute renal failure has been reported in postmarketing experience (see Section 4.4 Special warnings and precautions for use).

ETOPOPHOS was reported to lead to infertility.

Metabolic Complications

Tumour lysis syndrome (sometimes fatal) has been reported following the use of ETOPOPHOS 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://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

No proven antidotes have been established for ETOPOPHOS overdosage.

Metabolic acidosis and cases of serious hepatic toxicity have been reported in patients receiving higher than recommended intravenous doses of etoposide.

Total etoposide doses of 2.4g/m^2 to 3.5g/ m^2 administered intravenously over three days have resulted in severe mucositis and myelotoxicity.

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.

ETOPOPHOS, a lyophilised powder form of etoposide (VP-16-213), a semi-synthetic derivative of podophyllotoxin, is an anti-neoplastic drug for intravenous use, which can be used alone or in combination with other oncolytic drugs.

Etoposide phosphate is converted *in vivo* to the active moiety, etoposide, by dephosphorylation. The mechanism of action of etoposide phosphate is believed to be the same as that of etoposide. Etoposide

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 (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 micro tubular assembly. The predominant macromolecular effect of etoposide appears to be DNA synthesis inhibition.

5.2 Pharmacokinetic properties

Following intravenous administration of ETOPOPHOS, etoposide phosphate is rapidly and completely converted to etoposide in plasma. A direct comparison of the pharmacokinetic parameters (AUC and C_{max}) of etoposide following intravenous administration of molar equivalent doses of ETOPOPHOS and etoposide was made in two randomized cross-over studies in patients with a variety of malignancies. Results from both studies demonstrated no statistically significant differences in the AUC and C_{max} for etoposide when administered as ETOPOPHOS or etoposide. In addition, there were no statistically significant differences in the pharmacodynamic parameters (haematologic toxicity) after administration of ETOPOPHOS or etoposide. Because of the pharmacokinetic and pharmacodynamic bioequivalence of ETOPOPHOS to etoposide, the following information on etoposide should be considered.

On intravenous administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. Total body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min/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.

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. An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children. Phenyl butazone, sodium salicylate and aspirin at concentrations achieved in vivo displace protein-bound etoposide.

After intravenous administration of ^{14}C-etoposide (100-124 mg/m^2), mean recovery of radioactivity in the urine range was 56% of the dose at 120 hours, 45% of which was excreted as etoposide; faecal recovery of radioactivity was 44% of the dose at 120 hours.

In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m^2 or about 35% of the total body clearance over a dose range of 80 to 600 mg/m^2. 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.

Biliary excretion of unchanged drug and/or metabolites is an important route of etoposide elimination as faecal recovery of radioactivity is 44% of the intravenous dose. The hydroxy acid metabolite [4'-demethylepipodophyllic acid-9-(4,6-0-(R)-ethylidene-b –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 radiolabelled

metabolites of ^{14}C-etoposide. In addition, 0-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, 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 higher steady state volume of distribution (see Section 4.2 Dose and method of administration). In children, elevated serum SGPT levels are associated with reduced drug total body clearance. Prior use of cisplatin may also result in a decrease of etoposide total body clearance in children.

5.3 Preclinical safety data

Carcinogenesis

The carcinogenic potential of ETOPOPHOS has not been studied. However, based upon its pharmacodynamic mechanism of action, ETOPOPHOS is a potential carcinogenic and genotoxic agent.

Mutagenicity

Etoposide has been shown to be mutagenic in mammalian cells and ETOPOPHOS is expected to have similar mutagenic effects.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextran 40
Nitrogen
Sodium citrate dihydrate

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

36 months.

When reconstituted as directed, ETOPOPHOS solutions can be stored in glass or plastic containers under refrigeration 2°- 8°C for 7 days.

At controlled room temperature 20°- 25°C for 24 hours following reconstitution with Sterile Water for Injection, USP, 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP.

At controlled room temperature 20°- 25°C for 48 hours following reconstitution with Bacteriostatic Water for Injection with Benzyl Alcohol or Bacteriostatic Sodium chloride for Injection with Benzyl Alcohol. ETOPOPHOS solutions further diluted as directed can be stored under refrigeration 2°- 8°C or at controlled room temperature 20°- 25°C for 24 hours.

Solutions of ETOPOPHOS should be prepared in an aseptic manner.

6.4 Special precautions for storage

Store at 2° to 8°C (Refrigerate, do not freeze).

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

ETOPOPHOS injection is packed in cartons of single vials each vial containing 113.6 mg or 568 mg etoposide phosphate (equivalent to 100 mg or 500 mg etoposide respectively).

6.6 Special precautions for disposal

As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of ETOPOPHOS. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If ETOPOPHOS solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Procedures for proper handling and disposal of anti-cancer agents should be considered. Several guidelines on this subject have been published.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Link Pharmaceuticals Ltd.
Suite 38, Level 8
139 Quay Street
Auckland 1010
New Zealand

Tel: +64 9 358 7146

9 NEW ZEALAND DATE OF FIRST APPROVAL

16/1/1997 – Etopophos 100 mg

25/5/2000 – Etopophos 500 mg

10 DATE OF REVISION OF THE TEXT

19 March 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Addition of information on opportunistic infections
8	Update of sponsor address