

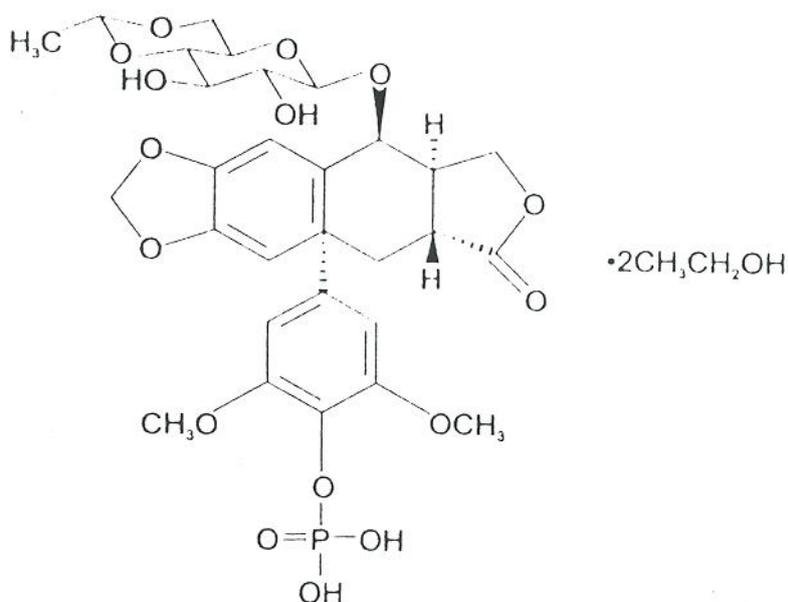
## PRODUCT INFORMATION

### ETOPOPHOS<sup>®</sup> (etoposide phosphate)

#### NAME OF MEDICINE

ETOPOPHOS (etoposide phosphate).

ETOPOPHOS contains a lyophilised powder form of etoposide phosphate (as the diethanolate). Etoposide phosphate is a water-soluble prodrug 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. The CAS number for etoposide phosphate is 117091-64-2 [USAN] and for etoposide phosphate diethanolate is 149028-00-2 [USAN]. The structure is:



[5*S*,5*aR*,8*aR*,9*S*]-5-[3,5-dimethoxy-4-(phosphonooxy)phenyl]-9-[4,6-*O*-(*R*)-ethylidene- $\beta$ -D-glucopyranosyloxy]-5,8,8*a*,9-tetrahydroisobenzofuro[5,6-*f*][1,3]benzodioxol-6(5*aH*)-one, (as the diethanolate).

Molecular weight 760.69

Molecular formula  $C_{29}H_{33}O_{16}P \cdot 2C_2H_6O$

#### DESCRIPTION

ETOPOPHOS injection is available in single use vials. Each vial contains 113.6mg of etoposide phosphate (equivalent to 100mg etoposide) as a lyophilised powder for injection. In addition each single dose vial contains 32.7mg sodium citrate and 300mg of Dextran 40.

ETOPOPHOS injection is also available in pharmacy bulk vials containing either 568mg of

etoposide phosphate (equivalent to 500mg etoposide) or 1136mg of etoposide phosphate (equivalent to 1g etoposide). These vials contain 163.5mg and 327.0mg of sodium citrate and 1.5g and 3g of Dextran 40 respectively. These are for hospital use only.

## PHARMACOLOGY

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<sub>2</sub> 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 micro tubular assembly. The predominant macromolecular effect of etoposide appears to be DNA synthesis inhibition.

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 CMAX) 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 CMAX 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 48mL/min or 16 to 36mL/min/m<sup>2</sup> and, like the terminal elimination half-life, are independent of dose over a range 100-600mg/m<sup>2</sup>. Over the same dose range, the areas under the plasma concentration vs. time curves (AUC) and the maximum plasma concentration (Cmax) values increase linearly with dose. Etoposide does not accumulate in the plasma following daily administration of 100mg/m<sup>2</sup> 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<sup>2</sup>. 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 (i.e. higher serum albumin and lower renal clearance) is found in children and adolescents. Phenyl butazone, sodium salicylate and aspirin at concentrations achieved in vivo displace protein-bound etoposide.

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.

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/m<sup>2</sup> or about 35% of the total body clearance over a dose range of 80 to 600mg/m<sup>2</sup>. Etoposide, therefore, is cleared by both renal and nonrenal processes, i.e. metabolism and biliary excretion. The effect of renal disease on

plasma etoposide clearance is not known.

Biliary excretion 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.

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

## INDICATIONS

ETOPOPHOS (etoposide phosphate) 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.
5. Testicular tumours.

## CONTRAINDICATIONS

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

ETOPOPHOS is contraindicated in 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.

ETOPOPHOS must not be given by intra-cavity injection.

## PRECAUTIONS

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ETOPOPHOS (etoposide phosphate) 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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**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<sup>®</sup> (etoposide phosphate).**

## 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 course of ETOPOPHOS: platelet count, haemoglobin, white blood cell count and differential. The

occurrence of a platelet count below 50,000/mm<sup>3</sup> or an absolute neutrophil count below 500/mm<sup>3</sup> 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 septicæmia.

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, which can be fatal. Treatment is symptomatic. The administration should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

Cardiac arrest has been reported secondary to acute allergic reactions during the infusion of etoposide, the active form of ETOPOPHOS.

Injection site reactions may occur during the administration of ETOPOPHOS (see ADVERSE REACTIONS). 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.

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

ETOPOPHOS should be given cautiously in individuals with a degree of hepatic and renal dysfunction (see DOSAGE AND ADMINISTRATION).

### **Effects on Fertility**

Studies with male animals indicate that ETOPOPHOS treatment causes irreversible atrophy of the testes with accompanying spermatogenesis defects in the testes and epididymis, and reduced seminal vesicle and prostrate secretions.

### **Use in Pregnancy**

Pregnancy Category (Category D)

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 expected that 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.

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.

### **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 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.

### **Paediatric Use**

Safety and effectiveness in children have not been systematically studied.

### **Carcinogenicity and Genotoxicity**

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. Etoposide has been shown to be mutagenic in mammalian and bacterial 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.

Studies with male animals indicate that ETOPOPHOS treatment causes irreversible atrophy of the testes with accompanying spermatogenesis defects in the testes and epididymis, and reduced seminal vesicle and prostrate secretions.

### **General**

In all instances where the use of ETOPOPHOS 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 ETOPOPHOS 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.

### **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 defense 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 INTERACTIONS WITH OTHER MEDICINES, Other interactions).

## **INTERACTIONS WITH OTHER MEDICINES**

ETOPOPHOS should not be physically mixed with any other drug.

Caution should be exercised when administering ETOPOPHOS with drugs that are known to inhibit phosphatase activities (eg, levamisole hydrochloride). High dose cyclosporin (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.

### **Other interactions**

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 PRECAUTIONS, Vaccinations).

### **ADVERSE 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 the recommended dose. Adverse events reported were those occurring during or following the first course of therapy, and have, where possible, been grouped by frequency according to the following criteria.

Very common	> 1/10
Common	> 1/100 and < 1/10
Uncommon	> 1/1000 and < 1/100
Rare	> 1/10000 and < 1/1000
Very rare	< 1/10000

#### Cardiovascular

Common	Hypotension, hypertension
Rare	One case of death from heart failure has been reported 5 days after a patient completed 15 days of infusion of ETOPOPHOS. See also the cardiovascular reactions associated with etoposide (below).

#### Hepatobiliary Disorders

Common	Hepatotoxicity
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#### Haematological

Very common	Leukopenia, neutropenia, thrombocytopenia,
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	Common	anaemia Extravasation*/phlebitis
Gastrointestinal	Very common Common Rare	Nausea, vomiting, mucositis, anorexia Constipation, abdominal pain, diarrhoea, taste alteration Dysphagia
Pulmonary	Rare	Interstitial pneumonitis; pulmonary fibrosis
Musculoskeletal	Very common	Asthenia, malaise
Neurological	Very common Common	Chills and/or fever Dizziness
Neoplasms Benign and Malignant (including cysts and polyps)	Unknown	Acute leukaemia
Skin and Appendages	Very common Uncommon Rare	Alopecia Pigmentation Toxic epidermal necrolysis (one fatal case reported), radiation recall dermatitis, urticaria, rash, maculopapular rash, pruritis
Hypersensitivity	Common Rare	Anaphylactic-type reactions (chills, fever, tachycardia, bronchospasm, dyspnea, hypotension, hypertension, diaphoresis, loss of consciousness, facial flushing, seizures, apnea, rigors, nausea and vomiting), Anaphylactic-like reactions (facial/tongue swelling, coughing, cyanosis, tightness in throat, laryngospasm, back pain), Stevens Johnson Syndrome. Pruritic erythematous maculo papular rash (consistent with perivasculitis has been reported at investigational doses).
Ophthalmological	Rare	Optic neuritis, transient cortical blindness

\*Postmarketing complications reported for extravasation included local soft tissue toxicity, swelling, pain, cellulitis, and necrosis including skin necrosis.

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.

Cardiovascular	Common	Hypotension, myocardial infarction, arrhythmia
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	Rare	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.
Haematological	Very common	Leukopenia, neutropenia, thrombocytopenia, anaemia
	Uncommon	Leukaemia (with or without preleukaemic phase in combination therapy)
Gastrointestinal	Very common	Nausea, vomiting, mucositis, anorexia, abdominal pain
	Common	Stomatitis, diarrhoea, esophagitis taste alteration
Metabolism and Nutrition Disorders	Unknown	Tumour lysis syndrome
Neurological	Very common	Fever
	Uncommon	Peripheral neuropathy, somnolence, fatigue, seizures (occasionally associated with allergic reactions)
Skin and Appendages	Very common	Alopecia
	Uncommon	Rash, pigmentation, pruritis, urticaria, soft tissue irritation and inflammation (following extravasation)
Hypersensitivity	Common	Anaphylactic-like reactions, Stevens Johnson syndrome.
	Very rare	Radiation recall dermatitis
Hepatobiliary	Uncommon	Elevated liver enzymes
Respiratory	Rare	Bronchospasm, Apnoea, interstitial pneumonitis/pulmonary fibrosis
	Rare	Optic neuritis

## DOSAGE AND 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<sup>2</sup> /day, days 1 to 5 or 100-150 mg/m<sup>2</sup>/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. Contains no antimicrobial agent. The

reconstituted solution is for single use only. Discard any residue.

### 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 Phosphate
> 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 < 15mL/min and further dose reductions should be considered in these patients.

Prior to use, the contents of each vial must be reconstituted with Sterile Water for Injection, 5% Glucose 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 20mg/mL or 10mg/mL etoposide (22.7mg/mL or 11.4mg/mL etoposide phosphate), respectively.

Use the following quantity of diluent:

Vial Strength	Volume of Diluent	Final Concentration (Etoposide Equivalent)
113.6mg	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)
1136 mg	50 mL	22.7 mg/mL (20 mg/mL)
	100 mL	11.4 mg/mL (10 mg/mL)

When reconstituted as above the solution contains 3.3 mg/mL of sodium citrate and 30 mg/mL of Dextran 40.

Following reconstitution the solution may be administered without further dilution or it can be further diluted to concentrations as low as 0.1mg/mL etoposide (0.11mg/mL etoposide

phosphate) with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection.

When reconstituted as directed, ETOPOPHOS solutions are chemically and physically stable when stored in glass or plastic containers under refrigeration 2°-8 °C (36 °-46 °F) for 7 days; at controlled room temperature 20°-25 °C (68°-77 °F) for 24 hours following reconstitution with Sterile Water for Injection, USP, 5% Glucose Injection, USP, or 0.9% Sodium Chloride Injection, USP; or at controlled room temperature 20°-25 °C (68°-77 °F) for 48 hours following reconstitution with Bacteriostatic Water for Injection with Benzyl Alcohol or Bacteriostatic Sodium chloride for Injection with Benzyl Alcohol.

Solutions of ETOPOPHOS should be prepared in an aseptic manner. To reduce microbiological hazard, the reconstituted product and any further dilutions made from it should be used as soon as practicable after reconstitution/preparation. If storage is necessary hold at 2°-8 °C for not more than 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

The intravenous solution is suitable for infusion in glass or PVC containers. The pharmacy bulk vials contain a 2% overage and the single use vials a 6% overage to ensure the nominal amount can be withdrawn after reconstitution.

## **OVERDOSAGE**

No proven antidotes have been established for ETOPOPHOS overdose.

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<sup>2</sup> to 3.5g/ m<sup>2</sup> administered intravenously over three days have resulted in severe mucositis and myelotoxicity.

For information on the management of an overdose, contact the Poison Information Centre on 131126 (within Australia).

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

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. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

## **PRESENTATION AND STORAGE CONDITIONS**

Single use vials containing 113.6mg or pharmacy bulk vials containing 568mg or 1136mg etoposide phosphate lyophilised powder. Supplied in pack of 1.

ETOPOPHOS Injection. Store at 2°C to 8°C. Protect from light, do not freeze. Shelf-life is 36 months.

**NAME AND ADDRESS OF SPONSOR**

Bristol-Myers Squibb Australia Pty Ltd  
4 Nexus Court, Mulgrave,  
Victoria 3170, Australia

**DATE OF FIRST INCLUSION IN THE ARTG**

**113.6 mg:** 18 December 1996

**500 mg:** 29 January 2001

**1 g:** 29 January 2001

**DATE OF MOST RECENT AMENDMENT**

6 October 2015

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