**PROFESSIONAL INFORMATION:**

**SCHEDULING STATUS:**

S4

## 1. NAME OF THE MEDICINE:

EPOSIN, 20 mg per ml, concentrate for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Active ingredient: Each ml contains etoposide 20 mg.

*Excipients with known effect:*

1 ml of concentrate for solution for infusion contains 243 mg ethanol.

Preservative: Benzyl alcohol 3 % *m/v.*

For full list of excipients, see **section 6.1**.

## 3. PHARMACEUTICAL FORM:

Concentrate for infusion.

Clear, yellowish viscous solution.

The pH is between 3,0 and 4,0.

## 4. CLINICAL PARTICULARS:

### 4.1 Therapeutic indications:

EPOSIN is indicated for the management of:

***Testicular tumour - First line:***

The intravenous form of EPOSIN is recommended in combination with other approved chemotherapeutic medicines.

***Refractory testicular tumours:***

In combination with other approved medicines, for those with refractory testicular tumours who have already received appropriate surgical, chemotherapeutic and radiotherapeutic treatment.

***Small cell anaplastic lung tumours:***

In combination with other approved chemotherapeutic medicines for small cell anaplastic lung tumours.

***Malignant (Non-Hodgkin's) lymphomas, especially of the histiocytic (large cell diffuse) variety:***

In combination with other approved chemotherapeutic medicines.

**4.2 Posology and method of administration:**

**Posology:**

Safety and efficacy in paediatric patients have not been established.

Dosage should be adjusted according to the individual requirements of each patient, based on clinical response and the appearance or severity of toxicity.

Patients should be carefully monitored for signs of toxicity, such as myelosuppression.

The dosage may also need to be adjusted if the patient has received radiation or other chemotherapy.

***Intravenous dosage:***

The usual intravenous dose of EPOSIN is 50 to 100 mg/m$^2$/day, for days 1 to 5 or 100 mg/m$^2$/day on days 1, 3 and 5. These regimens are given every 3 to 4 weeks in combination with other approved relevant medicines.

***Dosage in renal impairment:***

Dose adjustments for measured creatinine clearance are recommended as follows:

| Measured creatinine clearance | Dose of etoposide |
|---|---|
| > 50 ml/min | 100 % of dose |
| *15-50 ml/min | 75 % of dose |

* Data not available for creatinine clearance <15 ml/min and further dose reduction should be considered.

***Administration precautions:***

Hypotension following rapid intravenous administration of EPOSIN has been reported.

It is recommended that the medicine be given by slow intravenous infusion over 30 to 60 minutes. Hypotension usually responds to cessation of infusion and/or other supportive therapy as appropriate.

Caution should be exercised with handling and preparation of EPOSIN.

Skin reactions with accidental exposure may occur. Use of gloves and masks is recommended. If EPOSIN does come into contact with skin or mucosae, the area should be washed immediately with soap and water.

When restarting the infusion, a slower rate of administration should be used.

**During intravenous infusion, great care must be taken to ensure the catheter stays in the vein, as leakage into surrounding tissue is highly irritant. EPOSIN should not be administered intra-arterially, intra-pleurally, or intra-peritoneally. EPOSIN SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS PUSH.**

**Method of administration:**

Infusion.

For instructions on reconstitution and dilution of EPOSIN before administration, see **section 6.6**.

**4.3 Contraindications:**

- Hypersensitivity to EPOSIN or to any components of the formulation.

- Severe hepatic dysfunction.
- Severely impaired medullary haematopoiesis (particularly after extensive radio- and/or chemotherapy or secondary to neoplastic infiltration). This may be evidenced by mild to marked leukopenia and/or thrombocytopenia.
- Renal function impairment.
- Chickenpox, existing or recent (including recent exposure).
- Herpes Zoster.
- Bone marrow depression.
- Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients (see **section 4.5**).
- Pregnancy and lactation (see **section 4.6**).

**4.4 Special warnings and precautions for use:**

EPOSIN should be administered under the supervision of a doctor experienced in the use of cancer chemotherapeutic medicines.

In all instances where the use of etoposide is considered for chemotherapy, the medical practitioner 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 judgment of the doctor. Reinstitution of etoposide therapy should be carried out with caution, and with adequate consideration of the further need for the drug and close attention to possible recurrence of toxicity.

**Myelosuppression:**

Severe bone marrow suppression may occur, complicated by bleeding or infection, which may be fatal.

Patients being treated with EPOSIN should be observed for myelosuppression carefully and frequently both during and after therapy.

Myelosuppression (bone marrow suppression) is the most significant toxicity associated with the use of EPOSIN. Regular testing of the haemoglobin, leukocyte count, platelet count and albumin are recommended at the start of therapy and before each subsequent dose.

If radiotherapy or chemotherapy has been given prior to starting etoposide treatment, an adequate interval should be allowed to enable the bone marrow to recover. Etoposide should not be administered to patients with neutrophil counts less than 1 500 cells/mm $^3$ or platelet counts less than 100 000 cells/mm$^3$, unless caused by malignant disease. Doses subsequent to initial dose should be adjusted if neutrophil count less than 500 cells/mm$^3$ occurs for more than 5 days or is associated with fever or infection, if platelet count less than 25 000 cells/mm$^3$ occurs, if any grade 3 or 4 toxicity develops or if renal clearance is less than 50 ml/min.

Severe myelosuppression with resulting infection or haemorrhage may occur. Bacterial infections should be brought under control before treatment with etoposide.

If thrombocytopenia occurs as a consequence of administration of EPOSIN, patients should be observed carefully for signs of bleeding (skin, intravenous puncture sites, mucosae, unusual bruising, melaena stools, haematuria). Intramuscular injections, alcohol, aspirin and contact sports should be avoided. Platelet transfusions may be required. Patients who develop leukopenia should be carefully observed for signs of infection. Antibiotic support may be necessary.

**Hypersensitivity:**

If anaphylactic reactions manifested by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension occur, administration of EPOSIN should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the medical professional. Treatment is symptomatic. An increased risk for infusion-related hypersensitivity reactions was observed when in-line filters were used during etoposide administration. In-line filters should not be used.

**Secondary leukaemia:**

The occurrence of acute leukaemia, which can occur with or without myelodysplastic syndrome, has been described in patients that were treated with etoposide containing chemotherapeutic regimens. 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.

**Hypotension:**

EPOSIN should be given only by slow intravenous infusion (usually over a 30 to 60 minute period) since hypotension has been reported as a possible side effect of rapid intravenous injection.

**Injection site reaction:**

Injection site reactions may occur during administration of EPOSIN. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration.

**Low serum albumin:**

Low serum albumin is associated with increased exposure to etoposide. Therefore patients with low serum albumin may be at increased risk for etoposide-associated toxicities.

**Impaired renal function:**

In patients with moderate (CrCl =15 to 50 mL/min), or severe (CrCl <15ml/min) renal impairment undergoing haemodialysis, EPOSIN should be administered at a reduced dose (see section 4.2). Haematological parameters should be measured and dose adjustments in subsequent cycles considered based on haematological toxicity and clinical effect in moderate and severe renal impaired patients.

**Acute renal failure:**

Mostly in children, reversible acute renal failure has been reported when high dose (2 220 mg/m$^2$ or 60 mg/kg) EPOSIN and total body irradiation were used for haematopoietic stem cell transplantation. Renal function should be evaluated prior to and after EPOSIN administration until complete renal function recovery (see section 4.8).

**Impaired hepatic function:**

Patients with impaired hepatic function should regularly have their hepatic function monitored due to the risk of accumulation.

**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.

**Mutagenic potential:**

Due to the genotoxic potential of EPOSIN, women of childbearing or conceiving potential should use effective contraceptive measures while being treated with EPOSIN for 6 months following completion of treatment (see **section 4.6**). Genetic consultation is recommended if the patient wishes to have children after ending the treatment. Men are recommended to use effective contraceptive measures and to not father a child while

receiving etoposide (i.e., EPOSIN) and for 3 months following completion of treatment (see **section 4.6**). As etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood (see **section 4.6**).

Immunisations should be avoided unless approved by the attending doctor.

**EPOSIN contains ethanol and benzyl alcohol.**

EPOSIN contains 24,3 % *m/v* ethanol. Each 5 ml vial contains up to 1,215 g of ethanol equivalent to 24,1 ml of beer, 10,1 ml of wine.

Harmful for those suffering from alcoholism.

To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

EPOSIN contains 150 mg benzyl alcohol in 5 ml unit which is equivalent to 30 mg/ml.

Benzyl alcohol may cause allergic reactions.

Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ('gasping syndrome'). The minimum amount of benzyl alcohol at which toxicity may occur is not known.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

**4.5 Interactions with other medicines and other forms of interaction:**

- High dose ciclosporin may increase the AUC of EPOSIN, with a decrease in total body clearance of EPOSIN.
- Concomitant cisplatin therapy is associated with a reduced total body clearance of EPOSIN.

- Concomitant administration of EPOSIN with blood dyscrasia-causing medications, bone marrow depressants or radiation therapy may potentiate the risk of bone marrow suppression. Dose reduction of EPOSIN may need to be considered (depending on blood counts).
- Co-administration of warfarin and etoposide may result in elevated international normalised ratio (INR). Close monitoring of INR is recommended.
- Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy, and other enzyme-inducing antiepileptic therapy may be associated with increased etoposide clearance and reduced efficacy.
- Co-administration of antiepileptic medicines and etoposide can lead to decreased seizure control due to pharmacokinetic interactions.
- *In vitro* plasma protein binding is 97 %. Phenylbutazone, sodium salicylate, and aspirin may displace etoposide from plasma protein binding.
- There is increased risk of fatal systemic vaccinal disease with the use of yellow fever vaccine. Live vaccines are contraindicated in immunosuppressed patients (see **section 4.3**).
- Prior or concurrent use of other medicines with similar myelosuppressant action as etoposide may be expected to have additive or synergetic effects (see **section 4.4**).

**4.6 Fertility, pregnancy and lactation:**

***Women of childbearing potential/contraception in men and women:***

Women of childbearing age should be advised not to fall pregnant while using EPOSIN. Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during EPOSIN therapy. Etoposide has been shown to be teratogenic in mice and rats. Due to the genotoxic potential of EPOSIN (see **section 4.4**), women of childbearing or conceiving potential should use effective contraceptive measures while being treated with EPOSIN for 6 months following completion of treatment (see **section 4.4**). Genetic consultation is recommended if the patient wishes to have children after ending treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving etoposide (i.e., EPOSIN) and for 3 months following completion of treatment (see **section 4.4**).

***Pregnancy:***

Safety and efficacy in pregnancy has not been established (see **section 4.3**). EPOSIN can cause foetal harm when administered during pregnancy. If this medicine is used during pregnancy, or if a woman falls pregnant on treatment, she should be advised of possible danger to the foetus.

***Breastfeeding:***

Etoposide is excreted in human milk. There is the potential for serious adverse reactions in nursing infants from etoposide. A decision must be made whether to discontinue breast feeding or to discontinue etoposide, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman (see **section 4.3**).

***Fertility:***

As etoposide (e.g., EPOSIN) may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood (see **section 4.4**).

**4.7 Effects on ability to drive and use machines:**

There have been no studies to investigate the effect of EPOSIN on driving performance or the ability to operate machinery. However, EPOSIN may cause fatigue, somnolence, nausea, vomiting, cortical blindness, hypersensitivity reactions with hypotension which may influence the ability to drive and use machines (see **section 4.8**).

**4.8 Undesirable effects:**

| **MedDRA System Organ Class** |
|---|
| **Infections and infestations:** |

| | |
|---|---|
| *Frequent*: | Infections* have been reported in patients with bone marrow depression. |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps):** | |
| *Frequent*: | Acute leukaemia. |
| **Blood and lymphatic system disorders:** | |
| *Frequent:* | Anaemia, leukopenia, myelosuppression**, neutropenia, thrombocytopenia. |
| **Immune system disorders:** | |
| *Frequent:* | Anaphylaxis ***(chills, fever, tachycardia, bronchospasm, dyspnoea, hypotension, apnoea). |
| *Frequency unknown:* | Angioedema. |
| **Metabolism and nutrition disorders:** | |
| *Frequency unknown:* | Tumour lysis syndrome. |
| **Nervous system disorders:** | |
| *Frequent:* | Somnolence, fatigue, peripheral or central neuropathies, malaise, dizziness. |
| *Less frequent:* | Seizures****, transient cortical blindness. |
| **Eye disorders:** | |
| *Unknown frequency*: | Optic neuritis. |
| **Cardiac disorders:** | |
| *Frequent:* | Dysrhythmia, myocardial infarction. |
| **Vascular disorders:** | |
| *Frequent:* | Hypotension with rapid intravenous infusion, hypertension and flushing have also been reported. |
| *Less frequent:* | Haemorrhage. |
| **Respiratory, thoracic and mediastinal disorders:** | |
| *Less frequent*: | Interstitial pneumonitis, pulmonary fibrosis. |
| *Frequency unknown*: | Bronchospasm. |

| | |
|---|---|
| **Gastrointestinal disorders:** | |
| *Frequent:* | Nausea, vomiting, anorexia, abdominal pain, diarrhoea, constipation, stomatitis, mucositis, oesophagitis. |
| *Less frequent*: | Dysgeusia and dysphagia. |
| **Hepato-biliary disorders:** | |
| *Frequent:* | Alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, bilirubin increased, hepatotoxicity. |
| **Skin and subcutaneous tissue disorders:** | |
| *Frequent:* | Alopecia, rash, urticarial, pigmentation, pruritus. |
| *Less frequent:* | Radiation recall dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis. |
| **Renal and urinary disorders:** | |
| *Unknown frequency:* | Acute renal failure. |
| **Reproductive system and breast disorders:** | |
| *Unknown frequency*: | Infertility. |
| **General disorders and administration site conditions:** | |
| *Frequent*: | Chemical phlebitis, asthenia, malaise, extravasation*****. |
| *Less frequent:* | Fever. |
| * Including opportunistic infections like pneumocystis jirovecii pneumonia.<br>**Myelosuppression with fatal outcome has been reported.<br>***Anaphylactic reactions can be fatal.<br>****Seizure is occasionally associated with allergic reactions.<br>*****Post-marketing complications reported for extravasation included local soft tissue toxicity, swelling, pain, cellulitis, and necrosis including skin necrosis. | |

***Description of selected adverse reactions:***

In the paragraphs below the incidences of adverse events, given as the mean percent, are derived from studies that utilised single etoposide therapy.

*Haematological toxicity:*

Myelosuppression (see **section 4.4**) with fatal outcome has been reported following administration of EPOSIN. Myelosuppression is most often dose-limiting. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. Granulocyte and platelet nadirs tend to occur about 10 to 14 days after administration of etoposide depending on the way of administration and treatment scheme. Nadirs tend to occur earlier with intravenous administration compared to oral administration. Leukopenia and severe leukopenia (less than 1 000 cells/$mm^3$) were observed in 91 % and 17 %, respectively, for etoposide. Thrombocytopenia and severe thrombocytopenia (less than 50 000 platelets/$mm^3$) were seen in 23 % and 9 %, respectively, for EPOSIN. Reports of fever and infection were also very common in patients with neutropenia treated with etoposide. Bleeding has been reported.

*Gastrointestinal toxicity:*

Nausea and vomiting are the major gastrointestinal toxicities of etoposide. The nausea and vomiting can usually be controlled by antiemetic therapy.

*Alopecia:*

Reversible alopecia, sometimes progressing to total baldness, was observed in up to 44 % of patients treated with EPOSIN.

*Hypotension:*

Transient hypotension following rapid intravenous administration has been reported in patients treated with EPOSIN and has not been associated with cardiac toxicity or electrocardiographic changes. Hypotension usually

responds to cessation of infusion of etoposide and/or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used. No delayed hypotension has been noted.

*Hypertension:*

In clinical studies involving etoposide (e.g., EPOSIN), episodes of hypertension have been reported. If clinically significant hypertension occurs in patients receiving EPOSIN, appropriate supportive therapy should be initiated.

*Hypersensitivity:*

Anaphylactic reactions have been reported to occur during or immediately after intravenous administration of EPOSIN. The role that concentration or rate of infusion plays in the development of anaphylactic reactions is uncertain. Blood pressure usually normalises within a few hours after cessation of the infusion. Anaphylactic reactions can occur with the initial dose of EPOSIN.

Anaphylactic reactions (see **section 4.4**) manifested by chills, tachycardia, bronchospasm, dyspnoea, diaphoresis, pyrexia, pruritus, hypertension or hypotension, syncope, nausea, and vomiting have been reported to occur in 3 % (7 of 245 patients treated with etoposide in 7 clinical studies) of patients treated with etoposide. Facial flushing was reported in 2 % of patients and skin rashes in 3 %. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor medicines, corticosteroids, antihistamines, or volume expanders as appropriate.

Acute fatal reactions associated with bronchospasm have also been reported with EPOSIN. Apnoea with spontaneous resumption of breathing following cessation of infusion have also been reported.

*Metabolic complications:*

Tumour lysis syndrome (sometimes fatal) has been reported following the use of EPOSIN in association with other chemotherapeutic drugs (see **section 4.4**).

*Acute renal failure:*

Reversible acute renal failure has been reported in post-marketing experience (see **section 4.4**).

***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 providers are asked to report any suspected adverse reactions to SAHPRA via the '**6.04 Adverse Drug Reactions Reporting Form**', found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

**4.9 Overdose:**

(See **section 4.4** and **4.8**).

***Symptoms and signs of overdose:***

Severe nausea and vomiting, severe myelosuppression, severe mucositis, metabolic acidosis, hepatotoxicity.

***Treatment of overdose:***

There is no antidote for EPOSIN. Treatment of overdose is symptomatic and supportive. Etoposide and its metabolites are not dialysable.

**5. PHARMACOLOGICAL PROPERTIES:**

**5.1 Pharmacodynamic properties:**

Category and class: A 26 Cytostatic agents

Antineoplastic agents, plant alkaloids and other natural products, podophyllotoxin derivatives, ATC code: L01CB01

Etoposide is a semi-synthetic derivative of podophyllotoxin. The effect of etoposide in humans appears to be maximal at the S and $G_2$ level of the cell cycle. At high concentrations (10 μg/ml or more), cells are lysed as they enter mitosis. At lower concentrations, cells are inhibited from entering the prophase.

Although the etoposide binds to microtubules, it has no effect on microtubular structure or function. Etoposide forms a ternary complex with topoisomerase II and DNA. This results in double stranded DNA breaks, which cannot be resealed due to the bound etoposide and eventually leads to cell death.
Free radical formation may be another mechanism of cell injury.

**5.2 Pharmacokinetic properties:**

Etoposide, when administered intravenously, has a biphasic distribution, with a distribution half-life of 1,5 hours and an elimination half-life of 4 to 11 hours. The distribution in various tissues differs. Penetration into the cerebrospinal fluid (CSF) is poor. Etoposide concentrations in normal lung are higher than in lung metastases, but similar in both normal tissue and primary tumours of the myometrium. Etoposide is highly bound to plasma protein (> 97 %) with an inverse relationship between serum albumin and renal clearance of etoposide in the paediatric population.
Etoposide binding correlates directly with serum albumin in cancer patients and normal volunteers. Some cancer patients have unbound etoposide fractions that correlate significantly with serum bilirubin levels. Elimination is 40 to 60 % renal, up to 16 % faecal and less than 6 % biliary. The major urinary metabolite is a hydroxyacid product formed by opening of the lactone ring, whilst other urinary metabolites are glucuronide or sulphate conjugates.
In children, clearance is by both renal and non-renal mechanisms. The effect of renal disease on clearance of etoposide in children is not known, but raised liver enzymes and prior use of cisplatin may reduce total body clearance in children. Clearance in adults correlates with creatinine clearance, non-renal clearance and serum albumin levels, hence renal dysfunction increases the AUC.

Marked interindividual variability in bioavailability occurs with both intravenous and oral etoposide administration. The overall mean bioavailability for an oral dose is 50 % (range of 25 to 75 %). When comparing oral versus intravenous dosing, there appears to be no first pass effect for oral etoposide. No evidence exists for any further differences in metabolism or excretion of oral or intravenous forms of etoposide.

## 6. PHARMACEUTICAL PARTICULARS:

### 6.1 List of excipients:

Citric acid (for pH adjustments)

Benzylalcohol

Ethanol dehydrated

Polysorbate 80

Polyethylene glycol 300

### 6.2 Incompatibilities:

Hard plastic devices made from acrylic or ABS (a polymer of acrylonitrile, butadiene and styrene) can crack or leak when used for undiluted EPOSIN injection. This effect has not been reported with the diluted form.

This medicine must not be mixed with other medicines except those mentioned in **section 6.6**.

### 6.3 Shelf life:

*Before opening*: 3 years

*After dilution:*

After dilution to a concentration of 0,2 mg/ml or 0,4 mg/ml etoposide the resulting solution is stable for respectively 96 and 24 hours at room temperature under normal light conditions.

**6.4 Special precautions for storage:**

Store at or below 25 °C and protect from light. Do not freeze.

If the solution is not clear or an undissolvable precipitate is formed the solution must not be used.

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

Solutions showing any sign of precipitation should not be used.

**6.5 Nature and contents of container:**

100 mg (5 ml): Packed into 10 ml colourless glass vials covered with a transparent sleeve and with chlorobutyl rubber stoppers, aluminium seals and snap-on caps. Each vial is packed in an outer carton.

**6.6 Special precautions for disposal and other handling:**

Preparation for intravenous infusion

Hard plastic devices made from acrylic or ABS (a polymer of acrylonitrile, butadiene and styrene) can crack or leak when used for undiluted EPOSIN injection. This effect has not been reported with the diluted form.

EPOSIN can be diluted with 5 % dextrose water or 0,9 % sodium chloride solution to give a final concentration of 0,2 to 0,4 mg/ml. More concentrated solutions may show crystal formation within 5 minutes and should not be given intravenously.

If a 0,4 mg/ml solution of EPOSIN is administered through tubing connected to a peristaltic pump, it may precipitate out of solution. The final mixture of EPOSIN for parenteral use should be visually inspected for particulate matter and discolouration prior to administration.

Procedures for proper handling and disposal of anti-cancer medicines should be followed.

Care must be taken whenever handling cytostatic products. Always take steps to prevent exposure. Caution should be exercised in handling and preparing EPOSIN solutions. Skin reactions associated with accidental exposure to EPOSIN may occur. The use of gloves is recommended. If etoposide phosphate should contact the

skin or mucosa, immediately wash the skin with soap and water and flush the mucosa with water. EPOSIN solutions must be prepared under aseptic conditions.

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

## 7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

South Africa

2090

## 8. REGISTRATION NUMBER(S):

32/26/0263

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Date of publication: 02 March 2012

## 10. DATE OF REVISION OF THE TEXT:

22 April 2024