PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

ETOPOSIDE 100 mg/5 mL FRESENIUS (concentrate for solution for infusion)

ETOPOSIDE 200 mg/10 mL FRESENIUS (concentrate for solution for infusion)

ETOPOSIDE 500 mg/25 mL FRESENIUS (concentrate for solution for infusion)

ETOPOSIDE 1000 mg/50 mL FRESENIUS (concentrate for solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains 20 mg etoposide.

Each 5 mL vial contains 100 mg of etoposide.

Each 10 mL vial contains 200 mg of etoposide.

Each 25 mL vial contains 500 mg of etoposide.

Each 50 mL vial contains 1 000 mg of etoposide.

Excipients with known effect:

Ethanol: 241,4 mg/mL (30,5 % *v/v*)

Benzyl alcohol: 30 mg/mL (3 % *m/v*)

Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The product is a clear, light yellow to pale yellow solution, which is practically free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Testicular tumours – first line

ETOPOSIDE FRESENIUS 20 mg/mL intravenous injection is indicated 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

ETOPOSIDE FRESENIUS 20 mg/mL injection is indicated in combination with other approved chemotherapeutic medicines for the treatment of small cell anaplastic lung tumours.

Malignant (non-Hodgkin's) lymphomas

ETOPOSIDE FRESENIUS 20 mg/mL injection is indicated for the treatment of malignant (non-Hodgkin's) lymphoma, especially of the histiocytic (large cell diffuse) variety in combination with other approved chemotherapeutic medicines.

4.2 Posology and method of administration

Safety and efficacy in paediatric patients have not been established.

ETOPOSIDE FRESENIUS 20 mg/mL injection should only be administered and monitored under the supervision of a qualified medical practitioner experienced in the use of antineoplastic medicines (see section 4.4).

Posology

Adult population

The recommended intravenous dose of ETOPOSIDE FRESENIUS 20 mg/mL in adult patients is 50 to 100 mg/m^2 per day on days 1 to 5, or 100 to 120 mg/m^2 on days 1, 3, and 5 every 3 to 4 weeks in combination with other approved relevant medicines.
Dosage should be adjusted according to the individual requirements of each patient, based on clinical response and the appearance or severity of toxicity.
The dosage may also need to be adjusted if the patient has received radiation or other chemotherapy.

Renal impairment

In patients with renal impairment the following initial dose adjustment should be considered based on measured creatinine clearance:

Measured creatinine clearance	**Dose of ETOPOSIDE FRESENIUS 20 mg/mL**
> 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.

Method of administration

Administration precautions:

Caution should be exercised in the handling and preparation of ETOPOSIDE FRESENIUS 20 mg/mL. Skin reactions associated with unintentional exposure to ETOPOSIDE FRESENIUS 20 mg/mL may occur. The use of gloves and masks is recommended. If ETOPOSIDE FRESENIUS 20 mg/mL Injection comes into contact with skin or mucosa, immediately wash the skin with soap and water and flush the mucosa with water (see section 6.6).

Hypotension following rapid intravenous infusion of ETOPOSIDE FRESENIUS 20 mg/mL has been reported.

It is recommended that ETOPOSIDE FRESENIUS 20 mg/mL is administered by slow intravenous infusion (usually over a 30 to 60 minute period) (see section 4.4 and 6.6). Hypotension usually responds when the infusion is stopped and/or other supportive therapy as appropriate. When restarting the infusion, a slower rate of administration should be used.

During intravenous infusion, great care must be taken to ensure that the catheter stays in the vein, as any leakage into surrounding tissue is highly irritant.

ETOPOSIDE FRESENIUS 20 mg/mL should not be administered intra-arterially, intra-pleurally or intra-peritoneally.

ETOPOSIDE FRESENIUS 20 mg/mL SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS PUSH.

For instructions on dilution of ETOPOSIDE FRESENIUS 20 mg/mL before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to etoposide or to any of the excipients of ETOPOSIDE FRESENIUS 20 mg/mL, listed in section 6.1.
- Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients (see section 4.5).
- 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.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

ETOPOSIDE FRESENIUS 20 mg/mL should only be administered and monitored under the supervision of a qualified medical practitioner experienced in the use of antineoplastic medicines.

In all instances where the use of ETOPOSIDE FRESENIUS 20 mg/mL is considered for chemotherapy, the medical practitioner should evaluate the need and usefulness of the medicine against the risk of adverse reactions.

If severe reactions occur, ETOPOSIDE FRESENIUS 20 mg/mL should be reduced in dosage or discontinued, and appropriate corrective measures should be taken according to the clinical judgment of the medical practitioner.

Reinstitution of ETOPOSIDE FRESENIUS 20 mg/mL therapy should be carried out with caution, and with adequate consideration of the further need for the treatment and close attention to possible recurrence of toxicity.

Injection site reaction

Injection site reactions may occur during administration of ETOPOSIDE FRESENIUS 20 mg/mL. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during administration of the medicine.

Hypersensitivity

Medical practitioners should be aware of the possible occurrence of an anaphylactic reaction with ETOPOSIDE FRESENIUS 20 mg/mL, manifested by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension, which can be fatal. Treatment is symptomatic.

The infusion of ETOPOSIDE FRESENIUS 20 mg/mL should be terminated immediately, followed by the administration of pressor medicines, corticosteroids, antihistamines or volume expanders at the discretion of the medical practitioner. 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

Myelosuppression

Dose-limiting bone marrow suppression is the most significant toxicity associated with ETOPOSIDE FRESENIUS 20 mg/mL therapy.

Fatal myelosuppression has been reported. Patients being treated with ETOPOSIDE FRESENIUS 20 mg/mL should be observed for myelosuppression carefully and frequently both during and after therapy.

The following haematological parameters should be measured at the start of therapy and prior to each subsequent dose of ETOPOSIDE FRESENIUS 20 mg/mL: platelet count, haemoglobin, white blood cell count and differential.

If radiotherapy or chemotherapy has been given prior to starting ETOPOSIDE FRESENIUS 20 mg/mL treatment, an adequate interval should be allowed to enable the bone marrow to recover.

ETOPOSIDE FRESENIUS 20 mg/mL 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. Dosage should be modified to consider the myelosuppressive effects of other medicines in the combination or the effects of prior radiation therapy or chemotherapy which may have compromised bone marrow reserve.

Severe myelosuppression with resulting infection or haemorrhage may occur. Bacterial infections should be brought under control before treatment with ETOPOSIDE FRESENIUS 20 mg/mL.

Tumour lysis syndrome

Tumour lysis syndrome (sometimes fatal) has been reported following the use of ETOPOSIDE FRESENIUS 20 mg/mL in association with other chemotherapeutic medicines.

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.

Thrombocytopenia

If thrombocytopenia occurs because of administration of ETOPOSIDE FRESENIUS 20 mg/mL, 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.

Immunisations should be avoided unless approved by the attending doctor.

Secondary leukaemia

The occurrence of acute leukaemia, which can occur with or without myelodysplastic syndrome, has been described in patients treated with ETOPOSIDE FRESENIUS 20 mg/mL 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 FRESENIUS 20 mg/mL 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

ETOPOSIDE FRESENIUS 20 mg/mL 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.

Low serum albumin

Low serum albumin is associated with increased exposure to ETOPOSIDE FRESENIUS 20 mg/mL. 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 < 15 mL/min) renal impairment undergoing haemodialysis, ETOPOSIDE FRESENIUS 20 mg/mL 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.

Impaired hepatic function

Patients with impaired hepatic function should regularly have their hepatic function monitored due to the risk of accumulation of ETOPOSIDE FRESENIUS 20 mg/mL.

Paediatric use

Safety and efficacy in paediatric patients have not been established.

Excipient (s) that the medical practitioner should be aware of:

Ethanol

ETOPOSIDE FRESENIUS 20 mg/mL contains 30,5 % *v/v* ethanol (alcohol), which corresponds to 0,305 mL (241 mg) of ethanol per ml of concentrate, i.e. up to 1,2 g ethanol per 5 mL vial.

Harmful for those suffering from alcoholism. To be considered in pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

Benzyl alcohol

Benzyl alcohol may cause allergic reactions.

This medicine contains 30 mg benzyl alcohol in each mL.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children.

Caution should be exercised if the patient has a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in the body and may cause side effects (called “metabolic acidosis”). ETOPOSIDE FRESENIUS 20 mg/mL is contraindicated for use in pregnancy or breastfeeding. See section 4.3 “Contraindications”.

Polysorbate 80

ETOPOSIDE FRESENIUS 20 mg/mL Injection contains polysorbate 80.

In new-born infants a life-threatening syndrome of liver, cholestasis and renal failure, pulmonary deterioration, thrombocytopenia and ascites has been associated with an injectable vitamin E product containing polysorbate 80.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on the pharmacokinetics of etoposide

High dose ciclosporin, resulting in plasma concentrations above 2 000 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 in comparison with etoposide alone.

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

Concomitant phenytoin or phenobarbital 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.

In vitro, plasma protein binding is 97 %. Phenylbutazone, sodium salicylate, and acetylsalicylic acid may displace etoposide from plasma protein binding.

Effect of etoposide on the pharmacokinetics of other medicines

Co-administration of antiepileptic medicines and ETOPOSIDE FRESENIUS 20 mg/mL injection can lead to decreased seizure control due to pharmacokinetic interactions between the medicines.

Co-administration of warfarin and etoposide may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.

Pharmacodynamic interactions

There is an 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 FRESENIUS 20 mg/mL may be expected to have additive or synergetic effects (see section 4.4).

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3).

Women of childbearing potential/ Contraception in males and females

Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during ETOPOSIDE FRESENIUS 20 mg/mL therapy.

Etoposide has been shown to be teratogenic in mice and rats.

Given the mutagenic potential of ETOPOSIDE FRESENIUS 20 mg/mL, 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.

Pregnancy

There are no or limited amount of data from the use of etoposide in pregnant women. Studies in animals have shown reproductive toxicity. In general etoposide can cause foetal harm when administered to pregnant women. ETOPOSIDE FRESENIUS 20 mg/mL injection should not be used during pregnancy unless the clinical condition of the woman requires treatment with ETOPOSIDE FRESENIUS 20 mg/mL. Women of childbearing potential should be advised to avoid becoming pregnant. Women of childbearing potential should be advised to use effective contraception during and up to 6 months after treatment. If ETOPOSIDE FRESENIUS 20 mg/mL is used during

pregnancy, or if the patient becomes pregnant while receiving the medicine, the patient should be informed of the potential hazard (mutagenic potential) to the foetus.

Breastfeeding

ETOPOSIDE FRESENIUS 20 mg/mL is excreted in human milk. There is the potential for serious adverse reactions in nursing infants from etoposide. A decision should be made whether to discontinue breastfeeding or to discontinue ETOPOSIDE FRESENIUS 20 mg/mL injection (see section 4.3).

Benzyl alcohol is probably excreted into breastmilk and can be orally absorbed by the infant (see section 4.4).

Fertility

As etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of future 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 FRESENIUS 20 mg/mL 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. See section 4.8. Patients who experience such adverse reactions should be advised to avoid driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Dose-limiting bone marrow suppression is the most significant toxicity associated with ETOPOSIDE FRESENIUS 20 mg/mL therapy. In clinical studies in which etoposide was administered as monotherapy at a total dose of ≥ 450 mg/m^2 the most frequent adverse reactions of any severity were leucopenia (91 %), neutropenia

(88 %), anaemia (72 %) thrombocytopenia (23 %), asthenia (39 %), nausea and/or vomiting (37 %), alopecia (33 %) and chills and/or fever (24 %).

Tabulated list of adverse reactions

System organ class	Frequency	Adverse reaction
Infections and infestations	*Frequent*	opportunistic infections like pneumocystis jirovecii pneumonia[1]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	*Frequent*	acute leukaemia
Blood and lymphatic system disorders	*Frequent*	anaemia, leukopenia, myelosuppression (including fatal outcome), neutropenia, thrombocytopenia, acute leukaemia
Immune system disorders	*Frequent*	anaphylactic reactions (can be fatal)
	Unknown	angioedema, bronchospasm
Metabolism and nutrition disorders	*Unknown*	tumour lysis syndrome (sometimes fatal)
Nervous system disorders	*Frequent*	dizziness

[1] Ref 1 (a) Page 1, Page 4 (d)

	Less frequent	neuropathy peripheral, seizure (sometimes due to allergic reactions), cortical blindness transient, neurotoxicities (e.g., somnolence and fatigue), optic neuritis.
Cardiac disorders	*Frequent*	dysrhythmia, myocardial infarction
Vascular disorders	*Frequent*	hypertension, transient systolic hypotension following rapid intravenous administration
	Less frequent	haemorrhage
Respiratory, thoracic and mediastinal disorders	*Less frequent*	interstitial pneumonitis, pulmonary fibrosis
	Unknown	bronchospasm
Gastrointestinal disorders	*Frequent*	abdominal pain, anorexia, constipation, nausea and vomiting, diarrhoea, mucositis (including stomatitis and esophagitis)
	Less frequent	dysgeusia, dysphagia
Hepatobiliary disorders	*Frequent*	alanine aminotransferase increased, alkaline phosphatase increased, aspartate amino transferase increased, bilirubin increased, hepatotoxicity
Skin and subcutaneous		

tissue disorders	*Frequent*	alopecia, pigmentation, pruritus, rash, urticaria
	Less frequent	radiation recall dermatitis, Stevens-Johnsons syndrome, toxic epidermal necrolysis
Reproductive system and breast disorders	*Unknown*	infertility
General disorders and administration site conditions	*Frequent*	asthenia, malaise, extravasation (including local soft tissue toxicity, swelling, pain, cellulitis, and necrosis including skin necrosis), phlebitis
	Less frequent	pyrexia

Description of selected adverse reactions

In the paragraphs below the incidences of adverse events, given as the mean percent, are derived from reported studies using etoposide as monotherapy.

Haematological toxicity:

Myelosuppression (see section 4.4) with fatal outcome has been reported following administration of etoposide. 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 10-14 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 etoposide. The reports of fever and infection were also very common in patient with neutropenia treated with etoposide. Bleeding has been reported.

Gastrointestinal toxicity

Nausea and vomiting are the main 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 66% of patients treated with etoposide.

Hypotension

Transient hypotension following rapid intravenous administration has been reported in patients treated with etoposide 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 injection, episodes of hypertension have been reported. If clinically significant hypertension occurs in patients receiving etoposide, appropriate supportive therapy should be initiated.

Hypersensitivity

Anaphylactic reactions have been reported to occur during or immediately after intravenous administration of etoposide. The role that concentration or rate of infusion plays in the development of anaphylactic reactions is uncertain. Blood

pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic reactions can occur with the initial dose of ETOPOSIDE FRESENIUS 20 mg/mL.

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 been reported with etoposide. 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 etoposide in association with other chemotherapeutic medicines (see section 4.4).

Paediatric population

The safety profile between paediatric patients and adults is expected to be similar.

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the

Holder of the Certificate of Registration at the following email address:

safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Total doses of 2,4–3,5 g/m^2 of etoposide administered intravenously over 3 days have resulted in severe mucositis and myelotoxicity. Metabolic acidosis and severe hepatic toxicity have been reported in patients receiving higher than recommended intravenous doses of ETOPOSIDE FRESENIUS 20 mg/mL.

There is no specific antidote available. Treatment should therefore be symptomatic and supportive, and patients should be closely monitored. Etoposide and its metabolites are not dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

Mechanism of action

Etoposide is a semi-synthetic derivative of podophyllotoxin.

Pharmacodynamic effects

The effect of etoposide in humans appears to be maximal at the S and G2 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

Absorption

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.

Distribution

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.

Biotransformation

The major urinary metabolite is a hydroxy acid product formed by opening of the lactone ring, while other urinary metabolites are glucuronide or sulphate conjugates.

Elimination

Elimination is 40 to 60 % renal, up to 16 % faecal and less than 6 % biliary.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous (E330)

Benzyl alcohol (E1519)

Polysorbate 80 (E433)

Macrogol 300

Ethanol

6.2 Incompatibilities

ETOPOSIDE FRESENIUS 20 mg/mL Injection must not be mixed with other medicines when administered.

ETOPOSIDE FRESENIUS 20 mg/mL must not be mixed with other medicines excepts those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 2 years

After dilution:

Chemical and physical in-use stability of the solution diluted to a concentration of 0,2 mg/mL and 0,4 mg/mL has been demonstrated in sodium chloride injection (0,9 %

m/v) and glucose injection (5 % *m/v*) for up to 24 hours at controlled room temperature (25 °C).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 15 °C to 25 °C, unless dilution has taken place in controlled and validated aseptic conditions. Do not store the diluted product in a refrigerator (2-8 °C) as this might cause precipitation.

6.4 Special precautions for storage

Store at or below 25 °C. Keep the vial in the outer carton in order to protect from light. Do not refrigerate or freeze.

For storage precautions of diluted medicine, refer section 6.3.

6.5 Nature and contents of container

The ETOPOSIDE FRESENIUS 20 mg/mL concentrate is filled in 5 mL, 10 mL, 25 mL or 50 mL clear Type 1 glass vials with 20 mm bromobutyl grey rubber stoppers and colour coded aluminium flip-off seals:

- 20 mm green aluminium flip-off over seal (for 100 mg/5 mL)
- 20 mm blue aluminium flip-off over seal (for 200 mg/10 mL)
- 20 mm red aluminium flip-off over seal (for 500 mg/25 mL) and
- 20 mm yellow aluminium flip-off over seal (for 1 000 mg/50 mL).

Each carton contains:

1 × 5 mL vial (for 100 mg/5 mL)

1 × 10 mL vial (for 200 mg/20 mL)

1 × 25 mL vial (for 500 mg/25 mL)

1 × 50 mL vial (for 1 000 mg/50 mL)

A Professional information leaflet and a Patient information leaflet is included in each carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Procedures for proper handling and disposal of cytotoxic medicines should be followed.

Instructions on how to dilute, store and dispose of ETOPOSIDE FRESENIUS 20 mg/mL

Dilution

ETOPOSIDE FRESENIUS 20 mg/mL concentrate for solution for infusion must be diluted immediately prior to use with either 50 mg/ mL (5 %) dextrose in water, or 9 mg/ mL (0,9 %) sodium chloride solution to give a final concentration of 0,2 mg/mL to 0,4 mg/mL. At higher concentrations precipitation of etoposide may occur.

Hard plastic devices made from acrylic or ABS (a polymer of acrylonitrile, butadiene and styrene) can crack or leak when used for undiluted ETOPOSIDE FRESENIUS 20 mg/mL injection. This effect has not been reported with the diluted form. ETOPOSIDE FRESENIUS 20 mg/mL 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 ETOPOSIDE FRESENIUS 20 mg/mL is administered through tubing connected to a peristaltic pump, it may precipitate out of solution. The final mixture of ETOPOSIDE FRESENIUS 20 mg/mL for parenteral use should be visually inspected for particulate matter and discolouration prior to administration.

ETOPOSIDE FRESENIUS 20 mg/mL is administered by slow intravenous infusion (usually over a 30 to 60-minute period). ETOPOSIDE FRESENIUS 20 mg/mL SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS PUSH.

Handling and disposal

The normal procedures for proper handling and disposal of anti-cancer medicines should be adopted:

- Staff should be trained to reconstitute the medicine.
- Pregnant staff should be excluded from working with ETOPOSIDE FRESENIUS 20 mg/mL.
- Staff handling this medicine during dilution should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

Disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

FRESENIUS KABI SOUTH AFRICA (PTY) LIMITED

Stand 7 Growthpoint Park Business Park

162 Tonetti Street

Halfway House Extension 7,

Midrand, Gauteng,

1685

SOUTH AFRICA

Telephone number: (011) 545 0000

8. REGISTRATION NUMBER(S)

Etoposide 100 mg/5 mL Fresenius	47/26/1174
Etoposide 200 mg/10 mL Fresenius	47/26/1175
Etoposide 500 mg/25 mL Fresenius	47/26/1176
Etoposide 1000 mg/50 mL Fresenius	47/26/1177

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 February 2021

10. DATE OF REVISION OF THE TEXT

02 September 2024