

## **1.7 Product Information**

### **1.7.1 Summary of Product Characteristics (SmPC) (Enclosed)**

Summary Of Product Characteristics  
**ETOPOSIDE INJECTION 100mg/5ml**

**1) Name of The Medicinal Product:**

Etoposide Injection 100mg/5ml

**2) Qualitative & Quantitative Composition:**

Each ml contains,

Etoposide USP ..... 20mg

Benzyl alcohol NF ..... 30mg

Ethyl alcohol ..... 30.5%v/v

**3) Pharmaceutical Form:**

Clear colorless solution

**4) Clinical Particulars:**

**4.1) Therapeutic Indications:**

*Testicular cancer*

Etoposide is indicated in combination with other approved chemotherapeutic agents for the treatment of first line, recurrent or refractory testicular cancer in adults.

*Small cell lung cancer*

Etoposide is indicated in combination with other approved chemotherapeutic agents for the treatment of small cell lung cancer in adults.

*Hodgkin's lymphoma*

Etoposide is indicated in combination with other approved chemotherapeutic agents for the treatment of Hodgkin's lymphoma in adult and paediatric patients.

*Non-Hodgkin's lymphoma*

Etoposide is indicated in combination with other approved chemotherapeutic agents for the treatment of non-Hodgkin's lymphoma in adult and paediatric patients.

*Acute myeloid leukaemia*

Etoposide is indicated in combination with other approved chemotherapeutic agents for the treatment of acute myeloid leukaemia in adult and paediatric patients.

*Gestational trophoblastic neoplasia*

Etoposide is indicated for first line and second line therapy in combination with other approved chemotherapeutic agents for the treatment of high risk gestational trophoblastic neoplasia in adults.

*Ovarian cancer*

Etoposide is indicated in combination with other approved chemotherapeutic agents for the treatment of non-epithelial ovarian cancer in adults.

Etoposide is indicated for the treatment of platinum-resistant/refractory epithelial ovarian cancer in adults.

## 4.2) Posology & Method of Administration:

### Posology

Etoposide should only be administered and monitored under the supervision of a qualified physician experienced in the use of anti-neoplastic medicinal products.

#### *Adult population*

The recommended dose of etoposide in adult patients is 50 to 100 mg/m<sup>2</sup>/day on days 1 to 5 or 100 to 120 mg/m<sup>2</sup> on days 1, 3, and 5 every 3 to 4 weeks in combination with other drugs indicated in the disease to be treated. Dosage should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior radiotherapy or chemotherapy which may have compromised bone marrow reserve. The doses after the initial dose should be adjusted if neutrophil count is below 500 cells/mm<sup>3</sup> for more than 5 days. In addition the dose should be adjusted in case of occurrence of fever, infections, or at a thrombocyte count below 25,000 cells/mm<sup>3</sup>, which is not caused by the disease. Follow up doses should be adjusted in case of occurrence of grade 3 or 4 toxicities or if renal creatinine clearance is below 50 ml/min. At decreased creatinine clearance of 15 to 50 ml/min a dose reduction by 25% is recommended.

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

#### *Elderly population*

No dosage adjustment is necessary in elderly patients (age > 65 years old), other than based on renal function.

#### *Paediatric population*

##### Hodgkin's lymphoma; non-Hodgkin's lymphoma; acute myeloid leukaemia

Etoposide in paediatric patients has been used in the range of 75 to 150 mg/m<sup>2</sup>/day for 2 to 5 days in combination with other antineoplastic agents. The treatment regimen should be chosen according to the local standard of care.

##### Ovarian cancer; small cell lung cancer; gestational trophoblastic neoplasia; testicular cancer

The safety and efficacy of etoposide below 18 years of age have not been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

### **Special Populations**

#### *Renal impairment*

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

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

In patients with creatinine clearance less than 15 ml/min and on dialysis further dose reduction is likely to be required as etoposide clearance is further reduced in these patients. Subsequent dosing in moderate and severe renal impairment should be based on patient tolerance and clinical effect. Since etoposide and its metabolites are not dialyzable, it can be administered pre- and post-haemodialysis.

## **Method of Administration**

Etoposide is administered by slow intravenous infusion (usually over a 30 to 60 minute period)

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6

## **4.3) Contraindications:**

Hypersensitivity to the active substance or to any of the excipients listed

- Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients
- Lactation

## **4.4) Special Warnings & Precautions for Use:**

Etoposide should only be administered under the supervision of a qualified physician experienced in the use of anti-neoplastic medicinal products. In all instances where the use of etoposide is considered for chemotherapy, the physician must evaluate the need and usefulness of the medicinal product against the risk of adverse reactions. Most such adverse reactions are reversible if detected early. If severe reactions occur, the medicinal product should be reduced in dose or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of etoposide therapy should be carried out with caution, and with adequate consideration of the further need for the medicinal product and close attention to possible recurrence of toxicity.

### *Myelosuppression*

Dose-limiting bone marrow suppression is the most significant toxicity associated with etoposide therapy. Fatal myelosuppression has been reported following etoposide administration. Patients being treated with etoposide must 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: platelet count, haemoglobin, white blood cell count and differential. 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 below 1,500 cells/mm<sup>3</sup> or platelet counts below 100,000 cells/mm<sup>3</sup>, unless caused by malignant disease.

Doses subsequent to the initial dose should be adjusted if neutrophil count below 500 cells/mm<sup>3</sup> occurs for more than 5 days or is associated with fever or infection, if platelet count below 25,000 cells/mm<sup>3</sup> occurs, if any other 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.

### *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.

#### *Hypersensitivity*

Physicians should be aware of the possible occurrence of an anaphylactic reaction with etoposide, manifested by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension, which can be fatal. Treatment is symptomatic. Etoposide should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

#### *Hypotension*

Etoposide 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 the administration of etoposide. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during administration of the medicinal product.

#### *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 < 15 ml/min) renal impairment undergoing haemodialysis, etoposide should be administered at a reduced dose.

Haematological parameters should be measured and dose adjustments in subsequent cycles considered based on haematological toxicity and clinical effect in patients with moderate and severe renal impairment.

#### *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 medicinal products. 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*

Given the mutagenic potential of etoposide, an effective method of 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.

### *Paediatric population*

The clinician should be aware that Etoposide contains ethanol and polysorbate 80 as excipients.

### *Excipients*

This medicinal product contains 33 vol % ethanol (alcohol), i.e. 262 mg per ml. With a dose of 120 mg/m<sup>2</sup>, 2.7 g ethanol is applied to a patient with a body surface of 1.73 m<sup>2</sup>, equivalent to 68 ml beer, 28 ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

Consideration should be given to possible effects on the central nervous system.

The amount of alcohol in this medicinal product may alter the effects of other medicinal products.

The amount of alcohol in this medicinal product may impair the patient's ability to drive or use machines.

Etoposide injection contains polysorbate 80. In premature infants a life threatening syndrome of liver 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 Medicinal Products & Other Forms of Interaction:**

### *Effects of other medicinal products on the pharmacokinetics of etoposide*

High-dose cyclosporine, resulting in concentrations above 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 etoposide clearance.

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.

*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 medicinal products*

Co-administration of antiepileptic medicinal products and etoposide can lead to decreased seizure control due to pharmacokinetic interactions between the medicinal products.

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

### *Pharmacodynamic interactions*

There is increased risk of fatal systemic vaccinal disease with the use of yellow fever vaccine. Live vaccines are contraindicated in immunosuppressed patients.

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

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 & Lactation**

#### *Women of childbearing potential/Contraception in males and females*

Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during etoposide therapy. Etoposide has been shown to be teratogenic in mice and rats. Given the mutagenic potential of etoposide, an effective method of contraception is required for both male and female patients during treatment and up to 6 months after 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 should not be used during pregnancy unless the clinical condition of the woman requires treatment with etoposide.

Women of childbearing potential should be advised to avoid becoming pregnant. Women of childbearing potential have to use effective contraception during and up to 6 months after treatment. If this medicinal product is used during pregnancy, or if the patient becomes pregnant while receiving this medicinal product, the patient should be informed of the potential hazard to the fetus.

#### *Breastfeeding*

Etoposide is excreted in human milk. There is the potential for serious adverse reactions in nursing infants from etoposide. Therefore, etoposide is contraindicated during breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue etoposide taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

#### *Fertility*

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 & Use Machines:**

No studies on the effects on the ability to drive and use machines have been performed with etoposide. The amount of ethanol in Etoposide may impair the ability to drive or use machines after a course of treatment. In general, etoposide 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:

The table below lists adverse events presented by system organ class and frequency, which is defined by the following categories: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), not known (cannot be estimated from the available data).

<b>ADVERSE EVENTS REPORTED with etoposide</b>		
<b>System Organ Class</b>	<b>Frequency</b>	<b>Adverse Reaction</b>
Infections and infestations	Common	Infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Acute leukaemia
Blood and lymphatic system disorders*	Very common	Anaemia, leukopenia, myelosuppression*, neutropenia, thrombocytopenia
Immune system disorders	Common	Anaphylactic-type reactions**
	Not known	Angioedema, bronchospasm
Metabolism and nutrition disorders	Not known	Tumour lysis syndrome
Nervous system disorders	Common	Dizziness
	Uncommon	Neuropathy peripheral
	Rare	Cortical blindness transient, neurotoxicities (e.g., somnolence and fatigue), optic neuritis, seizure***
Cardiac disorders	Common	Arrhythmia, myocardial infarction
Vascular disorders	Common	Hypertension, transient systolic hypotension following rapid intravenous administration
	Uncommon	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Rare	Interstitial pneumonitis, pulmonary fibrosis
	Not known	Bronchospasm
Gastrointestinal disorders	Very common	Abdominal pain, anorexia, constipation, nausea and vomiting
	Common	Diarrhoea, mucositis (including stomatitis and oesophagitis)
	Rare	Dysgeusia, dysphagia
Hepatobiliary disorders	Very common	Alanine aminotransferase increased, alkaline phosphatase increased, aspartate amino transferase increased, bilirubin increased, hepatotoxicity
Skin and subcutaneous tissue disorders	Very common	Alopecia, pigmentation
	Common	Pruritus, rash, urticaria
	Rare	Radiation recall dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis
	Not known	Oedema of face and tongue
Reproductive system and breast disorders	Not known	Infertility
General disorders and	Very common	Asthenia, malaise



administration site conditions	Common	Extravasation****, phlebitis
	Rare	Pyrexia
<p>* Myelosuppression with fatal outcome has been reported.  ** Anaphylactic-type reactions can be fatal.  ***Seizure is occasionally associated with allergic reactions.  **** Postmarketing complications reported for extravasation included local soft tissue toxicity, swelling, pain, cellulitis, and necrosis including skin necrosis.</p>		

#### 4.9) Overdose:

Total doses of 2.4 – 3.5 g/m<sup>2</sup> etoposide, administered intravenously over three days, have resulted in severe mucositis and myelotoxicity. Metabolic acidosis and cases of serious hepatic toxicity have been reported in patients receiving higher than recommended intravenous doses of etoposide. Similar toxicities can be expected with oral formulation.

A specific antidote is not available. Treatment should therefore be symptomatic and supportive, and patients should be closely monitored.

Etoposide and its metabolites are not dialysable.

### 5) Pharmacological Properties:

#### 5.1) Pharmacodynamic Properties:

The main effect of etoposide appears to be at the late S and early G<sub>2</sub> portion of the cell cycle in mammalian cells. Two dose-dependent responses are seen: At high concentrations (10 mcg/ml or more), cells entering mitosis are lysed; at low concentrations (0.3 to 10 mcg/ml), cells are inhibited from entering prophase. Microtubule assembly is not affected. The predominant macromolecular effect of etoposide seems to be the rupture of the double strand by an interaction with DNA-topoisomerase II or by the formation of free radicals. Etoposide has been shown to cause metaphase arrest in chick fibroblasts.

#### 5.2) Pharmacokinetic Properties:

##### *Absorption*

After intravenous infusion, the maximum plasma concentration (C<sub>max</sub>) and area under the plasma concentration vs. time curve (AUC) values exhibit marked intra- and inter-subject variability.

##### *Distribution*

The mean volumes of distribution at steady state range from 18 to 29 liters. Etoposide shows low penetration into the cerebrospinal fluid (CSF). *In vitro*, etoposide is highly protein bound (97%) to human plasma proteins.

Etoposide binding ratio correlates directly with serum albumin in cancer patients and normal volunteers. Unbound fraction of etoposide correlates significantly with bilirubin in cancer patients.

##### *Biotransformation*

The hydroxyacid metabolite [4' dimethyl-epipodophyllic acid-9-(4,6 O-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. In addition, O-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

##### *Elimination*

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 a terminal elimination ranging from 4 to 11 hours.

Total body clearance values range from 33 to 48 ml/min or 16 to 36 ml/min/m<sup>2</sup> and, like the terminal elimination half-life, are independent of dose over a range 100 to 600 mg/m<sup>2</sup>. After intravenous administration of <sup>14</sup>C etoposide (100 to 124 mg/m<sup>2</sup>), mean recovery of radioactivity in the urine was 56% (45% of the dose was excreted as etoposide) and faecal recovery of radioactivity was 44% of the administered dose at 120 hours.

#### *Linearity/non-linearity*

Total body clearance and the terminal elimination half-life are independent of dose over a range 100 to 600 mg/m<sup>2</sup>. Over the same dose range, the AUC and the C<sub>max</sub> values increase linearly with dose.

#### *Renal impairment*

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

#### *Hepatic impairment*

In adult cancer patients with liver dysfunction, total body clearance of etoposide is not reduced.

#### *Elderly population*

Although minor differences in pharmacokinetic parameters between patients ≤ 65 years and > 65 years of age have been observed, these are not considered clinically significant.

#### *Paediatric population*

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<sup>2</sup> or about 35% of the total body clearance over a dose range of 80 to 600 mg/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 in children. In children, elevated SGPT levels are associated with reduced drug total body clearance. Prior use of cisplatin may also result in a decrease of etoposide total body clearance in children.

An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children.

#### *Gender*

Although minor differences in pharmacokinetic parameters between genders have been observed, these are not considered clinically significant.

#### *Drug interactions*

In a study of the effects of other therapeutic agents on in vitro binding of <sup>14</sup>C etoposide to human serum proteins, only phenylbutazone, sodium salicylate, and aspirin displaced protein-bound etoposide at concentrations generally achieved in vivo.

### **5.3) Preclinical Safety Data**

### *Chronic toxicity*

Anaemia, leukopenia, and thrombocytopenia were observed in rats and mice, while dogs had mild reversible deterioration of liver and kidney functions. The dose multiple (based on mg/m<sup>2</sup> doses) for these findings at the no-observed adverse-effect-level in the preclinical studies were  $\geq$  approximately 0.05 times compared to the highest clinical dose. Historically, preclinical species have been more sensitive compared to humans towards cytotoxic agents. Testicular atrophy, spermatogenesis arrest, and growth retardation were reported in rats and mice.

### *Mutagenicity*

Etoposide is mutagenic in mammalian cells.

### *Reproductive toxicity*

In animal studies etoposide was associated with dose-related embryo toxicity and teratogenicity.

### *Carcinogenic potential*

Given its mechanism of action, etoposide should be considered a possible carcinogen in humans.

## **6) Pharmaceutical Particulars:**

### **6.1) List of Excipients:**

PEG 300  
Citric acid (anhydrous)  
Benzyl alcohol  
Absolute alcohol  
Polysorbate 80

### **6.2) Incompatibilities:**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Plastic devices made of acrylic or ABS polymers have been reported to crack when used with undiluted Etoposide 20 mg/ml, concentrate for solution for infusion. This effect has not been reported with etoposide after dilution of the concentrate for solution for infusion according to instructions.

### **6.3) Shelf Life:**

24 Months

### **6.4) Special Precautions for Storage:**

Store below 30°C. Protect from light. Do not freeze.

### **6.5) Nature & Contents of Container:**

Etoposide Injection USP is available in a vial containing Etoposide USP 20mg/ml.

### **6.6) Special Precautions for Disposal & Other Handling:**

Handle according to guidelines for Cytotoxics.

Concentrate for solution for infusion must not be used undiluted.

Etoposide should not be mixed with other medicinal products.

Etoposide should be stored out of the sight and reach of children.

Etoposide should only be diluted with sodium chloride 9 mg/ml (0.9 %) solution for injection or 5 % glucose solution. The concentration of etoposide in the reconstituted solution for infusion should not exceed 0.4 mg/ml due to the risk of precipitation.

As with other potentially cytotoxic compounds caution should be exercised when handling etoposide (gloves, mask, overall). Contact with skin or mucosa should be avoided.

Skin reactions associated with accidental exposure to etoposide may occur. If etoposide comes into contact with skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Only for intravenous use.

Unused solution should be discarded.

Syringes, containers, absorbent materials, solution and any other contaminated material should be placed in a designated impervious container and incinerated, in accordance with local procedures.

Only clear solutions practically free from particles should be used.

Cytotoxics should not be handled by pregnant personnel.

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

**7) Marketing Authorisation Holder:**

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N/A