SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Etoposide Accord 20 mg/ml 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 12.5 ml vial contains 250 mg of Etoposide.
Each 20 ml vial contains 400 mg of Etoposide.
Each 25 ml vial contains 500 mg of Etoposide.
Each 50 ml vial contains 1000 mg of Etoposide.

Excipients with known effect:
Benzyl alcohol: 30 mg/ml
Ethanol, anhydrous: 240.64 mg/ml

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for Solution for infusion.

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

pH: 3.0 - 4.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Hodgkin's lymphoma
Etoposide Accord 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 Accord 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 Accord 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 Accord 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 Accord is indicated in combination with other approved chemotherapeutic agents for the treatment of non-epithelial ovarian cancer in adults. Etoposide Accord is indicated for the treatment of platinum-resistant/refractory epithelial ovarian cancer in adults.

4.2 Posology and method of administration

Etoposide Accord should only be administered and monitored under the supervision of a qualified physician experienced in the use of anti-neoplastic medicinal products (see section 4.4).

Adult population
The recommended dose of etoposide in adult patients is 50 to100 mg/m^2/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 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 (see section 4.4) which may have compromised bone marrow reserve. The doses after the initial dose should be adjusted if neutrophil count is below 500 cells/mm^3 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^3, 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 preparation of etoposide. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If Etoposide Accord 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).

Paediatric population

This medicinal product contains Benzyl alcohol. For warnings and precautions to be considered prior to the start of the treatment cycle (see section 4.4).

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

Etoposide Accord in paediatric patients has been used in the range of 75 to 150 mg/m^2/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.

Elderly population
The dosage does not need to be adjusted in elderly patients (age > 65 years old), other than based on renal function (see section 5.2).

Renal impairment

In patients with renal impairment 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 (see section 4.4).Subsequent dosing in moderate and severe renal impairment should be based on patient tolerance and clinical effect (see section 4.4).
Since etoposide and its metabolites are not dialyzable, it can be administered pre- and post-haemodialysis (see section 4.9).

Method of administration
Etoposide is administered by slow intravenous infusion (usually over a 30 to 60 minute period) (see section 4.4).

For instructions on 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 in section 6.1.

Lactation (see section 4.6)

Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients (see section 4.5).

4.4 Special warnings and precautions for use

Etoposide should only be administered and monitored 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 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 physician. 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

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 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.

Secondary leukaemia

The occcurrence of acute leukemia, which can occur with or without myelodysplastic syndrome, has been described in patients 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, pyrexia, 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. 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.

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 administration of etoposide. 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, etoposide 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 (2220 mg/m2 or 60 mg/kg) Etoposide Accord and total body irradiation were used for haematopoietic stem cell transplantation. Renal function should be evaluated prior to and after Etoposide Accord 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
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 (see section 4.6).

Excipient (s) that the clinician should be aware of :
Ethanol
Etoposide Accord contains 30.5% alcohol (ethanol), which corresponds to 240.64 mg of ethanol per ml of concentrate i.e up to 1.2 gm of ethanol per 5 ml vial, equivalent to 30 ml of beer or 12.55 ml of wine and up to 3 gm of ethanol per 12.5 ml vial, equivalent to 75 ml of bear or 31.4 ml of wine.

There is a health risk to hepatic patients, alcoholics, epileptics, patients with organic brain diseases, pregnant women, breastfeeding women, and children, amongst others. The effect of other drugs may be reduced or increased.

Benzyl alcohol
Etoposide Accord contains benzyl alcohol. Benzyl alcohol may cause allergic reactions. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children.
Should not be given to newborn babies (up to 4 weeks old).
Should not be used for more than a week in young children (less than 3 years old).
Caution should be exercised in pregnant or breast-feeding patients or 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”).

Polysorbate 80
Etoposide Accord contains polysorbate 80. In newborn 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 medicinal products and other forms of interaction

Effects of other drugs on the pharmacokinetics of etoposide

High dose cyclosporin , resulting in plasma 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 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 drugs

Co-administration of antiepileptic drugs and Etoposide Accord can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.

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 (see section 4.3).

Prior or concurrent use of other drugs with similar myelosuppressant action as etoposide 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

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 (see section 5.3). Given the mutagenic potential of etoposide, an effective contraceptive is required for both male and female patients during treatment and up to 6 months after ending treatment (see section 4.4). Genetic consultation is recommended if the patient wishes to have children after ending 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 (see section 5.3). In general etoposide can cause fetal harm when administered to pregnant women. Etoposide Accord 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 the drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, 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. A decision must be made whether to discontinue breast-feeding or to discontinue Etoposide Accord, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman (see section 4.3).

Benzyl alcohol is probably excreted into breast milk and can be orally absorbed by the infant.

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 and use machines

No studies on the effects on the ability to drive and use machines have been performed . 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

Summary of the safety profile
Dose limiting bone marrow suppression is the most significant toxicity associated with etoposide therapy. In clinical studies in which etoposide was administered as a single agent at a total dose of ≥450 mg/m2 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 summary of adverse reactions
The following adverse reactions have been reported from etoposide clinical studies and post-marketing experience. These adverse reactions are presented by system organ class and frequency, which is defined by the following categories: *very common* (≥1/10), *common* (≥1/100 , <1/10), *uncommon* (≥1/1,000 **,** <1/100) , *rare* (≥1/10,000 , <1/1,000) ,*not known* (cannot be estimated from the available data)

System Organ Class	**Frequency**	**Adverse Reaction (MedDRA Terms)**
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 , leucopenia, myelosuppression*, neutropenia, thrombocytopenia
Immune system disorders	common	anaphylactic reactions**
	not known	angioedema, bronchospasm
Metabolism and nutrition disorders	not known	tumour lysis syndrome
	common	dizziness

Nervous system disorders	uncommon	neuropathy peripheral
	rare	cortical blindness transient, neurotoxicities (*e.g.*, somnolence and fatigue), optic neuritis, seizure***
Cardiac disorders	common	arrythmia, 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 esophagitis)
	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-Johnsons syndrome, toxic epidermal necrolysis
Renal and urinary disorders	not known	acute renal failure
Reproductive system and breast disorders	not known	infertility
General disorders and administration site conditions	very common	asthenia, malaise
	common	extravasation****, phlebitis
	rare	pyrexia

*Myelosuppression with fatal outcome has been reported
**Anaphylactic 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.
*****including opportunistic infections like *pneumocystis jirovecii* pneumonia.

Description of selected adverse reactions

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

Hematological 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.

Leucopenia and severe leucopenia (less than 1,000 cells/mm^3) were observed in91% 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 toal baldness, was observed in upto 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.

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 agents, 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.

Acute renal failure
Reversible acute renal failure has been reported in postmarketing experience (see section 4.4).

Metabolic complications
Tumour lysis syndrome (sometimes fatal) has been reported following the use of etoposide in association with other chemotherapeutic drugs (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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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. 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

Pharmacotherapeutic group: Cytostatics, plant alkaloids and other natural products, podophyllotoxin derivatives
ATC code: L01CB01

Mechanism of action
The main effect of etoposide appears to be at the late S and early G_2 portion of the cell cycle in mammalian cells. Two dose-dependent responses are seen: At high concentrations (10 mcg/ml or more), lysis can be observed of the cells entering mitosis; at low concentrations (0.3 to10 mcg/ml), the cells are inhibited from entering the 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

DNAtopoisomerase II or by the formation of free radicals. Etoposide has been shown to cause metaphase arrest in chick fibroblasts.

5.2 Pharmacokinetic properties

Distribution
The mean volumes of distribution at steady state range from 18 to 29 liters . Etoposide shows low penetration into the 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 (see section 4.4). Unbound fraction of etoposide correlates significantly with bilirubin in cancer patients.

Following intravenous infusion, the Cmax and AUC values exhibit marked intra- and inter-subject variability.

Biotransformation
The hydroxyacid metabolite [4' dimethyl-epipodophyllic acid-9-(4,6 0-ethylidene-β-Dglucopyranoside)], 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 sulphate 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 terminal elimination half-life ranging from of 4–11 hours. The total body clearance values range from 33 to 48 mL/min or 16–36 ml/minute/m^2 and, like the terminal elimination half-life, are independent of dose over a range of 100-600 mg/m^2. After intravenous administration of 14C etoposide (100 to 124 mg/m^2), 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 adminitered 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^2. 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.

Renal impairment
Patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and higher steady state volume of distribution (see section 4.2).

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/m2 or about 35% of the total body clearance over a dose range of 80 to 600 mg/m2. Etoposide, therefore, is cleared by both renal and nonrenal processes, ie, 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 14C etoposide to human serum proteins, only phenylbutazone, sodium salicylate, and acetylsalicylic acid displaced protein-bound etoposide at concentrations generally achieved in vivo (see section 4.5).

5.3 Preclinical safety data

Chronic toxicity
Anaemia, leucopenia, 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/m2 doses) for these findings at the no-observed adverse-effect-level in the preclinical studies were ≥ 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 embryotoxicity 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

Citric acid, anhydrous
Benzyl alcohol
Polysorbate 80
Macrogol 300
Ethanol, anhydrous

6.2 Incompatibilities

Etoposide Accord must not be mixed with other drugs when administered.

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

6.3 Shelf life

Unopened vial: 3 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 % w/v) and glucose injection (5% w/v) for up to 96 hours and 48 hours at temperature 20°- 25° C respectively.

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. Do not store the diluted product in a refrigerator (2-8 °C) as this might cause precipitation.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.
Do not refrigerate or freeze.

For storage precaution of diluted medicinal product, refer section 6.3

6.5 Nature and contents of container

The concentrate is filled in 5 ml, 10 ml, 12.5 ml, 20 ml, 25 ml or 50 ml clear glass vials with Teflon rubber stoppers and aluminium flip-off seals.

Pack sizes:
1 × 5 ml vial
1 × 10 ml vial
1 × 12.5 ml vial
1 × 20 ml vial
1 × 25 ml vial
1 × 50 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Care must be taken whenever handling cytostatic products. Always take steps to prevent exposure. As with other potentially toxic compounds, caution should be exercised in handling and preparing etoposide solutions. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If etoposide should contact the skin or mucosa, immediately wash the skin with soap and water and flush the mucosa with water.

If solution showing sign of precipitation or contains visible particles, it should be discarded.Etoposide Accord must be diluted prior to use with Sodium chloride injection (0.9 % w/v) or glucose injection (5% w/v) to concentration of 0.2 mg/mL (i.e 1 ml of concentrate in 100 ml of diluent) to 0.4 mg/mL (i.e 2 ml of concentrate in 100 ml of diluent). The concentration of diluted solution should not exceed 0.4 mg/mL because of risk of precipitation. During preparation and reconstitution a strictly aseptic technique should be used.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<to completed nationally>

8. MARKETING AUTHORISATION NUMBER(s)

<to completed nationally>

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

2024-02-05