Annex III

Product information

Note:

This product information is the outcome of the referral procedure to which this Commission decision relates.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ETOPOPHOS and associated names (see Annex 1) 100 mg powder for solution for infusion
ETOPOPHOS and associated names (see Annex 1) 1000 mg powder for solution for infusion

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 113.6 mg etoposide phosphate equivalent to 100 mg etoposide.
Each vial contains 1136 mg etoposide phosphate equivalent to 1000 mg etoposide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Testicular cancer

ETOPOPHOS and associated names 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

ETOPOPHOS and associated names is indicated in combination with other approved chemotherapeutic agents for the treatment of small-cell lung cancer in adults.

Hodgkin's lymphoma

ETOPOPHOS and associated names 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

ETOPOPHOS and associated names 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

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

Gestational trophoblastic neoplasia

ETOPOPHOS and associated names 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

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

ETOPOPHOS and associated names is indicated for the treatment of platinum-resistant/refractory epithelial ovarian cancer in adults.

4.2 Posology and method of administration

ETOPOPHOS and associated names 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 ETOPOPHOS and associated names in adult patients is 50 to 100 mg/m^2/day (etoposide equivalent) 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 preparing the solution of ETOPOPHOS and associated names. Skin reactions associated with accidental exposure to ETOPOPHOS and associated names may occur. The use of gloves is recommended. If ETOPOPHOS and associated names solution contacts the skin or mucosa, immediately wash the skin with soap and water and flush the mucosa with water (see section 6.6).

Elderly population

No dosage adjustment is necessary in elderly patients (age > 65 years old), other than based on renal function (see section 5.2).

Paediatric population

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

ETOPOPHOS and associated names in paediatric patients has been used in the range of 75 to 150 mg/m^2/day (etoposide equivalent) 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 ETOPOPHOS and associated names 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.

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 Phosphate
>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 phosphate is administered by slow intravenous infusion (usually over a 30 to 60 minute period) (see section 4.4).

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 in section 6.1.

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

Lactation (see section 4.6)

4.4 Special warnings and precautions for use

ETOPOPHOS and associated names 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 ETOPOPHOS and associated names 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 ETOPOPHOS and associated names 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 ETOPOPHOS and associated names therapy. Fatal myelosuppression has been reported following etoposide phosphate administration. Patients being treated with ETOPOPHOS and associated names 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 ETOPOPHOS and associated names: 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. ETOPOPHOS and associated names 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 ETOPOPHOS and associated names.

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 ETOPOPHOS and associated names, manifested by chills, pyrexia, tachycardia, bronchospasm, dyspnoea and hypotension, which can be fatal. Treatment is symptomatic. ETOPOPHOS and associated names should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

Hypotension

ETOPOPHOS and associated names 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 ETOPOPHOS and associated names. 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.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other drugs on the pharmacokinetics of etoposide phosphate

High dose ciclosporin, 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 compared to etoposide alone.

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

Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy, and other enzyme-inducing antiepileptic therapy may be associated with increased ETOPOPHOS and associated names clearance and reduced efficacy.

As etoposide phosphate is converted *in vivo* to etoposide by phosphorylation, caution should be exercised when administering etoposide phosphate with drugs that are known to inhibit phosphatase activity as such combination may reduce efficacy of etoposide phosphate.

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

Effect of etoposide phosphate on the pharmacokinetics of other drugs

Co-administration of antiepileptic drugs and ETOPOPHOS and associated names 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 phosphate 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. ETOPOPHOS and associated names 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 drug is used during pregnancy, or if the patient becomes pregnant while receiving this 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 ETOPOPHOS and associated names. A decision must be made whether to discontinue breast-feeding or to discontinue ETOPOPHOS and associated names, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman (see section 4.3).

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 phosphate 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 ETOPOPHOS and associated names therapy. In clinical studies in which ETOPOPHOS and associated names was administered as a single agent 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 summary of adverse reactions

The following adverse reactions were reported from ETOPOPHOS and associated names 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
Nervous system disorders	common	dizziness
	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
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.		

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 ETOPOPHOS and associated names therapy.

Haematological Toxicity

Myelosuppression (see section 4.4) with fatal outcome has been reported following administration of etoposide phosphate. 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 to14 days after administration of etoposide phosphate 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 in 91% and 17%, respectively, for etoposide phosphate. Thrombocytopenia and severe thrombocytopenia (less than 50,000 platelets/mm^3) were seen in 23% and 9% respectively, for etoposide phosphate. Reports of fever and infection were also very common in patients with neutropenia treated with etoposide phosphate. Bleeding has been reported.

Gastrointestinal Toxicity

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

Alopecia

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

Hypotension

Transient hypotension following rapid intravenous administration has been reported in patients treated with etoposide phosphate and has not been associated with cardiac toxicity or electrocardiographic changes. Hypotension usually responds to cessation of infusion of etoposide phosphate 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 phosphate, episodes of hypertension have been reported. If clinically significant hypertension occurs in patients receiving etoposide phosphate, appropriate supportive therapy should be initiated.

Hypersensitivity

Anaphylactic reactions have been reported to occur during or immediately after intravenous administration of etoposide phosphate. 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 phosphate.

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 ETOPOPHOS and associated names in 7 clinical studies) of patients treated with ETOPOPHOS and associated names. 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 also been reported with etoposide phosphate. 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 phosphate 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 g/m^2 to 3.5 g/m^2 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 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

Etoposide phosphate is metabolised *in vivo* into the active substance etoposide by a process of dephosphorylation. The mechanism of action of etoposide phosphate is considered to be the same as that of etoposide.

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), 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 either intravenous infusion or oral capsule administration, the C_{max} and 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 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.

Biotransformation

The hydroxyacid metabolite [4' dimethyl-epipodophyllic acid-9-(4,6 0-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 terminal elimination half-life ranging from 4 to 11 hours. Total body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min/m^2 and, like the terminal elimination half-life, are independent of dose over a range 100 to 600 mg/m^2. After intravenous administration of ^{14}C 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 (C_{max}) 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/m^2 or about 35% of the total body clearance over a dose range of 80 to 600 mg/m^2. 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 ^{14}C etoposide to human serum proteins, only phenylbutazone, sodium salicylate, and aspirin 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/m^2 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 phosphate should be considered a possible carcinogen in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Dextran 40

[To be completed nationally]

6.2 Incompatibilities

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

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

Not all pack sizes may be marketed.

[To be completed nationally]

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 ETOPOPHOS and associated names solutions. Skin reactions associated with accidental exposure to ETOPOPHOS and associated names may occur. The use of gloves is recommended. If etoposide phosphate should contact the skin or mucosa, immediately wash the skin with soap and water and flush the mucosa with water.

ETOPOPHOS and associated names solutions must be prepared under aseptic conditions.

Preparation of ETOPOPHOS and associated names 100 mg powder for solution for infusion

Before use the content of each vial must be reconstituted with 5 ml or 10 ml of:

- water for injections or,
- 5% glucose solution or,
- 0.9 % sodium chloride solution.

This will yield a reconstituted stock solution containing 20 mg/ml or 10 mg/ml etoposide.

After reconstitution, the solution can be administered without further dilution or it can be further diluted with 5% glucose solution or 0.9% sodium chloride solution to obtain concentrations as low as 0.1 mg/ml etoposide.

The products administered by parenteral route must be visually examined to check for any particulates or discoloration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

ETOPOPHOS and associated names is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation of ETOPOPHOS and associated names 1000 mg powder for solution for infusion

ETOPOPHOS and associated names 1000 mg is intended to be handled by pharmaceutical staff in central hospital units for the preparation of cytostatics. All steps of preparation must be carried out under Laminar Air Flow conditions. Solutions should be prepared under aseptic conditions. The stopper of the vial should be pierced only once and a sterile transfusion set or any other auxiliary device should be used for withdrawal for the solution. If spikes are used they should be equipped with particle filters or other measures should be taken (*e.g.* inline-filters) to ensure that only particle free solutions are administered.

The content of each injection vial of ETOPOPHOS and associated names 1000 mg has to be diluted in 100 ml of:

- water for injections or,
- 5% glucose solution or,
- 0.9% sodium chloride solution.

This will yield a reconstituted stock solution containing 10 mg/ml etoposide.

The resulting stock solution may be administered without further dilution or can be further diluted with 5% glucose solution or 0.9% sodium chloride solution to a final concentration of 0.1 mg/ml etoposide.

The stock solution should be withdrawn under aseptic conditions according to the physician's prescription and transferred to the infusion bottles and/or syringes for the individual patients. Exact measuring must be ensured for withdrawal. The stock solution should be used as soon as possible (see section 6.3).

Products administered by parenteral route must be visually examined to check for any particulates or discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

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

7. MARKETING AUTHORISATION HOLDER

[See Annex 1 - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

[To be completed nationally]

Detailed information on this medicinal product is available on the website of [name of MS Agency link].

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

ETOPOPHOS and associated names 100mg Powder for Solution for Infusion
ETOPOPHOS and associated names 1000mg Powder for Solution for Infusion

[See Annex I - To be completed nationally]

Etoposide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains etoposide 100 mg (as phosphate)
Each vial contains etoposide 1000 mg (as phosphate)

3. LIST OF EXCIPIENTS

Sodium citrate
Dextran 40

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic. Handle with caution.

8. EXPIRY DATE

Exp. Date

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch No.

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial Label (100 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ETOPOPHOS and associated names 100 mg powder for solution for infusion

[See Annex I - To be completed nationally]

Etoposide

2. METHOD OF ADMINISTRATION

Intravenous use.

3. EXPIRY DATE

Expiry Date

4. BATCH NUMBER

Batch No.

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

For single use only.
Cytotoxic. Handle with caution.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial Label (1000 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ETOPOPHOS and associated names 1000 mg powder for solution for infusion

[See Annex I - To be completed nationally]

Etoposide (as phosphate)

2. METHOD OF ADMINISTRATION

Intravenous use.

3. EXPIRY DATE

Expiry Date

4. BATCH NUMBER

Batch No.

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

Cytotoxic. Handle with caution.

PACKAGE LEAFLET

Package leaflet: Information for the patient

ETOPOPHOS and associated names (see Annex I) 100 mg powder for solution for infusion
ETOPOPHOS and associated names (see Annex I) 1000 mg powder for solution for infusion

Etoposide phosphate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ETOPOPHOS and associated names is and what it is used for

The name of this medicine is ETOPOPHOS and associated names. Each vial contains etoposide phosphate equivalent to etoposide 100 mg or 1000 mg as the active ingredient.

Etoposide belongs to the group of medicines called cytostatics which are used in the treatment of cancer.

ETOPOPHOS and associated names is used in the treatment of certain types of cancers in adults:

- testicular cancer
- small cell lung cancer
- cancer of the blood (acute myeloid leukaemia)
- tumour in the lymphatic system (Hodgkin's lymphoma, non-Hodgkin's lymphoma)
- reproductive system cancers (gestational trophoblastic neoplasia and ovarian cancer)

ETOPOPHOS and associated names is used in the treatment of certain types of cancers in children:

- cancer of the blood (acute myeloid leukaemia)
- tumour in the lymphatic system (Hodgkin's lymphoma, non-Hodgkin's lymphoma)

The exact reason why you have been prescribed ETOPOPHOS and associated names is best discussed with your doctor.

2. What you need to know before you are given ETOPOPHOS and associated names

Do not take ETOPOPHOS and associated names

- If you are allergic to etoposide or any of the other ingredients of this medicine (listed in section 6).
- If you have recently been given a live vaccine, including Yellow fever vaccine.

- If you are breast-feeding or planning to breast-feed.

If any of the above affects you, or if you are unsure if they do, tell your doctor who will be able to advise you.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before receiving ETOPOPHOS and associated names

- if you have any **infections**.
- if you have had **radiotherapy or chemotherapy** recently.
- if you have low levels of a protein called **albumin** in your blood.
- if you have liver or kidney problems.

Effective anti-cancer treatment can destroy cancer cells rapidly in large numbers. On very rare occasions this may cause harmful amounts of substances from these cancer cells to be released into the blood. If this happens it can cause problems with the liver, kidney, heart or blood, which may result in death if not treated.

In order to prevent this, your doctor will need to do regular blood tests to monitor the level of these substances during treatment with this medicine.

This medicine can cause a reduction in the level of some blood cells, which could cause you to suffer from infections, or may mean that your blood doesn't clot as well as it should if you cut yourself. Blood tests will be taken at the start of your treatment, and before each dose you take, to make sure that this isn't happening.

If you have reduced liver or kidney function, your doctor may also want you to take regular blood tests to monitor these levels.

Other medicines and ETOPOPHOS and associated names

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

This is especially important

- if you are taking a medicine called ciclosporin (a drug used to reduce the activity of the immune system).
- if you are being treated with cisplatin (a medicine used to treat cancer).
- if you are taking phenytoin or any other medicines used to treat epilepsy.
- if you are taking warfarin (a medicine used to prevent blood clots from forming).
- if you have recently been given any live vaccines.
- if you are taking phenylbutazone, sodium salicylate, or aspirin.
- if you are taking any anthracyclines (a group of medicines used to treat cancer).
- if you are taking any drugs with a similar mechanism of action as ETOPOPHOS and associated names.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

ETOPOPHOS and associated names must not be used during pregnancy unless clearly indicated by your doctor.

You must not breastfeed while you are receiving ETOPOPHOS and associated names.

Both male patients and female patients of child-bearing age should use an effective contraceptive method (*e.g.*, the barrier method or condoms) during treatment and for at least 6 months after the end of treatment with ETOPOPHOS and associated names.

Male patients treated with ETOPOPHOS and associated names are advised not to father a child during treatment and for up to 6 months after treatment. In addition, men are advised to seek counselling on sperm preservation before starting treatment.

Both male and female patients who are considering having a child after having treatment with ETOPOPHOS and associated names should discuss this with their doctor or nurse.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. However, if you feel tired, sick to your stomach, dizzy or light-headed you should not do so until you have discussed it with your doctor.

ETOPOPHOS and associated names contains

To be completed nationally

3. How you will be given ETOPOPHOS and associated names

ETOPOPHOS and associated names will be given to you by a doctor or nurse. It will be given as a slow infusion into a vein. This may take between 30 to 60 minutes.

The dose you receive will be specific to you, which the doctor will calculate. The usual dose, based on etoposide, is 50 to100mg/m^2 body surface area, daily for 5 days in a row or 100 to 120 mg/ m^2 body surface area on days 1, 3 and 5. This course of treatment may then be repeated, depending on the results of blood tests, but this will not be for at least 21 days after the first course of treatment.

For children being treated for cancer of the blood or lymphatic system the dose used is 75 to 150 mg/m^2 body surface area daily for 2 to 5 days.

The doctor may sometimes prescribe a different dose particularly if you are receiving, or have received, other treatments for your cancer or if you have kidney problems.

If you are given more ETOPOPHOS and associated names than you should

As ETOPOPHOS and associated names is given to you by a doctor or nurse, overdose is unlikely. However, if this does occur your doctor will treat any symptoms that follow.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse immediately if you get any of the following symptoms: swelling of your tongue or throat, breathing difficulties, fast heartbeat, flushing of the skin or a rash. These may be signs of a severe allergic reaction.

Severe **liver, kidney or heart damage** from a condition called tumour lysis syndrome, caused by harmful amounts of substances from the cancer cells getting into the blood stream, has been seen sometimes when ETOPOPHOS and associated names is taken along with other drugs used to treat cancer.

Possible side effects experienced with ETOPOPHOS and associated names that are;

Very common side effects (affecting more than 1 in 10 people)

- blood disorders (this is why you will be having blood tests between courses of treatment)
- temporary hair loss
- nausea and vomiting
- abdominal pain
- loss of appetite
- changes in skin colour (pigmentation)
- constipation
- feeling weak (asthenia)
- generally feeling unwell (malaise)
- damage to the liver (hepatotoxicity)
- increased liver enzymes
- jaundice (increased bilirubin)

Common side effects (affecting between 1 in 10 and 1 in 100 people)

- acute leukaemia
- irregular heart beat (arrhythmia), or a heart attack (myocardial infarction)
- dizziness
- diarrhoea
- reactions at the site of infusion
- severe allergic reactions
- high blood pressure
- low blood pressure
- sore lips, mouth or throat ulcers
- skin problems such as itching or rash
- inflammation of a vein
- infection

Uncommon side effects (affecting between 1 in 100 and 1 in 1000 people)

- tingling or numbness in hands and feet
- bleeding

Rare side effects (affecting between 1 in 1,000 and 1 in 10,000 people)

- acid reflux
- flushing
- difficulty swallowing
- a change in the way things taste
- severe allergic reactions
- convulsions (seizure)
- fever
- sleepiness or tiredness
- breathing problems
- temporary blindness
- serious reactions of the skin and/or mucous membranes which may include painful blisters and fever, including extensive detachment of the skin (Stevens-Johnson syndrome and toxic epidermal necrolysis)
- a sunburn-like rash that may occur on skin that has previously been exposed to radiotherapy and can be severe (radiation recall dermatitis)

Not known (frequency cannot be estimated from the available data)

- tumour lysis syndrome (complications of substances released from treated cancer cells entering the blood)
- face and tongue swelling
- infertility
- difficulty breathing

Reporting of side effects

1.

2. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

3.

5. How to store ETOPOPHOS and associated names

To be completed nationally

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

6. Contents of the pack and other information

What ETOPOPHOS and associated names contains

- The active substance is etoposide phophate. Each vial contains etoposide phosphate equivalent to etoposide 100 mg or 1000 mg.
- The other ingredients are Sodium citrate and Dextran 40.

To be completed nationally

What ETOPOPHOS and associated names looks like and contents of the pack

ETOPOPHOS and associated names is a white to off-white dry powder. It is supplied in a glass vial with a butyl rubber stopper and flip-off aluminium seal.

To be completed nationally

Marketing Authorisation Holder and Manufacturer

See Annex I - To be completed nationally

Corden Pharma Latina S.p.A.
Via del Murillo Km 2.800
04013 Sermoneta
Latina, Italy
<{tel}>
<{fax}>
<{e-mail}>

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

To be completed nationally

The following information is intended for healthcare professionals only:

Preparation of Intravenous Solution

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

ETOPOPHOS and associated names solutions must be prepared under aseptic conditions.

Before use the content of each vial must be reconstituted with 5 ml or 10 ml of:
- water for injections or,
- 5% glucose solution or,
- 0.9 % sodium chloride solution.

This will yield a reconstituted stock solution containing 20 mg/ml or 10 mg/ml etoposide.
After reconstitution, the solution can be administered without further dilution or it can be further diluted with 5% glucose solution or 0.9% sodium chloride solution to obtain concentrations as low as 0.1 mg/ml etoposide.

Only use clear solutions. Cloudy or discolored solutions must be discarded.

ETOPOPHOS and associated names is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation of ETOPOPHOS and associated names 1000 mg powder for solution for infusion

ETOPOPHOS and associated names 1000 mg is intended to be handled by pharmaceutical staff in central hospital units for the preparation of cytostatics. All steps of preparation must be carried out under Laminar Air Flow conditions. Solutions should be prepared under aseptic conditions. The stopper of the vial should be pierced only once and a sterile transfusion set or any other auxiliary device should be used for withdrawal for the solution. If spikes are used they should be equipped with particle filters or other measures should be taken (*e.g.* inline-filters) to ensure that only particle free solutions are administered.

The content of each injection vial of ETOPOPHOS and associated names 1000 mg has to be diluted in 100 ml of:

- water for injections or,
- 5% glucose solution or
- 0.9% sodium chloride solution.

This will yield a reconstituted stock solution containing 10 mg/ml etoposide.

The resulting stock solution may be administered without further dilution or can be further diluted with 5% glucose solution or 0.9% sodium chloride solution to a final concentration 0.1 mg/ml etoposide.

The stock solution should be withdrawn under aseptic conditions according to the physician's prescription and transferred to the infusion bottles and/or syringes for the individual patients. Exact measuring must be ensured for withdrawal. The stock solution should be used as soon as possible.

ETOPOPHOS and associated names should not be physically mixed with any other drug.

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

Administration and Dosage

ETOPOPHOS and associated names is administered 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. ETOPOPHOS and associated names SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION.

The recommended dose of ETOPOPHOS and associated names is 50 to 100 mg/m^2/day (etoposide equivalent) 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 radiation therapy or chemotherapy which may have compromised bone marrow reserve.

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

Care should be taken to avoid extravasation.

Elderly

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

Paediatric use

ETOPOPHOS and associated names in paediatric patients has been used in the range of 75 to 150 mg/m^2/day (etoposide equivalent) for 2 to 5 days in combination with other antineoplastic agents. The treatment regimen should be chosen according to the local standard of care.

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 Phosphate**
>50 mL/min	100% of dose
15-50 mL/min	75% of dose

Subsequent dosing should be based on patient tolerance and clinical effect. In patients with creatinine clearance less than 15 mL/min and on dialysis further dose reduction should be considered.