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medac

Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. **Why?**

Summary of Product Characteristics last updated on the eMC: 05/12/2011

SPC Eposin concentrate for solution for infusion 20mg/ml

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Legal Categories

POM – Prescription Only Medicine

Active Ingredients/Generics

etoposide

1. NAME OF THE MEDICINAL PRODUCT

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Eposin, concentrate for solution for infusion 20 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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1 vial with 5 ml concentrate for solution for infusion contains 100 mg etoposide, Ph.Eur.

1 vial with 25 ml concentrate for solution for infusion contains 500 mg etoposide, Ph.Eur.

1 ml concentrate for solution for infusion contains 20 mg etoposide.

Excipients:

1 ml concentrate for solution for infusion contains 30 mg benzyl alcohol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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Concentrate for solution for infusion (to dilute).

4. CLINICAL PARTICULARS

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4.1 Therapeutic indications

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Etoposide is indicated for the management of:

- testicular tumours in combination with other chemotherapeutic agents

- small cell lung cancer, in combination with other chemotherapeutic agents

- monoblastic leukemia (AML M5) and acute myelomonoblastic leukemia (AML M4) when standard therapy has failed (in combination with other chemotherapeutic agents).

4.2 Posology and method of administration

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Eposin, concentrate for solution for infusion 20 mg/ml must be diluted immediately prior to use with either 5% dextrose in water, or 0.9% sodium chloride solution to give a final concentration of 0.2 to 0.4 mg/ml. At higher concentrations precipitation of etoposide may occur.

The usual dose of etoposide, in combination with other approved chemotherapeutic agents, ranges from 100-120 mg/m²/day via continuous infusion over 30 minutes for 3-5 days, followed by a resting period of 10-20 days.

Generally 3 to 4 chemotherapy cycles are administered. Dose and amount of cycles should be adjusted to the level of bone marrow suppression and the reaction of the tumour.

In patients with renal function impairment the dose should be adjusted.

Etoposide is intended for intravenous administration only.

To prevent the occurrence of hypotension, the infusion should be given over at least 30 minutes.

Dosage adjustment in case of renal function impairment.

In patients with a measured creatinine clearance of greater than 50 ml/minute, no initial dose modification is required. In patients with a measured creatinine clearance of 15-50 ml/minute, 75% of the initial recommended etoposide dose should be administered. Although specific data are not available in patients with a measured creatinine clearance less than 15 ml/minute, further dose reduction should be considered. Subsequent etoposide dosing should be based on patient tolerance and clinical effect.

4.3 Contraindications

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• Severe myelosuppression, unless when this is caused by the underlying disease.

• Severe hepatic impairment.

• Hypersensitivity to etoposide or to any of the excipients.

• Breast-feeding (see section 4.6).

• Patients with severe renal impairment (creatinine clearance < 15 ml/min).

• This product contains benzyl alcohol. Must not be given to premature babies or neonates.

4.4 Special warnings and precautions for use

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If etoposide is to be used as part of a chemotherapy regimen, the physician should weigh the necessity to use the drug against the potential risk and side effects (see "Undesirable effects").

Etoposide should only be administered under strict observation by a doctor specialised in oncology, preferable in institutions specialised in such therapies. It should not be injected intraarterially, intrapleurally, or intraperitoneally. Eposin vials are intended for intravenous administration only. Extravasation should be strictly avoided. If extravasation

occurs, the administration should be terminated immediately and restarted in another vein. Cooling, flooding with normal saline and local infiltration with corticosteroids have been reported as therapeutic measures.

Etoposide should be given by slow intravenous infusion over a period of 30-60 minutes; rapid intravenous administration may cause hypotension.

One should be aware of the possible occurrence of an anaphylactic reaction manifested by flushing, tachycardia, bronchospasm, and hypotension (see "Undesirable effects" section).

The substance etoposide can have genotoxic effects. Therefore, men being treated with etoposide are advised not to father a child during and up to 6 months after treatment and to seek advice on cryoconservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with etoposide. Women should not become pregnant during treatment with etoposide, or for at least 6 months after treatment with etoposide.

The occurrence of a leucopenia with a leucocyte count below 2,000/mm³ is an indication to withhold further therapy until the blood counts have sufficiently recovered (usually after 10 days).

The administration of etoposide should be terminated at the occurrence of thrombocytopenia.

Bacterial infections should be treated before the start of the therapy with etoposide. Great care should be taken on giving etoposide to patients who have, or have been exposed to infection with herpes zoster.

The occurrence of bone marrow depression, caused by radiotherapy or chemotherapy, necessitates a resting period. It is advised not to restart treatment with etoposide until the platelet count has reached at least 100,000/mm³.

Peripheral blood counts and liver function should be monitored.

Patients with a low serum albumin concentration may have an increased risk of etoposide toxicity.

The occurrence of acute leukemia, which can occur with or without myelodysplastic syndrome, has been described in patients that were treated with etoposide in association with other antineoplastic drugs, e.g. bleomycin, cisplatin, ifosfamide, methotrexate.

Experimentally confirmed cross-resistance between anthracyclines and etoposide has been reported.

This product contains 24% m/v of ethanol. Each 5 ml vial contains up to 1.2 g of alcohol, each 25 ml vial contains up to 6 g of alcohol. This can be harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for children and pregnant women. Alcohol also may modify or increase the effect of other medicines.

This product contains benzyl alcohol. May cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

Handling precautions: see section 6.6 "Special precautions for disposal and other handling".

4.5 Interaction with other medicinal products and other forms of interaction

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The action of oral anticoagulants can be increased.

Phenylbutazone, sodium salicylate and salicylic acid can affect protein binding of etoposide.

Etoposide may potentiate the cytotoxic and myelosuppressive action of other drugs.

The coadministration of etoposide and high-dose cyclosporine may greatly increase etoposide serum concentrations and risk of adverse reactions. This is probably a result of decreased clearance and increased volume of distribution of etoposide when cyclosporine serum concentration exceeds 2000 ng/ml. The dose of etoposide should be reduced by 50% with concurrent use of high-dose cyclosporine infusion.

Co-administration of myelosuppressive drugs (such as cyclophosphamide, BCNU, CCNU, 5-fluorouracil, vinblastine, doxorubicin and cisplatin) may increase the effect of etoposide and/or co-administered drug on the bone marrow.

Experimentally confirmed cross-resistance between anthracyclines and etoposide has been reported.

The occurrence of acute leukemia, which can occur with or without preleukemic phase has been reported in patients treated with etoposide in association with other antineoplastic drugs, e.g. bleomycin, cisplatin, ifosfamide, methotrexate.

4.6 Pregnancy and lactation

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Pregnancy

There is no experience with the use of etoposide during the first trimester of human pregnancy and very limited experience (isolated case reports) during the second and third trimester. Etoposide was teratogenic in animals (see section 5.3). On the basis of the results from animal studies and the mechanism of action of the substance, men being treated with etoposide are advised not to father a child during and up to 6 months after treatment. The use of etoposide during pregnancy, in particular during the first trimester, is advised against. A waiting period of at least 6 months after treatment with etoposide is recommended. In every individual case, the expected advantages of the treatment should be weighed against the possible risk for the embryo/foetus.

Lactation

Etoposide is excreted into human breast milk. Breast-feeding is contraindicated during treatment with etoposide.

4.7 Effects on ability to drive and use machines

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Due to the frequent occurrence of nausea and vomiting, driving and operation of machinery should be discouraged.

4.8 Undesirable effects

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The following frequencies have been used:

• Very common (>1/10)

• Common (>1/100, <1/10)

• Uncommon (>1/1,000, <1/100)

• Rare (>1/10,000, <1/1,000)

• Very rare (<1/10,000)

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

System Organ Class	Very common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1,000)	Very rare (<1/10,000)	Not known
Infections and infestations						Infections have been reported in patients with bone marrow depression
Neoplasms benign and malignant		Leukemia secondary to oncology chemo-therapy*				Acute promyelocytic leukemia
Blood and lymphatic systems disorders	Myelosuppression**, leucopenia, thrombo-cytopenia, anaemia					
Immune system disorders		Anaphylactic-like reactions***				
Metabolism and nutrition disorders	Anorexia			Hyperuricaemia		
Nervous system disorders	Central nervous system disorders (fatigue, drowsiness)		Peripheral neuropathies	Insults, paresthesiae, optic neuritis, taste disturbance		
Eye disorders				Reversible loss of vision, transient cortical blindness		
Cardiac disorders			Arrhythmia, myocardial infarction,			

			cyanosis			
Vascular disorders		Hypotension[%], haemorrhage (in patients with severe myelosuppression)		Phlebitis[+]		
Respiratory, thoracic and mediastinal disorders			Bronchospasm, coughing, laryngospasm	Apnoea, interstitial pneumonitis or pulmonary fibrosis		
Gastrointestinal disorders	Nausea, vomiting	Abdominal pain, diarrhoea, stomatitis	Mucositis, oesophagitis	Constipation, swallowing disorders (dysphagia)		
Hepatobiliary disorders		Hepatic dysfunction				
Skin and subcutaneous tissue disorders	Reversible alopecia (sometimes progressing to total baldness)		Rash, urticaria, pigmentation and pruritus		Toxic epidermal necrolysis, radiation “recall” dermatitis, hand-foot syndrome	
Renal and urinary disorders	Etoposide has been shown to reach high concentrations in the liver and kidney, thus presenting a potential for accumulation in cases of functional impairment					
General disorders and administration site conditions		Fatigue		Asthenia; after extra-vasation, irritation of soft tissue and inflam-mation occur occasionally.		
Investigations		Bilirubin increased, SGOT increased, alkaline phosphatase increased				

* The risk of secondary leukemia among patients with germ-cell tumours after treatment with etoposide is about 1%. This leukemia is characterised with a relatively short latency period (mean 35 months), monocytic or myelomonocytic FAB subtype, chromosomal abnormalities at 11q23 in about 50% and a good response to chemotherapy. A total cumulative dose (etoposide > 2 g/m²) is associated with increased risk.

Etoposide is also associated with development of acute promyelocytic leukemia (APL). High doses of etoposide (> 4,000 mg/m^2) appear to increase the risk of APL.

** Myelosuppression is dose limiting, with granulocyte nadirs occurring 5 to 15 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 21, and no cumulative toxicity has been reported.

Fatal cases of myelosuppression have been reported.

Infections have been reported in patients with bone marrow depression.

*** Anaphylactic-like reactions characterised by fever, flushing, tachycardia, bronchospasm, and hypotension have been reported (incidence 0.7-2%), also apnoea followed by spontaneous recurrence of breathing after withdrawal of etoposide infusion, increase in blood pressure. The reactions can be managed by cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines and/ or volume expanders as appropriate.

Anaphylactoid-like reactions may occur after the first intravenous administration of etoposide.

Erythema, facial and tongue oedema, coughing, sweating, cyanosis, convulsions, laryngospasm and hypertension have also been observed. The blood pressure usually returns to normal within few hours following cessation of therapy.

% Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. To prevent this rare occurrence, it is recommended that etoposide be administered by slow intravenous infusion over a 30- to 60-minute period. If hypotension occurs, it usually responds to supportive therapy after cessation of the administration. When restarting the infusion, a slower administration rate should be used.

+ Phlebitis has been observed following bolus injection of etoposide. This adverse reaction can be avoided by IV infusion over 30 to 60 minutes.

Etoposide has been shown to reach high concentrations in the liver and kidney, thus presenting a potential for accumulation in cases of functional impairment.

Paediatric patients

In children receiving dosages higher than recommended, anaphylactoid-like reactions have been reported more frequently. (See section 4.3)

4.9 Overdose

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Acute overdosage results in severe forms of normally occurring adverse reactions, in particular leucopenia and thrombopenia.

Severe mucositis and elevated values of serum bilirubin, SGOT and alkaline phosphatase have been reported after administration of high doses of etoposide. Metabolic acidosis and severe hepatic toxicity have been reported after administration of dosages higher than recommended.

The management of bone marrow depression is symptomatic, including antibiotics and transfusions.

If hypersensitivity to etoposide occurs, antihistamines and intravenously administered corticosteroids are appropriate.

5. PHARMACOLOGICAL PROPERTIES

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5.1 Pharmacodynamic properties

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Pharmacotherapeutic classification: podophyllotoxine derivatives (ATC: L01CB01)

Etoposide is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. Podophyllotoxins inhibit mitosis by blocking microtubular assembly. Etoposide inhibits cell cycle progression at a premitotic phase (late S and G2).

It does not interfere with the synthesis of nucleinic acids.

5.2 Pharmacokinetic properties

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The concentration of etoposide in blood and organs is low with maximum values in the liver and the kidneys. Protein binding could be as high as 98%.

On intravenous administration, the disposition of etoposide is best described as a biphasic process with an initial half-life of about 1.5 hours. After distribution, half-life is about 40 hours. The terminal half-life is 6-8 hours.

Following a single intravenous dose etoposide is excreted in the urine for about 63% and in the faeces for about 31% after 80 hours.

Etoposide is cleared by both renal and nonrenal processes i.e. metabolism and biliary excretion. In patients with renal dysfunction plasma etoposide clearance is decreased.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration and nonrenal clearance. In children, elevated serum ALT levels are associated with reduced drug total body clearance. Prior use of cisplatin may result in a decrease of etoposide total body clearance.

5.3 Preclinical safety data

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Etoposide has been shown to be embryotoxic and teratogenic in animal experiments with rats and mice.

There are positive results from in vitro and in vivo test with regard to gene and chromosome mutations induced by etoposide. The results justify the suspicion of a mutagenic effect in humans.

No animal tests with regard to carcinogenicity were performed. Based on the DNA-damaging effect and the mutagenic properties, etoposide is potentially carcinogenic.

6. PHARMACEUTICAL PARTICULARS

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6.1 List of excipients

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Macrogol 300, polysorbate 80, benzyl alcohol, ethanol, citric acid, anhydrous.

6.2 Incompatibilities

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

6.3 Shelf life

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Vial before opening

3 years.

After dilution

Chemical and physical in-use stability of the solution diluted to a concentration of 0.2 mg/ml or 0.4 mg/ml has been demonstrated for 24 hours at 15-25 °C. From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 15-25 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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Store below 25 °C, protected from light (keep vials in the outer carton). Do not freeze.

Diluted solutions: see section 6.3

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

Solutions showing any sign of precipitation should not be used.

6.5 Nature and contents of container

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Each injection vial contains 100 mg (5 ml) of etoposide.

Each injection vial contains 500 mg (25 ml) of etoposide.

One package contains 1 vial or 10 vials of Eposin.

6.6 Special precautions for disposal and other handling

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Eposin should not be used without diluting! Dilute with 0.9% sodium chloride or 5% dextrose. Solutions showing any signs of precipitation should not be used.

For waste-disposal and safety information guidelines on safe-handling of antineoplastic drugs should be followed. Any contact with the fluid should be avoided. During preparation and reconstitution a strictly aseptic working technique should be used; protective measures should include the use of gloves, mask, safety goggles and protective clothing. Use of a vertical laminar airflow (LAF) hood is recommended.

Gloves should be worn during administration. Waste-disposal procedures should take into account the cytotoxic

nature of this substance.

If etoposide contacts skin, mucosae or eyes, immediately wash thoroughly with water. Soap may be used for skin cleansing.

7. MARKETING AUTHORISATION HOLDER

Go to top of the page

Pharmachemie B.V.

P.O. Box 552

2003 RN Haarlem

The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

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PL 04946/0018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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17 December 1996 / 10 January 2005 / 03 May 2010

10. DATE OF REVISION OF THE TEXT

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April 2010

More information about this product

Link to this document from your website: http://www.medicines.org.uk/emc/medicine/12973/SPC/

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