PRESCRIBING INFORMATION

Etoposid “EBEWE”

20 mg/ml concentrate
for solution for infusion

COMPOSITION

1 vial of 2.5 ml contains: 50 mg etoposide
1 vial of 5 ml contains: 100 mg etoposide
1 vial of 10 ml contains: 200 mg etoposide
1 vial of 20 ml contains: 400 mg etoposide
1 vial of 50 ml contains: 1,000 mg etoposide

CLINICAL PARTICULARS

Therapeutic Indications

Etoposide may be administered alone or in combination with other cytostatic drugs in the treatment of small cell lung cancer or resistant non-seminomatous testicular carcinoma.

Etoposide, when given in combination with other chemotherapeutic agents, has been shown to be of benefit in treating the following malignancies: Hodgkin's and non-Hodgkin's lymphoma, acute myelocytic leukemia.

Pharmacotherapeutic Group

Podophyllotoxin derivative
ATC Code: LO1CB

Dosage and Method of Administration

Etoposid “EBEWE” is only administered by slow infusion over 30 minutes to 2 hours.

Etoposide concentrate for solution for infusion must be diluted before use (see *Instructions for Use and Handling*).

Adults: The recommended dose of Etoposid “EBEWE” is 60-120 mg/m^2 i.v. per day for 5 subsequent days. As Etoposid “EBEWE” causes myelosuppression, the course of treatment must not be repeated more often than with intervals of 21 days. Repeated courses of treatment with Etoposid “EBEWE” infusion must not be given before the blood picture has been controlled for signs of myelosuppression and found satisfactory.

Paediatric patients: Safety and efficacy in children have not been established.

Elderly: Dose adjustment is not necessary.

Renal impairment: In patients with renal impairment but with normal hepatic function, the dose of etoposide must be reduced and haematological minimum values and renal function must be monitored.

Recommended dose regimen on the basis of creatinine clearance is as follows:

Creatinine clearance (ml/min)	Recommended daily dose (% of standard dose)
>50	100
15-50	75
<15	Contraindicated (*Contraindications*)

The diluted solution for intravenous infusion prepared according to the instructions in section *Instructions for Use and Handling* should be administered by slow intravenous infusion over a period of at least 30 minutes. Be careful in order to avoid extravasation.

Contraindications

Etoposide is contraindicated in:

- patients who have shown hypersensitivity to podophyllotoxin derivatives or to any of the excipients.
- patients with severe hepatic impairment.
- patients with severe renal impairment (creatinine clearance <15 ml/min, see section *Dosage and Method of Administration*).
- patients with severe myelosuppression.

Warnings and Precautions

Etoposide should only be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

Etoposide should not be administered intra-arterially or intracavitarily (pleura, peritoneum or other cavities).

When etoposide is given intravenously, care is advised in order to avoid extravasation.

If radiation and/or chemotherapy are given before initiation of etoposide treatment, an adequate intervals should be allowed to enable the bone marrow to recover.
If the leukocyte level falls below 2,000/mm^3 or the thrombocyte level is below 50,000/mm^3, the treatment must be discontinued until the blood cells again have reached acceptable levels (thrombocytes above 100,000/mm^3, leukocytes above 4,000/mm^3). Depending on whether etoposide is used alone or as combination treatment, the blood levels regenerate typically within 21 days. Peripheral blood counts and hepatic function must be monitored (see *Undesirable Effects*).

Bacterial infections must be brought under control before initiation of treatment with etoposide.

Anaphylactic reactions such as flush, tachycardia, bronchospasm and hypotension may occur (see *Undesirable Effects*).

Nausea and vomiting occur in app. 30-40% of the patients. Antiemetics are beneficial in control of these adverse reactions.

Etoposide may have genotoxic effects (see *Preclinical Safety Data*). Men treated with etoposide are therefore advised to use appropriate contraceptive measures to avoid pregnancy during treatment and for up to 6 months after treatment. There is a possibility of irreversible infertility.

Interactions with Other Medicaments and Other Forms of Interaction

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

The effect of oral anticoagulants may be increased.

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

There are no data about administration of etoposide with drugs that are known to inhibit phosphatase activity (e.g. levamisole hydrochloride).

Potentially Beneficial Interactions

Etoposide is usually used together with other cytotoxic drugs and synergistic effects are assumed to occur, mostly expressed by cytotoxic effect. Such a synergy has been documented *in vitro* for certain drugs including methotrexate and cisplatin.

Pregnancy and Lactation

Pregnancy: Etoposide should not be administered to patients who are pregnant, as safe use has not been established. Animal studies have shown etoposide to be teratogenic and embryotoxic. Women of child-bearing potential should be advised to avoid becoming pregnant whilst receiving etoposide therapy; it should only be used in women of child-bearing potential if the expected benefits outweigh the risks of therapy.

If the patient becomes pregnant whilst receiving the drug she should be advised of the potential hazard to the foetus.

If a patient plans to have children following etoposide therapy, genetic consultation is strongly recommended.

Lactation: It is not known whether etoposide is excreted in breast milk, so breast-feeding should be discontinued during etoposide therapy in lactating women.

Effects on Ability to Drive and Use Machines

Adverse reactions such as fatigue and transient cortical blindness indicate that car driving or handling of machines cannot be recommended shortly after treatment with etoposide.

Undesirable Effects

Blood and the lymphatic system disorders: The dose-limiting toxicity of etoposide is myelosuppression, mainly leukopenia and thrombocytopenia. Anaemia occurs rarely. The lowest leukocyte value occurs app. 21 days after treatment.

The occurrence of acute leukemia, with or without a preleukemic phase, has rarely been reported in patients treated with etoposide in combination with other antineoplastic drugs.

Nervous system disorders: Peripheral neuropathy has been reported (1-2%). It appears, that the risk and/or severity of peripheral neuropathy may be increased when etoposide is administered concurrently with other potentially neurotoxic agents such as vincristine. Confusion, hyperkinesias, somnolence, dizziness, fatigue, changes in taste and transient cortical blindness have been rarely reported.

Cardiac and vascular disorders: Hypotension may occur after too rapid infusion and may be reversed by lowering the infusion rate. Hypertension and/or flush have also

been reported. The blood pressure returns usually to normal level within a few hours after discontinuation of infusion.

Myocardial infarction and arrhythmia have rarely been reported after use of etoposide.

Respiratory disorders: Apnoea with spontaneous resumption of breathing has been reported after discontinuation of etoposide treatment. Sudden, fatal reactions in connection with bronchospasms have been reported. Pneumonia has rarely been reported.

Gastrointestinal disorders: Nausea and vomiting are the most common gastrointestinal toxicities and occur in app. 30-40% of the patients (see *Warnings and Precautions*). Abdominal pain, diarrhoea, constipation, anorexia, oesophagitis and stomatitis occur rarely.

Hepato-biliary disorders: Etoposide has shown to reach high concentrations in liver and kidneys and presents hereby a possibility of accumulation in case of reduced function. After high doses of etoposide, an increase in liver enzymes has been reported.

Skin and subcutaneous tissue disorders: Reversible alopecia sometimes progressing to total baldness has occurred in app. 66% of the patients. Stevens-Johnson syndrome, rash, urticaria, pigmentation and pruritus have been reported in rare cases after administration of etoposide. A single case of radiation recalled dermatitis has also been reported.

General disorders: Anaphylactic-like reactions characterised by shiver, flush, tachycardia, bronchospasm and hypotension have been reported after administration of etoposide. A higher frequency of anaphylactic reactions in children who received infusions in higher concentrations than recommended, have been reported. The role the concentration of the infusion (or the infusion rate) plays in development of anaphylactic reactions is uncertain. These reactions have usually responded on discontinuation of treatment and administration of pressor agents, e.g. adrenaline (epinephrin), corticosteroids, antihistamines or volume expanders, if relevant.

Fever has been reported in rare cases during use of etoposide and sepsis has rarely been reported.

Hyperuricaemia has been reported in rare cases during use of etoposide.

Overdose

Total doses of 2.4 to 3.5 g/m^2 administered intravenously over 3 days have resulted in severe mucousal inflammation and myelotoxicity. Metabolic acidosis and cases of severe hepatic toxicity have been reported in patients receiving higher doses of etoposide than recommended.

Tested antidotes against etoposide overdosage have not been established. Symptomatic and supporting treatment must be given.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Etoposide is a semisynthetic derivative of podophyllotoxin with significant cytotoxic activity. Etoposide affects the function of topoisomerase II (DNA-opening enzyme) and inhibits hereby DNA synthesis in the terminal phase of the effect of topoisomerase. This results in cleavage of DNA single and double strings. Cell death occurs in relation to the concentration of etoposide and time of exposure. Etoposide is phase-specific with cell arrest in S and early G2 phases of the cell cycle.

Pharmacokinetic Properties

The pharmacokinetic properties of etoposide underlie substantial interindividual variation. It is rapidly distributed and is bound to proteins by app 94% in human serum. Plasma decay kinetics follow a bi-exponential curve and correspond to a two-compartment model. The average volume of distribution is app. 32% of body weight. Etoposide shows a relatively bad penetration property into cerebral spinal fluid. App. 45% of an administered dose is excreted through the urine, two-thirds are excreted unchanged within 72 hours. Phenylbutazone, sodium salicylate and salicylic acid may affect the protein binding of etoposide.

Preclinical Safety Data

Reproduction toxicity: Etoposide is teratogeneous in rats at dose levels corresponding to the levels at clinical use.

Mutagenicity: Positive results from *in vitro* and *in vivo* tests regarding gene and chromosomal mutations caused by etoposide indicating that it is mutagenic, are available.

Carcinogenicity: Animal trials demonstrating the carcinogenicity of etoposide have not been performed.

However, based on the DNA-damaging effect and the mutagenic potential, etoposide should be considered as potentially carcinogenic in humans.

PHARMACEUTICAL PARTICULARS

List of Excipients

Benzyl alcohol, ethanol, anhydrous citric acid, macrogol 300, polysorbate 80, nitrogen.

Incompatibilities

Etoposide should only be diluted with isotonic sodium chloride or isotonic glucose infusion solutions. The concentration of etoposide in the reconstituted solution for infusion should not exceed 0.4 mg/ml due to the risk of precipitation.

Etoposide should not be diluted in buffered solution with a pH>8, because of the probability of a precipitation.

Plastic devices made of acryl or polymers composed of acrylonitrile, butadiene and styrene have been reported to crack and leak when used with undiluted Etoposid “EBEWE”.

Etoposid “EBEWE” contains 20 mg/ml benzyl alcohol as solvent.

Special Precautions for Storage

SHELF LIFE: In the intact container 36 months. Store below 25^{o}C, protect from light in outer packaging.

Keep in the safe place out of the reach of children.

Take the solution from vial immediately before use. Etoposid “EBEWE” is a single-use presentation.

Chemical and physical in-use stability for the drug product with a concentration of 0.2 mg/ml, prepared with a Saline solution or a 5% Glucose solution, has been demonstrated for 7 days at 2-8^{o}C or 20-25^{o}C.

Chemical and physical in-use stability for the drug product with a concentration of 0.4 mg/ml, prepared with a Saline solution or a 5% Glucose solution, has been demonstrated for 24 hours at 2-8^{o}C or 20-25^{o}C.

From a microbiological point of view, the product should be used immediately. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8^{o}C, unless dilution has taken place in controlled and validated aseptic conditions.

Instructions for Use and Handling

- Concentrate for solution for infusion must not be used undiluted.
- Cytotoxic drugs should be handled only by trained personnel and in a designated area.
- The work surface should be protected by disposable plastic-backed absorbent paper.
- Protective clothing (goggles, gowns and disposable gloves and masks) should be worn by staff handling parenteral etoposide.
- Contact with skin and/or mucous membranes must be avoided.
- Cytotoxic preparations should not be handled by pregnant staff.
- All items used for reconstitution, administration or cleaning, including gloves, should be placed in high risk, waste disposal bags for high temperature incineration.
- Any spillage or waste material may be disposed of by incineration.

Presentations

Etoposid “EBEWE” 50 mg - vial of 2.5 ml
Etoposid “EBEWE” 100 mg - vial of 5 ml
Etoposid “EBEWE” 200 mg - vial of 10 ml
Etoposid “EBEWE” 400 mg - vial of 20 ml
Etoposid “EBEWE” 1,000 mg - vial of 50 ml

Manufacturer

EBEWE Pharma Ges.m.b.H.,
A-4866 Unterach, Austria

License Holder and Importer

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