Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Etoposide ”Ebewe” 20 mg/ml – Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

1, 5, or 10 vials of 2.5 ml concentrate for solution for infusion contains 50 mg etoposide.
1, 5, or 10 vials of 5 ml concentrate for solution for infusion contains 100 mg etoposide.
1, 5, or 10 vials of 10 ml concentrate for solution for infusion contains 200 mg etoposide.
1, 5, or 10 vials of 20 ml concentrate for solution for infusion contains 400 mg etoposide.
1, 5, or 10 vials of 50 ml concentrate for solution for infusion contains 1000 mg etoposide.

Excipients: Benzyl alcohol, ethanol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, light yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Etoposide is a antineoplastic agent for intravenous use. It can be used alone or in combination with other oncolytic agents.

Available data show that etoposide may be used in treatment of small-celled lung cancer, resistant non-seminomatous testicular carcinoma, acute myelomonocytic and myelocytic leukaemia (AML, FAB subtype M4 or M5) as part of combination therapy after failure of induction chemotherapy.

4.2 Posology and method of administration

Etoposide should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Pregnant personnel should not handle chemotherapeutic agents.

Method of administration
Etoposid “Ebewe Etoposide is administered by slow intravenous infusion (see below). **ETOPOSIDE SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION.**

Etoposide concentrate for solution for infusion must be diluted before use (see section 6.6).
Immediately before administration, the required dose of Etoposid "Ebewe" must be diluted in glucose 5% or 0.9% saline solution for injection to give a concentration range from 0.2 to 0.4mg/ml, usually not more than 0.25mg/ml for the final concentration. It should then be given by intravenous infusion over a period of not less than 30 minutes.

Administration Precautions
Hypotension following rapid intravenous administration has been reported. Hence it is recommended that the Etoposid ”Ebewe” solution be administered over a 30 to 60 minute period. Longer infusion times may be required based on patient tolerance. As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of Etoposid ”Ebewe”. Skin reactions associated with accidental exposure to Etoposid ”Ebewe” may occur. The use of gloves is recommended. If Etoposid ”Ebewe” solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Posology

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 in intervals of 10 to 20 days. For non-haematological indications courses may not be repeated more frequently than at 21 day intervals. 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.

Overall, a dosage schedule of 100 mg/m² for 5 days or 120 mg/m² every other day on days 1, 3, and 5 is used most frequently.

Dose adjustments
Dosage of Etoposid “Ebewe” should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior X-ray therapy or chemotherapy which may have compromised bone marrow reserve.
Patients should not begin a new cycle of treatment with Etoposid “Ebewe” if the neutrophil count is less than 1,500 cells/mm^3 or the platelet count is less than 100,000 cells/mm^3, unless caused by malignant disease.

Doses subsequent to the 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 other grade 3 or 4 toxicity develops or if renal clearance is less than 50 ml/min.
Care should be taken to avoid extravasation.

Paediatric population:
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.

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

Creatinin clearance (ml/min)	Recommended daily dose (% of standard dose)
>50	100
15-50	75
<15	Contraindicated (see section 4.3)

Subsequent dosing should be based on patient tolerance and clinical effect. Data are not available in patients with creatinine clearance <15 mL/min and further dose reductions should be considered in these patients.

For instructions on use/handling and disposal see Section 6.6.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Severe hepatic dysfunction.
• Severe renal impairment (creatinin clearance <15 ml/min, see section 4.2)
• Severe myelosuppression
• Intra-arterial or intra-cavitary injection
• Breast-feeding (see section 4.6.)
• Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Etoposide should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Injection site reactions may occur during the administration of

When etoposide is given intravenously, care is advised in order to avoid extravasation. It is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

Severe myelosuppression with resulting infection or bleeding may occur.
Fatal myelosuppression has been reported following etoposide administration. Patients being treated with Etoposid "Ebewe" must be observed for myelosuppression carefully and frequently both during and after therapy. Dose limiting bone marrow suppression is the most significant toxicity associated with etoposide therapy. The following studies should be obtained at the start of therapy and prior to each subsequent dose of etoposide: platelet count, hemoglobin, 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.

Peripheral blood counts and hepatic function must be monitored. Etoposid "Ebewe" should not be administered to patients with neutrophil counts less than 1,500 cell/mm3 or platelet counts less than 100,000 cells/mm3, unless caused by malignant disease.

Doses subsequent to the 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 other grade 3 or 4 toxicity develops or if renal clearance is less than 50 ml/min. 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.
Depending on whether etoposide is used alone or as combination treatment, the blood levels regenerate typically within 21 days.

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

Physicians should be aware of the possible occurrence of an anaphylactic reaction with etoposide, manifested by chills, fever, flush, tachycardia, bronchspasm, dyspnea and hypotension may occur, which can be fatal (see section 4.8). Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

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

Etoposide should be administered with caution in patients receiving radiotherapy or chemotherapy and in patients with cardiac arrhythmia, a previous myocardial infarction, hepatic dysfunction, renal dysfunction, peripheral neuropathy, disturbance of micturition, epilepsy or brain damage or inflammation of the oral mucosa.
Etoposid "Ebewe" 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.

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.

Patients with low serum albumin may be at increased risk for etoposide-associated toxicities. Patients with impaired hepatic and renal function should regularly have their renal and hepatic function monitored due to the risk of accumulation.

The occurrence of acute leukaemia, which can occur with or without a preleukaemic phase has been reported rarely in patients treated with etoposide in association with other anti-neoplastic drugs.
A total cumulative dose (etoposide > 2000mg/m²) increases the risk of secondary acute non lymphoblastic leukemias. 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.

Etoposide is mutagenic and carcinogenic (see section 5.3). This should be taken into consideration when designing long-term therapy.

Given the mutagenic potential of etoposide (see section 5.3 preclinical safety data). an effective contraception is required for both male and female patients during treatment and for up to 6 months after 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 4.6 Fertility, pregnancy and lactation).

In the event of contact with etoposide, skin and mucosae should be abundantly washed with water.

Paediatric population
Safety and effectiveness of etoposide in paediatric patients have not been systematically studied.

Excipient(s) with known effect
Etoposid ”Ebewe” contains 260.6mg ethanol per ml. At a dose of 120mg/m^2 etoposide, a patient with a body surface area of 1.6m^2 would receive 2.5g ethanol. This must be taken into account when etoposide is administered to patients with a history or alcohol abuse or in patients receiving disulfiram.
With respect to benzylalcohol content of Etoposid "Ebewe", it should not be administered to children younger than 6 months in view of the potential for metabolic acidosis developing.
Etoposid “Ebewe” contains polysorbate 80. In premature infants a life threatening syndrome of liver and renal failure, pulmonary deterioration, thrombocytopenia and ascites has been associated with an injectable vitamin E product containing polysorbate 80.

4.5 Interaction with other medicinal products and other forms of interaction

Etoposide may potentiate the cytotoxic and myelosuppressive effect of other drugs (e.g. ciclosporin). High-dose ciclosporin, resulting in concentrations above 2000 ng/mL, administered with oral etoposide has led to an 80% increase in etoposide exposure (AUC) with a 38% decrease in total body clearance of etoposide compared to etoposide alone.

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

Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy.

Prior or concurrent use of other drugs with similar myelosuppressant action as etoposide may be expected to have additive or synergetic effects (see 4.4 Special warnings and precautions for use).

The effect of oral anticoagulants may be increased. Concomitant warfarin therapy may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.

In vitro plasma protein binding is 97%. Phenylbutazone, sodium salicylate and salicylic acid may affect the protein binding of etoposide.

Cross-resistance between anthracyclines and etoposide has been demonstrated in preclinical experiments.

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

There is increased risk of fatal systemic vaccinal disease with the use of yellow fever vaccine. Vaccination of patients immunocompromised by a chemotherapeutic agent with live attenuated vaccines may result in severe and fatal infections, thereforelive vaccines are contraindicated in these patients. (See 4.3 Contraindications.)

Potentially beneficial interactions
Etoposide is usually used together with other cytotoxic drugs and has been found to be therapeutic synergistic with a range of cytotoxic drugs (e.g. methotrexate and cisplatin).

4.6 Fertility, pregnancy and lactation

Pregnancy
Etoposide is suspected to cause serious birth defects when administered during pregnancy. Etoposide has been shown to be teratogenic in mice and rats. There are no adequate and well controlled studies in pregnant women. Etoposide should not be used during pregnancy unless clearly necessary. Women of child-bearing potential must use effective contraception during treatment with etoposide. If these drugs are used during pregnancy, or if the patient becomes pregnant while receiving these drugs, appropriate prenatal counselling should be provided and the benefit of treatment must be weighed up against the possible risk to the foetus.

Breastfeeding
It is not known if etoposide is secreted in human breast milk. A risk to the suckling child cannot be excluded. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etoposide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Etoposide is strictly contraindicated during lactation and breast-feeding should be interrupted during treatment (see 4.3 Contraindications).

Fertility
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.

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 with etoposid. If the patient experiences side effects such as fatigue and somnolence they should avoid driving or operating machines.

4.8 Undesirable effects

The table below lists adverse events presented by system organ class and frequency, which is defined by the following categories: very common (≥1/10), common (≥1/100,<1/10), uncommon (≥1/1,000,<1/100), and rare (≥1/10,000,<1/1,000).

	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations				Fever, sepsis		
Neoplasms Benign and Malignant (including cysts and polyps)		acute leukemia, which may occur with or without a preleukemic phase				
Blood and the Lymphatic System Disorders*	Myelosuppression*, *, Leukopenia, thrombocytopenia, neutropenia, anemia	Infections and haemorrhage following severe myelosuppression				
Cardiac Disorders		Myocardial infarction, arrythmia				
Immune System Disorders		Anaphylactic reactions**		hypersensitivity reaction		
Metabolism and nutrition disorders				Hyperuricaemia		
Nervous System Disorders		Peripheral neuropathy, Effect of the central nervous system (1-3%), Dizziness	Convulsion, Opticus neuritis	Seizure***, neurotoxicities (e.g., somnolence, fatigue, confusin, hyperkinesias, akinesia, aftertaste)		
Cardiac disorders					Myocardial infarction, rhythm disturbances	
Vascular Disorders		Transient systolic hypotension following rapid intravenous administration, hypertension, Phlebitis				
Respiratory, Thoracic and Mediastinal Disorders			Apnoea, fatal reactions associated with bronchospasms, Cough, laryngospasm and cyanosis. Interstitial pneumonitis / pulmonary fibrosis	Pneumonia		
Gastrointestinal	Abdominal pain,	Mucositis		Dysphagia,		

Disorders	constipation, nausea and vomiting (30-40%), Diarrhoea (1-13%), anorexia (10-13%).	(including stomatitis and esophagitis)		dysgeusia		
Hepato-biliary Disorders	Hepatotoxicity		increase in liver enzymes			
Skin and Subcutaneous Tissue Disorders	reversible alopecia (66%), pigmentation		Oedema of the face and tongue, sweating	Rash, urticaria, pruritus	Stevens-Johnson syndrome, toxic epidermal necrolysis, radiation recall dermatitis	
Renal and urinary disorders						accumulation in cases of impaired renal function
Reproductive system and breast disorders						Ammenorrhea, anovulatory cycles, decreased fertility, hypomenorrhea
General Disorders and Administration Site Conditions	Asthenia, malaise,	Extravasation****				

* Myelosuppression with fatal outcome has been reported. Infections (rarely sepsis) and haemorrhage following severe myelosuppression.
** Anaphylactic-type reactions can be fatal. A higher frequency of anaphylactic reactions in children who received infusions at higher than recommended concentrations, has been reported.
***Seizure is occasionally associated with allergic reactions.
**** Postmarketing complications reported for extravasation included local soft tissue toxicity, swelling, pain, celullitis, and necrosis including skin necrosis.

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 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 or etoposide phosphate depending on the way of administration and treatment scheme. Nadirs tend to occur earlier with intravenous administration compared to oral administration.
Leukopenia and severe leukopenia (less than 1,000 cells/mm^3) were observed in 60 - 91% and 7 - 17%, respectively, for etoposide/etoposide phosphate. Thrombocytopenia and severe thrombocytopenia (less than 50,000 platelets/mm^3) were seen in 28 - 41% and 4 - 20%, respectively, for etoposide/etoposide phosphate. Reports of fever and infection were also very common in patients with neutropenia treated with etoposide/etoposide phosphate.

Gastrointestinal Toxicity:
Nausea and vomiting are the major gastrointestinal toxicities of etoposide**.** The nausea and vomiting can usually be controlled by antiemetic therapy. They have been noted in 31 − 43% of patients given intravenous etoposide. Anorexia was seen in 10 - 13% of patients and stomatitis in 1 − 6% of those patients given intravenous etoposide. Diarrhea was noted in 1 - 13% of these patients.

Alopecia:
Reversible alopecia, sometimes progressing to total baldness, has been observed in up to 66% of patients treated with etoposide and 44% of patients treated with Etoposide phosphate injection.

Blood Pressure Changes
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, episodes of hypertension have been reported. If clinically significant hypertension occurs in patients receiving etoposide, appropriate supportive therapy should be initiated.

Allergic Reactions:
Anaphylactic-type reactions have also 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-type reactions is uncertain. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-type reactions can occur with the initial dose of etoposide.

Acute fatal reactions associated with bronchospasm, cough, laryngospasm and cyanosis have been reported for etoposide. Facial flushing was reported in 2% of patients and skin rashes in 3% treated with Etoposide phosphate injection.

Metabolic Complications:
Tumour lysis syndrome (sometimes fatal) has been reported following the use of etoposide in association with other chemotherapeutic drugs.

4.9 Overdose

Total doses of 2.4 to 3.5 g/m^2 administered intraveneously over 3 days have resulted in severe mucosal inflammation and myelotoxicity.
Metabolic acidosis and cases of severe hepatic toxicity have been reported in patients receiving higher doses of etoposide than recommended.
A specific antidote is not available. Symptomatic and supporting treatment must be given and patients should be closely monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents/podophyllotoxin derivatives,
ATC-code: L 01 CB 01.

Etoposide is a semisynthetic derivative of podophyllotoxin with a significant cytotoxic activity and dosage-scheme-dependent properties. Etoposide affects the function of topoisomerase II (DNA opening enzyme) and inhibits DNA-synthesis in the terminal phase. This results in cleavage of single and double stranded DNA. Cell death occurs in relation to the concentration of etoposide and duration of exposure. Etoposide is phase specific with cell stop in S and early G_2-phases of the cell cycle but differs from other known podophyllcompounds through the fact that it doesn't cause accumulation in the metaphase, but prevents the cell from mitosis or destroys cells that prepare mitosis.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of etoposide are subject to substantial interindividual variation. It is rapidly distributed and approximately 94% bound to plasma proteins. Plasma decay kinetics follow a bi-exponential curve and correspond to a two compartment model with a distribution half-life about 1.5 hours and a terminal elimination ranging from 4 to 11 hours. The total body clearance values range from 33 to 38 ml/min and, like the terminal half-life are independent of the dose over a range 100 – 600 mg/m². Over the same dosage range AUC and Cmax increase linearly with dose.

The average volume of distribution is approximately 32% of body weight. Etoposide shows a relatively poor penetration property into cerebospinal fluid. Approximately 45% of an administered dose is excreted in the urine, about one third is excreted within 72 hours. Only 6% or less of an intravenous dose is recovered in the bile as etoposide.

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

5.3 Preclinical safety data

Reproduction toxicity: Etoposide is teratogenic in rats at a level lower than that used clinically on an applied dose basis.

Mutagenicity: Positive results from in vitro and in vivo genetic toxicity and chromosomal aberration studies indicate that etoposide is mutagenic.

Carcinogenicity: Animal trials to determine 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (20mg/ml)
Ethanol 96% (v/v) (260,60mg/ml)
Anhydrous citric acid
Macrogol 300
Polysorbate 80

6.2 Incompatibilities

Etoposide should not be physically mixed with any other drug except for the medicinal products declared in *section 6.6* Instructions for use and handling.

Plastic devices made of acrylic or ABS polymers have been reported to crack when used with undiluted Etoposid "Ebewe", concentrate for solution for infusion 20mg/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

Packaged for sale: 3 years (before reconstitution).
Diluted solutions: 24 hours

6.4 Special precautions for storage

No special precautions for storage for the concentrate.

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature.

From a microbiological point of view, the diluted medicinal 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 to 8^{o}C, unless dilution has taken place in controlled and validated aseptic conditions. See section 6.6 Instruction for use and handling and disposal.

6.5 Nature and contents of container

1, 5 or 10 amber vials of Type I glass according to Ph.Eur. with a nominal capacity of 5 ml (50mg/2.5ml, 100mg/5ml), 10ml (200mg/10ml), 20ml (400mg/20ml) and 50ml (1000mg/50ml) with or without a protective plastic overwrap (ONKO-SAFE).

The vials are closed with fluoropolymer-coated chlorobutyl rubber stoppers according to Ph.Eur.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handle according to guidelines for cytotoxics.
Concentrate for solution for infusion must not be used undiluted.

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.

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

If etoposide comes into contact with skin wash with water.

Only for intravenous use.
Single use only.
Unused solution should be discarded.
Syringes, containers, absorbent materials, solution and any other contaminated material should be placed in a designated impervious container and incinerated, in accordance with local procedures.
Any unused product or waste material should be disposed of in accordance with local requirements.
Only clear solutions practically free from particles should be used.

Cytotoxics should not be handled by pregnant personnel.

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

7 MARKETING AUTHORISATION HOLDER

Ebewe Pharma Ges m.b.H. Nfg. KG
A-4866 Unterach
Austria

8 MARKETING AUTHORISATION NUMBER

PA 0789/013/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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August 2013