Etoposide Teva
Concentrate for solution for infusion
For I.V. Infusion

SUMMARY OF PRODUCT CHARACTERISTICS

Etoposide Teva
Concentrate for solution for infusion
For I.V. Infusion

1. NAME OF THE MEDICINAL PRODUCT
Etoposide Teva

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of Etoposide Teva concentrate for solution for infusion contains 20 mg etoposide.

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

1 vial with 10 ml concentrate for solution for infusion contains 200 mg etoposide.

1 vial with 50 ml concentrate for solution for infusion contains 1000 mg etoposide.

Excipient with known effect:

Each ml of concentrate for solution contains 241 mg ethanol absolute.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion.

Clear, yellowish, slightly viscous solution, essentially free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
- Hodgkin's disease
- Malignant (non-Hodgkin's) lymphomas, especially of the histiocytic variety
- Acute non-lymphocytic leukemia
- Management of refractory testicular tumours and of small cell lung cancer.

4.2 Posology and method of administration
Etoposide must not be given by intra-cavity injection.

Dose adjustments

Dosage of etoposide 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.

Etoposide is administered by slow intravenous infusion. ETOPOSIDE SHOULD NOT BE ADMINISTERED BY RAPID INTRAVENOUS INJECTION.

Hypotension following rapid intravenous administration of etoposide has been reported. Therefore, it is recommended that the etoposide injection be administered by slow I.V. infusion 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 etoposide. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If etoposide solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Patients should not begin a new cycle of treatment with etoposide 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.

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

Testicular Tumours, Hodgkin's Disease, Malignant (non-Hodgkin's) Lymphomas - Especially of the Histiocytic Variety, Acute Non-Lymphocytic Leukemia

The usual dose of etoposide, in combination with other approved chemotherapeutic agents, ranges from 50-100 mg/m^2/day on days 1 through 5 to 100 mg/m^2/day on days 1, 3, and 5.

Small Cell Lung Cancer

The usual dose of etoposide, in combination with other approved chemotherapeutic drugs, ranges from

35 mg/m^2/day for 4 days to 50 mg/m^2/day for 5 days.

Chemotherapy courses should be repeated at 3 to 4-week intervals after adequate recovery from any toxicity.

The dosage 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.

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
Etoposide Teva should only be administered and monitored under the supervision of a qualified physician experienced in the use of anti-neoplastic medicinal products. In all instances where the use of etoposide is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most such adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of etoposide therapy should be carried out with caution, and with adequate consideration of the further need for the drug and close attention to possible recurrence of toxicity.

Myelosuppression

Dose limiting bone marrow suppression is the most significant toxicity associated with etoposide therapy. Fatal myelosuppression has been reported following etoposide administration. Patients being treated with etoposide must be observed for myelosuppression carefully and frequently both during and after therapy. The following haematological parameters should be measured at the start of therapy and prior to each subsequent dose of etoposide: platelet count, haemoglobin, white blood cell count and differential. If radiotherapy or chemotherapy has been given prior to starting etoposide treatment, an adequate interval should be allowed to enable the bone marrow to recover.

Etoposide should not be administered to patients with neutrophil counts less than 1,500 cells/mm^3 or platelet counts less than 100,000 cells/mm^3, unless caused by malignant disease.

Doses subsequent to initial dose should be adjusted if neutrophil count less than 500 cells/mm^3 occurs for more than 5 days or is associated with fever or infection, if platelet count less than 25,000 cells/mm^3 occurs, if any grade 3 or 4 toxicity develops or if renal clearance is less than 50 ml/min.

Severe myelosuppression with resulting infection or haemorrhage may occur. Bacterial infections should be brought under control before treatment with etoposide.

Secondary leukaemia

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

Hypotension

Etoposide Teva should be given only by slow intravenous infusion (usually over a 30 to 60 minute period) since hypotension has been reported as a possible side effect of rapid intravenous injection.

Injection site reaction

Injection site reactions may occur during administration of etoposide. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration.

Low serum albumin

Low serum albumin is associated with increased exposure to etoposide. Therefore, patients with low serum albumin may be at increased risk for etoposide-associated toxicities.

Acute renal failure

Mostly in children, reversible acute renal failure has been reported when high dose (2,220 mg/m^2 or 60 mg/kg) of this medicinal product and total body irradiation were used for haematopoietic stem cell transplantation. Renal function should be evaluated prior to and after etoposide administration until complete renal function recovery (see section 4.8).

Impaired renal function

In patients with moderate (CrCl =15 to 50 mL/min), or severe (CrCl <15 ml/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).

Excipients

Etoposide Teva 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.

This product contains 24.1% w/v (241 mg/ml) ethanol (alcohol).

Each 5 ml vial contains up to 1.2 g of alcohol.

Each 10 ml vial contains up to 2.4 g of alcohol.

Each 50 ml vial contains up to 12 g of alcohol.

This can be harmful for those suffering from liver alcoholism. To be taken into account in pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease, or epilepsy. The alcohol in this medicine may alter the effects of other medicines.

4.5 Interaction with other medicinal products and other forms of interactions
Effects of other drugs on the pharmacokinetics of etoposide

High dose ciclosporin, resulting in plasma concentrations above 2,000 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 etoposide clearance and reduced efficacy.

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

Effect of etoposide on the pharmacokinetics of other drugs

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

Co-administration of warfarin and etoposide may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.

Pharmacodynamic interactions

There is increased risk of fatal systemic vaccinal disease with the use of yellow fever vaccine. Live vaccines are contraindicated in immunosuppressed patients (see section 4.3).

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

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential / Contraception in males and females

Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during etoposide therapy. Etoposide has been shown to be teratogenic in mice and rats (see section 5.3).

Given the mutagenic potential of etoposide, an effective contraceptive is required for both male and female patients during treatment and up to 6 months after ending treatment (see section 4.4). Genetic consultation is recommended if the patient wishes to have children after ending treatment.

Pregnancy

There are no or limited amount of data from the use of etoposide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). In general etoposide can cause fetal harm when administered to pregnant women. Etoposide 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.

Breast-feeding

Etoposide is excreted in human milk. There is a potential for serious adverse reactions in nursing infants from etoposide. A decision must be made whether to discontinue breast-feeding or to discontinue etoposide, 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 may cause adverse reactions that affect the ability to drive or use machines such as fatigue, somnolence, nausea, vomiting, cortical blindness, hypersensitivity reactions with hypotension. Patients who experience such adverse reactions should be advised to avoid driving or using machines.

4.8 Undesirable effects
Summary of the safety profile

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

System Organ Class	Frequency	Adverse Reaction (MedDRA Terms)
Infections and infestations	Common	Infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Acute leukaemia
Blood and lymphatic system disorders	Very common	Myelosuppression*, leucopenia, thrombocytopenia, neutropenia, anaemia
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	Seizure***, optic neuritis, cortical blindness transient, neurotoxicities (e.g., somnolence, fatigue)
Cardiac disorders	Common	Myocardial infarction, arrythmia
Vascular disorders	Common	Transient systolic hypotension following rapid intravenous administration, hypertension
	Uncommon	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Rare	Pulmonary fibrosis, interstitial pneumonitis
	Not known	Bronchospasm
Gastrointestinal disorders	Very common	Abdominal pain, constipation, nausea and vomiting, anorexia
	Common	Mucositis (including stomatitis and esophagitis), diarrhea
	Rare	Dysphagia, dysgeusia
Hepatobiliary disorders	Very common	Alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, bilirubin increased, hepatotoxicity
Skin and subcutaneous tissue disorders	Very common	Alopecia, pigmentation
	Common	Rash, urticaria, pruritus
	Rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, radiation recall dermatitis
Renal and urinary disorders	Not known	Acute renal failure
Reproductive system and breast disorders	Not known	Infertility
General disorders and administration site conditions	Very common	Asthenia, malaise
	Common	Extravasation****, phlebitis
	Rare	Pyrexia

* Myelosuppression with fatal outcome has been reported.

** Anaphylactic reactions can be fatal.

*** Seizure is occasionally associated with allergic reactions.

**** Post-marketing 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 utilised single agent etoposide therapy.

Haematological toxicity

Myelosuppression (see section 4.4) with fatal outcome has been reported following administration of etoposide. Myelosuppression is most often dose-limiting. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported.

Granulocyte and platelet nadirs tend to occur about 10 to 14 days after administration of etoposide depending on the way of administration and treatment scheme. Nadirs tend to occur earlier with intravenous administration compared to oral administration.

Leucopenia and severe leucopenia (less than 1,000 cells/mm^3) were observed in 91% and 17%, respectively, for etoposide. Thrombocytopenia and severe thrombocytopenia (less than 50,000 platelets/mm^3) were seen in 23% and 9%, respectively, for etoposide. Reports of fever and infection were also very common in patients with neutropenia treated with etoposide. Bleeding has been reported.

Gastrointestinal toxicity

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

Alopecia

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

Hypotension

Transient hypotension following rapid intravenous administration has been reported in patients treated with etoposide and has not been associated with cardiac toxicity or electrocardiographic changes. Hypotension usually responds to cessation of infusion of etoposide and/or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

No delayed hypotension has been noted.

Hypertension

In clinical studies involving etoposide, episodes of hypertension have been reported. If clinically significant hypertension occurs in patients receiving etoposide, appropriate supportive therapy should be initiated.

Hypersensitivity

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

Anaphylactic reactions (see section 4.4), manifested by chills, tachycardia, bronchospasm, dyspnoea, diaphoresis, pyrexia, pruritus, hypertension or hypotension, syncope, nausea, and vomiting have been reported to occur in 3% (7 of 245 patients treated with etoposide in 7 clinical studies) of patients treated with etoposide. Facial flushing was reported in 2% of patients and skin rashes in 3%. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines, or volume expanders as appropriate.

Acute fatal reactions associated with bronchospasm have been reported with etoposide. Apnoea with spontaneous resumption of breathing following cessation of infusion have also been reported.

Metabolic complications

Tumour lysis syndrome (sometimes fatal) has been reported following the use of etoposide in association with other chemotherapeutic drugs (see section 4.4).

Acute renal failure

Reversible acute renal failure has been reported in post-marketing experience (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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

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.

A specific antidote is not available. Treatment should therefore be symptomatic and supportive, and patients should be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

The main effect of etoposide appears to be at the late S and early G_2 portion of the cell cycle in mammalian cells. Two dose-dependent responses are seen: At high concentrations (10 mcg/mL or more), 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 administered 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, i.e., 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 should be considered a possible carcinogen in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol absolute, polysorbate 80 (Tween 80), citric acid anhydrous, polyethylene glycol 300.

6.2 Incompatibilities

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

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf-life after dilution

The infusion has been shown to be physically and chemically stable for up to 120 hours at 25°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. Dilution should take place in controlled and validated aseptic conditions.

Multi-dose use

Etoposide Teva concentrate for solution for infusion is stable for up to 72 hours (3 days) at 25°C following piercing of the rubber stopper. It is therefore suitable for multi-dose use.

6.4 Special precautions for storage

Store the undiluted product between 15-25°C. Do not refrigerate. Keep in the original package in order to protect from light.

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

For storage conditions after dilution and first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear, colorless glass vial, closed with chlorobutyl rubber stopper (coated with black teflon) held by an aluminum with pink snap cap with insert disc.

Vials containing 20 mg/ml of etoposide as follows:

100 mg of etoposide/5 ml,

200 mg of etoposide/10 ml,

1000 mg of etoposide/50 ml.

Pack sizes:

All presentations are packaged as individual vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

Etoposide Teva must be prepared under aseptic conditions.

Etoposide Teva must be diluted with either 5% dextrose solution for injection or 0.9% saline solution for injection, to give a final concentration of 0.2 mg/ml.

Solutions showing any signs of precipitation should not be used.

Etoposide Teva should not be physically mixed with any other medicinal product.

As with all cytotoxic preparations, the following special precautions should be taken for safe handling and disposal:

1. Trained personnel only should dilute the drug. Pregnant staff should not be involved in its handling.
2. Preparation of the drug should be performed in a designated area, ideally in a vertical laminar flow hood (Biological Safety Cabinet - Class II). The work surfaces should be covered with disposable plastic-backed absorbent paper.
3. Adequate protective clothing should be worn, i.e., PVC gloves, safety glasses, disposable gowns and masks. In the event of contact with the eyes, wash with copious amounts of water or saline.
4. Luer-Lock fittings should be used on all syringes and sets. The possible formation of aerosols may be reduced by using large-bore needles and venting needles.
5. All unused material, needles, syringes, vials and other items which have come into contact with cytotoxic drugs should be segregated, placed in double-sealed polyethylene bags and incinerated at 1,000°C or more. Excreta should be similarly treated. Liquid waste should be flushed away with copious amounts of water.

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

7. LICENCE HOLDER AND MANUFACTURER

Licence holder:

Abic Marketing Ltd.

POB 8077, Netanya.

Manufacturer:

Pharmachemie B.V. (Teva Group)

Haarlem, The Netherlands.

8. REGISTRATION NUMBER

106.48.28897

The leaflet was revised in July 2021 according to MoH guidelines.