SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ETOPEX 100 mg/5 ml Concentrate for Solution for IV Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Each vial (5 ml) contains 100 mg etoposide.

Excipients: Benzyl alcohol, citric acid anhydrous, absolute ethanol, polysorbate 80, PEG 300.

Each 1 ml of ETOPEX contains 241 mg ethanol. A patient with a body surface area of 1.6 m^2 will receive 2.3 g ethanol through an etoposide dose of 120 mg/m^2. This can be harmful for those suffering from alcoholism. This amount should be taken into account in pregnant and breast-feeding women, children, high-risk groups such as patients with hepatic disease or epilepsy, and patients on disulfiram.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vial containing concentrate for solution for IV infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Etoposide is an antineoplastic agent administered intravenously. It can be administered as monotherapy or in combination with other antineoplastic agents.
Etoposide can be used in combination with other chemotherapeutic agents with proven efficacy in small-cell lung cancer and with other chemotherapeutic agents with proven efficacy for the treatment of non-seminomatous testicular carcinoma in patients who underwent appropriate surgery, chemotherapy or radiotherapy.
Additionally, it has been shown that objective response can be obtained in the palliative treatment of non-small-cell lung cancer, re-induction treatment of Hodgkin disease, induction treatment of non-Hodgkin lymphoma and acute myelocytic leukemia, and induction and re-induction treatment of choriocarcinoma.

4.2. Posology and method of administration

Posology/frequency and duration of administration

In adults
Dosage depends on whether etoposide is administered as monotherapy or in combination with other cytostatic agents. The recommended ETOPEX dose is 60-120 mg/m^2 daily administered IV for 5 subsequent days.

The solution is administered by intravenous infusion over a period of minimum 30 minutes up to 2 hours. Facial flushing is a sign of too rapid infusion.
Chemotherapy courses are repeated in 3-4-week intervals after adequate recovery of any toxicity.
As etoposide causes myelosuppression, the course of treatment must not be repeated more frequently

than in intervals of 3-week to allow the leukocyte and platelet counts to be normal. Before repeated courses of treatment with ETOPEX infusion are given, the blood picture must be controlled for signs of myelosuppression and found satisfactory.

Method of administration
ETOPEX should be initiated by or in consultation with a qualified physician experienced in cancer chemotherapeutic agents.
ETOPEX is administered only via slow intravenous infusion. Etoposide should not be administered as an injection into body cavities (pleura, peritoneum and others).
Only use fresh, colorless and clear solutions.
For detailed information on instructions for use and administration, see section 6.6.

Additional information on special populations

Renal impairment
The dose of etoposide should be reduced in patients with renal impairment but with normal liver functions, and hematological nadirs and renal functions should be monitored.

The recommended dose regime based on creatinine clearance is as follows:

Creatinine Clearance (ml/min)	Recommended Daily Dose (percentage of standard dose)
>50	100
15-50	75
<15	Contraindicated (see contradictions section).

Hepatic impairment
It should be administered by adjusting the dose based on severity of the disease and hepatic impairment in patients with hepatic impairment.

Pediatric population
Its effectiveness and safety in children has not been established.

Geriatric population
Dose adjustment is not necessary.

4.3. Contradictions
- Patients with hypersensitivity to the active substance or to any of the excipients
- Patients with severe hepatic impairment
- Patients with severe renal impairment (creatinine clearance <15 ml /min)
- Patients with severe myelosuppression (leukocyte ≤4000/mm^3, thrombocyte ≤1000/mm^3)
- Breast-feeding mothers
- Pregnancy *(*see section *4.6. Pregnancy and Lactation*.)
- Intrathecal use

4.4. Special warnings and precautions for use
ETOPEX should only be administered by healthcare professionals under strict observation by a physician specialized in the use of cancer chemotherapeutic agents.

As rapid intravenous administration may cause hypotension, ETOPEX should be administered by slow intravenous infusion. The duration of infusion is between 30 minutes to 2 hours. Paravenous

injection may cause ulceration and necrosis. Facial flushing is one of the signs of too rapid infusion.

Caution is advised due to the possibility of an anaphylactic reaction manifested as flush, chills, fever, tachycardia, bronchospasm, dyspnea and hypotension. Frequent anaphylactic-like reactions have been reported in children who received infusions at concentrations higher than those recommended. In such cases, the infusion must be stopped immediately and treated symptomatically.

Patients treated with ETOPEX should be monitored frequently for myelosuppression both during and after treatment. Dose limiting bone marrow suppression is the most significant toxicity associated with etoposide treatment. If radiotherapy and/or chemotherapy were carried out before the start of etoposide treatment, a suitable interval must elapse for the bone marrow to recover. If the leukocyte count is below 2000/mm^3 or the thrombocyte count is below 50.000/mm^3, further therapy is withheld until the blood count has reached appropriate levels (thrombocyte >100.000/mm^3, leukocyte >4.000/ mm^3). Depending on the use of etoposide as monotherapy or in combination therapy, blood count normally recovers within 21 days. Peripheral blood count and liver functions should be monitored (see section 4.8).

It should only be prescribed in patients with leukemia or lymphoma if provided benefit outweighs the potential risk.

Antiemetics are beneficial for the management of nausea and vomiting observed in patients.

Before starting etoposide treatment, bacterial and viral infections should be under control and close contact with patients who have just been vaccinated with poliovirus vaccine should be avoided.

Etoposide should be used with caution in patients receiving radiotherapy and chemotherapy; and in patients with cardiac arrhythmia, prior myocardial infarcts, hepatic dysfunction, renal dysfunction, peripheral neuropathy, urinary retention, epilepsy or brain damage or stomatitis.

Etoposide can have genotoxic effects (see section 5.3).

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.

This medicinal product contains 30 mg benzyl alcohol per vial. It must not be given to premature infants and neonates. It may cause toxic reactions and anaphylactic reactions in infants and children up to 3 years old.

4.5. Interactions with other medicinal products and other forms of interaction

Radiotherapy and co-administration of drugs that may cause myelosuppression may potentiate the myelosuppression induced by etoposide. Etoposide may potentiate the cytotoxic and myelosuppressive actions of other drugs (i.e. cyclosporine). High dose of cyclosporine has been found to lead to an increase in etoposide exposure with a decrease in etoposide clearance.

The effects of oral anticoagulants may increase.

Phenylbutazone, sodium salicylate and salicylic acid may affect binding of etoposide to plasma proteins.

Cross-resistance between anthracyclines and etoposide has been experimentally demonstrated.

There is no data available as to concomitant use of etoposide with drugs known to inhibit phosphatase activity (i.e. Levamisole hydrochloride).

Do not use with alcohol.

Potentially useful interactions:
Etoposide is generally used with other cytotoxic drugs, which are considered to exert a synergistic effect in the scope of cytotoxic activity; some drugs such as methotrexate and cisplatin have been shown *in vitro* to exhibit such synergy.
In animal models, synergistic effects have been demonstrated on tumor cells with the following chemotherapeutic agents: Cisplatin, carboplatin, mitomycin C, cyclophosphamide, BCNU, vincristine, dactinomycine and cytosine arabinoside.

4.6. Fertility, pregnancy and lactation

General principles
Pregnancy category: D

ETOPEX must not be administered to pregnant and breast-feeding mothers.

Women of child-bearing potential/Contraception
Women of childbearing potential should be advised to avoid becoming pregnant. 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.

Pregnancy
Etoposide has been shown to be teratogenic in mice and rats in doses equivalent to clinically administered doses. Safety of its use in pregnant women has not been established, there are no adequate and well-controlled studies as to its use in pregnancy.
ETOPEX should not be used in pregnancy unless required. Caution should be taken when administrating to pregnant women (see section 5.3).

Breastfeeding
ETOPEX must not be used in lactation.

Fertility
ETOPEX may decrease male fertility. There is a possibility of irreversible infertility.

4.7. Effects on ability to drive and use machines
Adverse reactions such as fatigue and reversible cortical blindness indicate that it is not pertinent to drive or use machines immediately after etoposide treatment.
ETOPEX contains ethanol, therefore it may impair the ability to drive or use machinery.

4.8. Undesirable effects
The undesirable effects are defined according to the system organ class as follows; Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very Rare (<1/10,000).

Infections and infestations
Rare: Fever and sepsis have been reported.

Blood and lymphatic system disorders
Very common: The dose-limiting toxicity of etoposide is myelosuppression, predominantly leukemia and thrombocytopenia. Leukemia in 60-91% and thrombocytopenia in 28% of patients have been observed. Leukocyte and thrombocyte nadirs tend to occur about 21 days and 11-17 days, respectively, after treatment. A decrease in hemoglobin levels occurs in approximately 40% of patients. Anemia has been rarely reported.

Common: Bleeding and infections following severe myelosuppression.

Rare: Occurrence of acute leukemia (can occur with or without preleukemic phase) has been reported in patients treated with etoposide in combination with other antineoplastic drugs.

Immune system disorders:
Uncommon: Following etoposide administration, anaphylactic reactions characterized with chills, shivering, flushing, fever, tachycardia, dyspnea, bronchospasm and hypotension have been reported. Higher rates of anaphylactic-like reactions have been reported in children who received infusions at concentrations higher than those recommended. However, the role that concentration of infusion (or rate of infusion) plays in the development of anaphylactic reactions is uncertain. These reactions have usually responded promptly to the cessation of the drug, and subsequent administration of vasopressor agents such as adrenalin, corticosteroids, antihistamines or plasma volume expanders. Furthermore, these reactions can be fatal.
Hypersensitivity may occur due to benzyl alcohol in ETOPEX. Hypertension, flushing, swelling of face/tongue, cough, sweating, cyanosis, tightness in throat, laryngospasm, loss of consciousness, and rarely apnea have been reported.

Very Rare: In the literature two cases of Stevens-Johnson syndrome were reported; however, a casual relationship with etoposide has not been established. Fatal toxic epidermal necrolysis was observed in one of the cases.

Metabolism and nutrition disorders
Rare: Hyperuricemia has been reported.

Nervous System disorders:
Common: Peripheral neuropathy has been observed in 0.7-2% of cases.

Uncommon: Convulsion.

Rare: As a result of the effect on central nervous system, confusion, hyperkinesia, tendency to sleep (somnolence), dizziness, fatigue, taste impairment (aftertaste) and reversible cortical blindness may occur.

Cardiac disorders
Very rare: Myocardial infarction and arrhythmias has been reported after use of etoposide; however, no casual relationship with etoposide has been revealed.

Vascular disorders
Common: Following rapid infusion hypotension may occur, which can be recovered by reducing the

rate of infusion.

Uncommon: Hypertension and flushing (hot flushes) have also been reported. The blood pressure usually returns to normal within few hours following cessation of infusion. Phlebitis may be observed.

Respiratory, thoracic and mediastinal disorders
Uncommon: Following withdrawal of etoposide treatment, apnea followed by spontaneous recurrence of breathing has been reported. Sudden, fatal reactions associated with bronchospasm have been reported. Pneumonia has been rarely observed. Coughing, laryngospasm and cyanosis, interstitial pneumonia/ pulmonary fibrosis may be observed.

Gastrointestinal disorders
Very Common: Nausea and vomiting occur in approximately 30-40% of patients. Antiemetics are useful in the management of these adverse effects.

Rare: Abdominal pain, diarrhea, constipation, loss of appetite, esophagitis and stomatitis (oral mucositis) may occur. Dysphagia has been reported. Oral mucositis may be dose-limiting in high doses.

Hepatobiliary Disorders
Uncommon: Etoposide has been showed to reach high concentrations in the liver and kidney and therefore, presenting a potential for accumulation in cases of functional impairment. Increases in liver enzymes have been reported due to high doses of etoposide.

Skin and subcutaneous tissue disorders
Very Common: Reversible alopecia, sometimes progressing to total baldness was observed in about 66% of patients.

Uncommon: Facial and tongue edema, sweating.

Rare: Following administration of etoposide, rush, urticaria, pigmentation and itching (pruritus) may occur.

Very Rare: Radiation “recall” dermatitis has been reported with one case.

Renal and urinary disorders
Etoposide has been shown to reach high concentrations in the kidney; therefore presenting a potential for accumulation in cases of functional impairment.

Reproductive system and breast disorders:
Amenorrhea, anovulatory cycles, decrease in fertility and hypomenorrhea.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkey Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: +90 800 314 00 08; fax: +90 312 218 35 99).

4.9 Overdose

Overdose

Total doses of 2.4-3.5 g/m^2/day of etoposide administered intravenously over 3 days have resulted in severe mucositis and myelotoxicity. Metabolic acidosis and severe hepatic toxicity have been reported in patients administered with etoposide doses that were higher than recommended.

Treatment

No proven antidotes have been established for etoposide overdosage. Symptomatic and supportive treatment should be instituted.

The risk of infection and severity of neuropathy can be reduced through administration of hematopoietic growth factor when leukemia is at the highest point.

Supportive treatment consists of the followings:

Nausea, vomiting: antiemetics.

Allergic reactions: cessation of etoposide treatment, corticosteroids, sympathomimetics, antihistamines, plasma volume expanders.

Bronchospasm: aminophylline, corticosteroids.

Hypotension: cessation of etoposide treatment, fluid and plasma volume expanders.

Hyperuricemia: Allopurinol.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent—podophyllotoxin derivatives.

ATC code: L01CB01.

Etoposide is a semi-synthetic lipophilic podophyllotoxin derivative. Etoposide acts as an antineoplastic and cytotoxic agent. It affects topoisomerase II (enzyme that cleaves DNA) and thereby inhibiting DNA synthesis in the terminal phase of the topoisomerase effect. This results in both single- and double-strand DNA cleavage. Its action is based on the induction of DNA single- and double-strand breaks by interaction with topoisomerase II enzyme or the formation of free radicals within the cell. Cell death is dependent on etoposide concentration and administration timing. The effect of etoposide is particular to phases of the cell cycle and its main effect seems to occur at the S and early G2 phase of the cell cycle. The cytotoxic effect on resting cells has only been observed at high concentrations.

5.2. Pharmacokinetic properties

General properties

Pharmacokinetic properties of etoposide significantly show inter-individual variations.

Absorption:

It passes directly into the blood stream due to its pharmaceutical form and administration site.

Distribution:

It is rapidly distributed. Its mean volume of distribution is approximately 32% of body weight. The mean volume of distribution at steady state falls in the range of 18 to 29 L or 7 to 17 L/m^2. Etoposide enters into the CSF poorly. Although it is detectable in CSF and intracerebral tumors, the concentrations are lower than in extracerebral tumors in plasma. Concentrations of etoposide are higher in normal lung than in lung metastases and are similar in primary tumors and normal tissues of the myometrium. *In vitro*, etoposide is highly protein bound (94%) to human plasma proteins. In

a study of the effects of other therapeutic drugs on *in vitro* binding of ^{14}C etoposide to human serum proteins, only phenylbutazone, sodium salicylate, salicylic acid and aspirin displace protein-bound etoposide at concentrations achieved *in vivo*.
Binding ratio of etoposide correlates directly with serum albumin concentration in normal volunteers and cancer patients. In other words, data indicate that there is a significant inverse correlation between serum albumin concentration and free etoposide fraction.

Biotransformation:
The main urinary metabolite of etoposide in adults and children is 4-hydroxyacid metabolite [4'-dimethyl-epipodophyllic acid-9-(4,6-0-(R)-ethylidene-β-D-glucopyranoside)], formed by opening of the lactone ring. It is also present in human plasma, as the trans isomer.
5-22% of received dose is excreted in human urine as glucuronide and/or sulfate conjugates. In addition, O- demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol. After intravenous infusion, the C_{max} and AUC values exhibit significant intra- and inter-subject variability.

Elimination:
The dissipation of etoposide fits the bi-exponential kinetic and two-compartment model. On IV administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. Total body clearance values range from 33-48 ml/min or 16 to 36 ml/min/m^2. The terminal half-life and total body clearance are independent of dose over a range 100 to 600 mg/m^2. Over the same dose range, the area under the curve (AUC) and maximum plasma concentration values increase linearly with dose. Etoposide does not accumulate in the plasma following daily administration of 100 mg/m^2 for 4 to 5 days.
Following intravenous administration of ^{3}H-etoposide (70-290 mg/m^2), recovery of radioactivity in the urine was 42-67% of the given dose and fecal recovery of radioactivity was 0-16%. Approximately 45% of the intravenous dose and 2/3 of this is excreted in the urine as unchanged within 72 hours. The mean renal clearance of etoposide is 7 to 10 ml/min/m^2 or 35% of the total body clearance over a dose of 80 to 600 mg/m^2. Therefore, etoposide is cleared by both renal and non-renal processes, such as metabolism and biliary excretion. Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is excreted in the bile. The main non-renal elimination route of etoposide is metabolism.
In adults the total body clearance etoposide is correlated with creatinine clearance, serum albumin concentration and non-renal clearance. Patients with impaired renal function have exhibited reduced total body clearance, increased AUC, and a lower volume of distribution at steady state. Cisplatin therapy is associated with reduced total body clearance.

Characteristics in patients

Age:
Although some minor differences in pharmacokinetic parameters have been observed among different age groups, they are not considered clinically significant.

Gender:
Although some minor differences in pharmacokinetic parameters have been observed between genders, they are not considered clinically significant.

Pediatric patients:
In children, there is an inverse correlation between plasma albumin levels and etoposide renal

clearance. Elevated serum GPT levels are associated with reduced drug total clearance. Prior use of cisplatin may also result in a decrease of etoposide total body clearance in children.
In children, approximately 50% of the given dose is excreted in the urine as etoposide in 24 hours.

Renal impairment:
Patients with impaired renal function have exhibited reduced total body clearance, increased AUC and a lower volume of distribution at steady state.

5.3. Preclinical safety data

Mutagenicity:
Etoposide has been shown to mutagenic and genotoxic in mammalian cells. There are positive results from *in vitro* and *in vivo* tests with regard to genetic and chromosomal mutations caused by etoposide. Etoposide induced aberrations in chromosome number and structure in embryonic murine cells and human hematopoietic cells; strand breaks, DNA damages and DNA-protein crosslinks in ovary cells of Chinese hamsters and leukemia cells of mice; and also an increase in sister chromatid exchanges based on dose in ovary cells of Chinese hamsters.

Reproductive Toxicity (teratogenicity):
Etoposide has been shown to have teratogenic effects on rats in clinically equivalent doses. It has been shown to be teratogenic and embryotoxic in mice and rats in 1 to 3% of the recommended clinical dose based on body surface area. Following intravenous etoposide administration to SPF rats at doses of 0.4, 1.2 and 3.6 mg/kg/day on days 6 to 15 of gestation, dose-related maternal toxicity, embryotoxicity (prenatal mortality, fetal resorption, low fetus weight) and teratogenicity (major skeletal abnormalities, exencephalia, encephaloceele and anophthalmia) were reported; Dose of 0.13 mg/kg induced an increase in retarded ossification. Dose-dependent embryotoxicity (intrauterine death of fetus and lower fetus weight) and teratogenicity (cranial abnormalities, major skeletal abnormalities) were reported by intraperitoneal administration of 1, 1.5 or 2 mg/kg on days 6, 7 or 8 of gestation in Swiss-Albino mice.

Carcinogenicity:
No animal studies with regard to carcinogenicity of etoposide have been carried out. However, based on the DNA-damaging effect and the mutagenic potential, etoposide is considered potentially carcinogenic in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Polysorbate 80
PEG 300
Citric Acid Anhydrous
Absolute ethanol
Benzyl alcohol

6.2 Incompatibilities
ETOPEX must not be diluted with buffer solutions with a pH >8 due to the increased likelihood of precipitation.
It must be diluted only with isotonic sodium chloride or isotonic glucose solutions for infusion. In order to avoid precipitation, etoposide concentration of the diluted solution should not be more than 0.4 mg/ml.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store the vial at room temperature below 25°C and protect from light.

6.5 Nature and contents of container
Colorless Type 1 glass vial with aluminum flip-off seal and grey bromobutyl rubber stopper. Each cardboard box contains 1 vial.

6.6 Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

As with all cytotoxic agents, etoposide must be held carefully by using protective clothing, glove, and facemask. Hold the solution in fume hood if possible. Contamination with the skin and mucosa membranes must be avoided. Pregnant healthcare professionals should not administer etoposide.
In the event of contamination with eyes, eyes should be rinsed with plenty of water and asked for a physician if needed.
Adequate care and precautions should be taken in disposal of materials (needle, syringe etc.) used to reconstitute cytotoxic drugs. Waste materials and body waste must be disposed of by placing in double sealed polyethylene bags and incinerating at a temperature of 1000°C. Liquid waste should be flushed with copious amounts of pressurized water.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece/İSTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER(S)

237/22

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 18.11.2011
Date of last renewal :

10. DATE OF REVISION OF THE TEXT

15.07.2017