ETOPOSIDE®
(Etoposide)

1. NAME OF THE MEDICINAL PRODUCT

ETOPOSIDE® Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ETOPOSIDE® Injection is a Solution for injection or infusion containing 20 mg of etoposide per milliliter (mL) of solution.

3. PHARMACEUTICAL FORM

Sterile solution for injection or infusion

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

For the treatment of small cell lung cancer and testicular tumors, either as a single agent or in combination with other anticancer agents.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Single agent therapy

The dose of etoposide must be based on the clinical and hematological response and tolerance of the patient. A repeat course of etoposide should not be administered until the patient's hematological function is within acceptable limits.

Adult population

The usual dose is 50-150 mg/m^2 given for 5 consecutive days or on days 1, 3, and 5. As etoposide produces myelosuppression, courses should not be repeated more frequently than at 21 day intervals. In any case, repeat courses should not be given until the hematological parameters have been checked for evidence of myelosuppression and found to be satisfactory.

Administer by intravenous infusion over at least 30-60 minutes.

Etoposide must be diluted before administration. Resultant concentrations should not be greater than 0.4 mg/mL since precipitation can occur.

Usually, etoposide is added to 250 mL of 0.9% sodium chloride or 5% glucose. Contact with buffered aqueous solutions with pH above 8 should be avoided.

Combination therapy

The dosage of etoposide may need to be adjusted when other cancer chemotherapy is given concurrently.

Elderly population

No dosage adjustment is necessary. Caution may be necessary in renal or hepatic impairment.

Pediatric population

The safety and effectiveness in children have not been established.

4.3. CONTRAINDICATIONS

- Known hypersensitivity to the drug or excipients.
- Severe myelosuppression.
- Severe hepatic impairment.
- Acute infections.
- Pregnancy and lactation. (see section **4.6. Fertility, Pregnancy and Lactation**).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Etoposide should only be administered by personnel experienced in the use of cancer chemotherapy.

Hematological effects

Cytotoxic agents, including etoposide, may produce myelosuppression (including, but not limited to, leukopenia, granulocytopenia, pancytopenia, and thrombocytopenia).[1]

If radiotherapy and/or chemotherapy have been given prior to starting etoposide treatment, an adequate interval should be allowed to enable the bone marrow to recover. If the leukocyte count falls below 2,000/mm^3, treatment should be suspended until the circulating blood elements have returned to acceptable levels (platelets above 100,000 mm^3, leukocytes above 4,000/mm^3), this is usually within 10 days. Peripheral blood counts should be periodically monitored.

Clinical consequences of severe myelosuppression include infections. Viral, bacterial, fungal and/or parasitic infections, either localized or systemic, may be associated with the use of etoposide alone or in combination with other immunosuppressive agents. These infections may be mild, but can be severe and at times fatal.

Generalized infections should be brought under control before treatment with etoposide commences.

Myocardial infarction

Myocardial infarction has been observed in patients treated with etoposide as part of multi-agent chemotherapy. Patients with prior history of mediastinal radiation or recipients of previous chemotherapies may be at risk (see section **4.8. Undesirable effects**).[3]

Renal and hepatic effects

Etoposide has been shown to reach high concentrations in the liver and kidney, thus presenting a potential for accumulation in cases of functional impairment. Transient elevations in liver enzymes and bilirubin may occur.[3] It is recommended to periodically monitor liver and kidney function.

Immune system effects

Anaphylactic responses have occurred which have usually responded to cessation of therapy and administration of pressor agents, corticosteroids, antihistamines or volume expanders, as appropriate.

Secondary leukemia

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

Neither the cumulative risk, nor the predisposing factors related to the development of secondary leukemia are known. The roles of both administration schedules and cumulative doses of etoposide have been suggested, but have not been clearly defined.[3]

Tumor lysis syndrome (TLS)

Tumor lysis syndrome, sometimes fatal, has been reported following the use of etoposide in association with other chemotherapeutic drugs. Patients at high risk of TLS such as patients with high proliferative rate, high tumor burden, and high sensitivity to cytotoxic agents should be monitored closely and appropriate precaution should be taken (see section **4.8. Undesirable effects**).[3]

Extravasation

Etoposide Injection is for administration by intravenous infusion only and is not to be administered by other routes. Care should be taken not to cause extravasation during infusion. However, should this occur:

- stop perfusion at the first sign of burns;
- subcutaneously inject a corticosteroid (hydrocortisone) around the lesion;
- apply a 1% hydrocortisone ointment to the affected area until the erythema disappears;
- apply a dry dressing to the affected area for 24 hours.

Immunosuppressant effects/increased susceptibility to infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including etoposide, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving etoposide. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Other

Etoposide injection also contains ethanol as an excipient: this may be a risk factor in patients suffering from liver disease, alcoholism, epilepsy and in pregnant women and children.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Etoposide injection should not be physically mixed with any other drug. The solution should be inspected for particulate matter and discoloration prior to use.

High dose cyclosporine, 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.[3]

Concomitant cisplatin therapy is associated with reduced total body clearance of etoposide.[3]

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.[3]

Co-administration of warfarin and etoposide may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.[3]

Cross-resistance between anthracyclines and etoposide has been reported in preclinical experiments.[3]

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Etoposide may cause fetal harm when administered to pregnant women. Etoposide has been shown to be teratogenic and embryotoxic in mice and rats and its use in pregnant women is not recommended. Etoposide should only be used in women of child-bearing potential if the expected benefits outweigh the risks of therapy and adequate contraception is used. If the patient becomes pregnant whilst receiving the drug, she should be advised of the potential hazard to the fetus.

Fertility

Etoposide may decrease male fertility.[3].Given its mutagenic potential, the drug could induce chromosomal damage in human spermatozoa; therefore males undergoing treatment with etoposide should employ contraceptive measures.

Lactation

It is not known whether etoposide is excreted into breast milk, therefore breast feeding should be discontinued during therapy with etoposide.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of etoposide on the ability to drive and use machinery has not been systematically evaluated.

4.8. UNDESIRABLE EFFECTS

Blood and lymphatic system disorders: The dose limiting toxicity of etoposide is myelosuppression, predominantly leukopenia and thrombocytopenia. Anemia occurs infrequently. The leukocyte count nadir occurs approximately 21 days after treatment (see section **4.4. Special Warnings and Precautions for Use**).

Cardiac disorders: Myocardial infarction, has been reported in patients treated with etoposide as part of multi-agent chemotherapy.[3]

Eye disorders: Transient cortical blindness has been reported.

Gastrointestinal disorders: Nausea and vomiting are the major gastrointestinal (GI) toxicities and occur in over one-third of patients. Anti-emetics are useful in controlling these side effects. Abdominal pain, anorexia, diarrhea, esophagitis, and stomatitis occur infrequently. Dysphagia has been reported.

General disorders and administration site conditions: Fatigue, pyrexia and asthenia have been reported.[3]

Immune system disorders: Anaphylactoid reactions have been reported following administration of etoposide. Higher rates of anaphylactoid reactions have been reported in children who received infusions at concentrations higher than those recommended. These reactions have usually responded to cessation of therapy and administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate (see section **4.4. Special Warning and Precautions for Use**).

Infections and infestations: Septic shock, sepsis, neutropenic sepsis, pneumonia, and infection.[1]

Injury, poisoning, and procedural complications: Radiation phenomenon has been reported.

Metabolism and nutrition disorders: Tumor lysis syndrome, sometimes fatal, has been reported following the use of etoposide in association with other chemotherapeutic drugs.[3]

Nervous system disorders: The use of etoposide has been reported infrequently to cause peripheral neuropathy. Somnolence and aftertaste also have been reported. Seizures have been reported.[3]

Respiratory, thoracic and mediastinal disorders: Apnoea with spontaneous resumption of breathing following discontinuation of Etoposide Injection has been reported. Sudden fatal reactions associated with bronchospasm have been reported.

Skin and subcutaneous tissue disorders: Alopecia occurs in approximately two-thirds of patients and is usually reversible on cessation of therapy. Rash, pigmentation disorder, pruritus, and urticaria have been reported.

Vascular disorders: Hypotension may occur following an excessively rapid infusion and may be reversed by slowing the infusion rate. Hypertension and/or flushing have also been reported. Blood pressure usually returns to normal within a few hours after cessation of the infusion.

4.9. OVERDOSE

Overdose data is limited. Hematological and GI toxic effects are expected to be the principle manifestations of etoposide overdosage. Treatment will be mainly supportive. There is no known antidote.[2]

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Etoposide is a semi-synthetic podophyllotoxin derivative.

Mechanism of action

The exact mechanism of action of etoposide is not known, however, it appears to produce cytotoxic effects by damaging DNA, thereby inhibiting or altering DNA synthesis. Etoposide is cell-cycle dependent, and cycle-phase specific, inducing G_2-phase arrest and preferentially killing cells in the G_2 and late S phases. Two different dose dependent responses have been observed. High concentrations (10 μg/mL or more) cause cell lysis in cells entering mitosis. Low concentrations (0.3 to 10 μg/mL) inhibit cells from entering prophase. Etoposide induced DNA damage appears to correlate well with the cytotoxicity of the drug. Etoposide appears to induce indirectly single-stranded DNA breaks.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Following intravenous administration, peak plasma concentrations and plasma concentration vs. time curves (AUC) exhibit marked inter-individual variation.

Distribution

Distribution of etoposide into human body tissues and fluids has not been fully evaluated. Etoposide administered intravenously undergoes rapid distribution. The apparent steady-state volume of distribution averages 20-28% of body weight. After intravenous administration, etoposide is distributed minimally into pleural fluid, and has been detected in the saliva, liver, spleen, kidney, myometrium, healthy brain, and also brain tumor tissue. Studies suggest distribution into bile is minimal. It is not known if etoposide is distributed into breast milk. Studies have shown that etoposide crosses the placenta in animals. Etoposide penetrates the central nervous system (CNS) poorly: cerebrospinal fluid (CSF) etoposide concentrations have ranged from undetectable to less than 5% of plasma concentrations.

Limited data suggests that etoposide distributes into brain tumor tissue more readily than into healthy brain tissue. Etoposide concentrations have been shown to be higher in healthy lung tissue than in lung metastases, but those achieved in primary myometrial tumors are similar to those achieved in healthy myometrial tissues. *In vitro*, etoposide is approximately 94% bound to serum proteins at a concentration of 10 μg/mL.

Metabolism

In vitro studies suggest that metabolic activation of etoposide by oxidation to the ortho-quinone derivative might play an essential role in its activity against DNA. Etoposide is approximately 66% metabolized.

Elimination

Following intravenous administration, plasma concentrations of etoposide have generally been reported to decline in a biphasic manner; however, some data indicate that the drug may exhibit triphasic elimination with a prolonged terminal phase. In adults with normal renal and hepatic function, the half-life of etoposide averages 0.6-2 hours in the initial phase and 5.3-10.8 hours in the terminal phase. In children with normal renal and hepatic function, the half-life averages 0.6-1.4 hours in the initial phase and 3-5.8 hours in the terminal phase.

After 72 hours, 44% of the administered dose was recovered in the urine, 29% as unchanged drug and 15% as metabolite. Recovery in the feces ranged from less than 2% to 16% over three days.

Total plasma clearance of etoposide has been reported as averaging 19-28 mL/minute/m^2 in adults and 18-39 mL/minute/m^2 in children with normal renal and hepatic function. Renal clearance approximates 30-40% of total plasma clearance.

Downwards dosage adjustment may be necessary in patients with impaired renal or hepatic function.

5.3. PRECLINICAL SAFETY DATA

The intravenous LD_{50} of etoposide was 220, 82 and 49 mg/kg for mice, rats and rabbits, respectively. In dogs, the maximum non-lethal dose was ≤ 20 mg/kg. The main targets after a single dose were the hemolymphopoietic system, GI tract, and testes. Mild signs of hepatic and renal toxicity were seen in dogs.

The toxic effects after repeated administration of parenteral etoposide were investigated in rats and dogs. The main targets in the above animal species were the hemolymphopoietic system, GI tract, urinary bladder, and male reproductive organs. As opposed to subacute toxicity, no severe effect on the GI tract was seen after chronic doses. Most of the changes regressed during the recovery period, with the exception of those detected in the genito-urinary apparatus.

Etoposide was genotoxic in the *in vitro* and *in vivo* tests performed and toxic to the male reproductive organs. In spite of this, fertility was not reduced in rats and etoposide did not modify gestation parameters in rats and rabbits, even at doses that proved to be markedly toxic for dams and fetuses in both species and caused malformations and abnormalities in rats. No long-term toxicity was noted in the F_1 generation, and the F_2 generation did not appear to be affected by treatment. There are no animal data available on the carcinogenicity of the compound but etoposide, like other cytotoxic drugs, must be considered potentially carcinogenic. The compound was found to be devoid of any antigenic potential. Specific mouse and rat studies indicate that administration of etoposide into any body cavities lined by a serous membrane should be avoided.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Macrogol 300 (or 400)

Citric Acid

Polysorbate 80

Ethanol

6.2. INCOMPATIBILITIES

Plastic devices made of acrylic or ABS (a polymer of acrylonitrile, butadiene, and styrene) has been reported to crack or leak when used with undiluted Etoposide Injection.

6.3. SHELF LIFE

A shelf life of 24 months from date of manufacture is recommended when stored below 25°C and protected from light.

Shelf life period after first opening container
Etoposide Injection is a single use presentation. Etoposide Injection has been shown to be microbiologically stable for at least 16 hours after the first piercing of the rubber stopper when stored below 25°C. It is recommended that any contents remaining in the vial after withdrawal of the required dose should be discarded.

Shelf life after dilution/reconstitution
Contact with buffered aqueous solutions with pH above 8 should be avoided. Prior to infusion, the etoposide formulation is to be diluted in 5% glucose or 0.9% sodium chloride to a concentration in the range of 0.2 - 0.4 mg/mL. The solution may be stored at room temperature (25°C) under normal fluorescent light in either glass or plastic containers. In line with good pharmaceutical practice it is recommended that the solution is used within 24 hours after dilution (preferably stored at 2-8°C).

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC. Protect from light. To reduce microbiological hazards, admixtures should be used as soon as practicable after preparation.
If storage is necessary, hold at 2-8ºC for no longer than 24 hours. Discard unused portion.
The expiry date (month/year) is stated on the package after EXP.

6.5. INSTRUCTIONS FOR USE/HANDLING

As with all antineoplastic agents, trained personnel should prepare Etoposide Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling etoposide. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as etoposide.

Luer-Lock fitting syringes are recommended.

Large bore needles are recommended to minimize pressure and possible formation of aerosols.
Aerosols may also be reduced by using a venting needle during preparation.
Items used to prepare Etoposide Injection, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100°C.

Spills and disposals - If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with absorbent material such as absorbent towel of adsorbent granules. Collect up

absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labeled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C' Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

6.6. HOW SUPPLIED

Etoposide Injection 100 mg in 5 mL (sterile)
Plastic Vial. (10's pack)

Etoposide/LPD/PK-01
According to CDS V 3.0 dated 17 October 2018; Supersedes CDS V 1.0 dated 17 August 2009

Packed and Marketed by:
Pfizer Pakistan Limited
B-2, S.I.T.E. Karachi.

7. REFERENCES

1. Lincoff A, Vo T. A Clinical Expert to support revisions to the etoposide Core Data Sheet. Safety & Risk Management, Pfizer Inc. August 2009.

2. MICROMEDEX Healthcare Series: POISONDEX Summary. 1974-2009 (Copyright). Online. Thomson Reuters. Available: www.thomsonhc.com. 16 June 2009.

3. 2.5 Clinical Overview To Support the Updates to Sections 4.4, 4.5, 4.6, and 4.8 of the Core Data Sheet October 2018.