Package Insert

MYLAN ETOPOSIDE
Concentrate for Solution for Injection 20 mg/mL

COMPOSITION
Mylan Etoposide Concentrate for Solution for Injection 20 mg/mL - Each mL contains Etoposide 20 mg.

PRODUCT DESCRIPTION
Mylan Etoposide Concentrate for Solution for Injection 20 mg/mL is nearly colourless to yellow liquid filled in type I flint vials with 20mm grey bromobutyl omniflex plus coated rubber closures with 20mm flip off aluminium seals. The reconstituted solution is a clear colourless liquid.

PHARMACODYNAMICS
Pharmacotherapeutic group: antineoplastic agent-podophyllotoxin derivatives
ATC code: L01CB01

Etoposide is a semi-synthetic podophyllotoxin derivative. Its main effect seems to occur during the G_2 phase of the cell cycle. Two dose-dependent reactions occur: at high concentrations (> 10 µg/ml), lysis can be observed of the cells entering mitosis; at low concentrations (0.3–10 µg/ml), the cells are prevented from entering the prophase. The main macromolecular effect appears to be inhibition of DNA synthesis.

PHARMACOKINETICS
The concentration of etoposide in blood and organs is low with maximum values in the liver and the kidneys. Protein binding could be as high as 98%. On intravenous administration, the disposition of etoposide is best described as a biphasic process with an initial half-life of about 1.5 hours. After distribution, half-life is about 40 hours. The terminal half-life is 6-8 hours.

Etoposide is cleared by both renal and nonrenal processes i.e. metabolism and biliary excretion. In patients with renal dysfunction plasma etoposide clearance is decreased.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration and nonrenal clearance. In children, elevated serum ALT levels are associated with reduced drug total body clearance. Prior use of cisplatin may result in a decrease of etoposide total body clearance.

Following a single intravenous dose etoposide is excreted in the urine for about 63% and in the faeces for about 31% after 80 hours.

INDICATIONS

Etoposide is indicated for the management of:

- Testicular tumors in combination with other chemotherapeutic agents.
- Small cell lung cancer, in combination with other chemotherapeutic agents.
- Monoblastic leukemia (AML M5) and acute myelomonoblastic leukemia (AML M4) when standard therapy has failed (in combination with other chemotherapeutic agents).

RECOMMENDED DOSAGE

Mylan Etoposide concentrate for solution for infusion 20 mg/ml must be diluted immediately prior to use with either 5% dextrose in water, or 0.9% sodium chloride solution to give a final concentration of 0.2 to 0.4 mg/ml. At higher concentrations precipitation of epotoside may occur. The usual dose of etoposide is, in combination with other approved chemotherapeutic agents, ranges from 100-120mg/m^2 /day *via* continuous infusion over 30 minutes for 3-5 days, followed by a resting period of 10-20 days. Generally 3 to 4 chemotherapy cycles are administered. Dose and amount of cycles should be adjusted to the level of bone marrow suppression and the reaction of the tumour. Dose adjustment is required in cases of renal function impairment. In patients with a measured creatinine clearance of greater than 50ml/minute, no initial dose modification is required. In patients with a measured creatinine clearance of 15-50ml/minute, 75% of the initial recommended etoposide dose should be administered. Although specific data are not available in patients with a measured creatinine clearance less than 15ml/minute, further dose reduction should be considered. Subsequent etoposide dosing should be based on patient tolerance and clinical effect.

CONTRAINDICATIONS

Severe myelosuppression, unless when this is caused by the underlying disease.

- Liver impairment.
- Hypersensitivity to etoposide or to any of the excipients.
- Patients with severe renal impairment (creatinine clearance < 15 ml/min).
- This product contains benzyl alcohol. Must not be given to premature babies or neonates.
- Breast feeding.

WARNINGS AND PRECAUTIONS

Etoposide should be administered under the supervision of qualified physician experienced in the use of cancer chemotherapeutic agents. Physicians should be aware that the treatment with etoposide may be an anaphylactic reaction manifested as chills, fever, flushing, tachycardia, bronchospasm, dyspnea and hypotension, which may be fatal. Treatment is symptomatic. The infusion must be stopped and followed by administration of pressor agents, corticosteroids, antihistamines or volume expanding resources by physician. There may be reactions at injection site during administration.

If etoposide is to be administered intravenously, paravenous injection must be carefully avoided. It is recommended to monitor the infusion site closely for possible infiltration during drug administration. There is no known specific treatment for extravasation at this time.

There may be severe myelosuppression with resultant infection or bleeding.

There have been reports of fatal myelosuppression after administration of etoposide. Patients treated with etoposide should be monitored closely and frequently for myelosuppression both during and after treatment. Dose limiting bone marrow suppression is the most significant toxicity associated with etoposide treatment. The following observations should be made at the start of treatment and before each subsequent dose etoposide: platelet count, hemoglobin and total and differential count of leukocytes. If radiotherapy or chemotherapy was carried out before the start of etoposide treatment, a suitable interval must elapse for the bone marrow to recover.

After the initial dose, subsequent doses adjusted if the neutrophil count below 500 cells/mm^3 occurring in more than 5 days or associated with fever or infection, if there is platelet counts below 25,000 cells/mm^3 if they develop any other toxicity of grade 3 or 4, or if the renal clearance is below 50 ml/min. The dosage should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of previous radiation therapy or chemotherapy which may have compromised bone marrow reserve.

Occurrence of acute leukemia, which can occur with or without a pre-leukaemic phase, has been reported rarely in patients treated with etoposide in combination with other antineoplastic drugs.

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.

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. An increased risk for infusion-related hypersensitivity reactions was observed when in-line filters were used during etoposide administration. In-line filters should not be used.

Before etoposide treatment is started, bacterial infections should be brought under control.

The infusion should be given slowly, during 30 to 60 minutes, to avoid hypotension or bronchospasm.

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 judgement 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 alertness as to possible recurrence of toxicity.

In patients with a lower serum albumin level, the risk of toxicity caused by etoposide can be elevated. Before the start of therapy, during the therapy, and before each course of treatment, a peripheral blood panel (white blood cells, platelets, haemoglobin), renal function, and hepatic function should be checked, and neurological functions should be investigated. Courses of therapy with etoposide should in generally be carried out only if the patient's liver and kidneys are functioning normally. If the patient is suffering from hepatic or renal dysfunction, renal and hepatic function should regularly monitored due to the risk of accumulation. Furthermore, courses of therapy with etoposide should be carried out only if the peripheral nervous system is functioning normally.

Etoposide is mutagenic and carcinogenic. This should be taken into account when a long-term treatment is performed.

In view of etoposide mutagenic potential, both male and female patients use effective contraception during treatment and up to 6 months after treatment. It is recommended to seek genetic counseling if the patient wants to have children after treatment. Since etoposide may reduce fertility in men, may be considered to allow sperm storage for subsequent paternity.

<u>Paediatric population</u>
Safety and efficacy in children has not been systematically studied.

Anaphylactic reactions have been reported in paediatric patients who received Etoposide Injection Excipient (s) that the clinician should be aware of:

Benzyl alcohol
As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age. Not to be used in neonates.

Polysorbate 80
Etoposide Injection contains polysorbate 80. In newborn infants a life threatening syndrome of liver, cholestasis and renal failure, pulmonary deterioration, thrombocytopenia and ascites has been associated with an injectable vitamin E product containing polysorbate 80.

Effects on ability to drive and use machines
No studies on the effects on the ability and use machines have been performed with etoposide. Fatigue, somnolence, nausea, vomiting and acute hypersensitivity reactions may occur due to a drop in blood pressure, and this may impair the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICAMENTS
The co-administration of high doses of cyclosporine (serum concentration >2000 ng/ml) and oral etoposide led to AUC values for etoposide that were elevated by 80% and to clearance that was reduced by 38% in comparison with etoposide monotherapy.

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

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

Prior or concurrent use of other drugs with similar myelosuppression action as etoposide may be expected to have additive or synergetic effects.

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

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

Concomitant warfarin therapy may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended. Cross resistance between anthracyclines and etoposide has been reported in preclinical experiments.

CAUTIONS FOR USAGE
Any contact with the fluid should be avoided. During preparation and reconstitution a strictly aseptic working technique should be used; protective measures should include the use of gloves,

mask, safety goggles and protective clothing. Use of a vertical laminar airflow (LAF) hood is recommended.

Gloves should be worn during administration. Waste-disposal procedures should take into account the cytotoxic nature of this substance. If etoposide contacts skin, mucosae or eyes, immediately wash thoroughly with water. Soap may be used for skin cleansing.

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

Etoposide Injection must not be mixed with other drugs when administered. This medicinal product must not be mixed with other medicinal products excepts those mentioned in section Recommended Dosage.

PREGNANCY AND LACTATION

Pregnancy
Etoposide can cause fetal harm when administered to pregnant women. Etoposide have been shown to be teratogenic in mice and rats. There are no adequate and well controlled studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus.

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.

Lactation
It is not known whether these drugs are excreted in human milk. 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.

Benzyl alcohol is probably excreted into breast milk and can be orally absorbed by the infant.

Fertility:
As etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.

SIDE EFFECTS
The following adverse events have been reported in association with Etoposide therapy:

System Organ Class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Infection				
Neoplasms Benign and malignant (including cysts and polyps)		Acute leukemia				
Blood and the lymphatic system disorders	Myelosuppression, Leukopenia, thrombocytopenia, neutropenia, anemia					
Cardiac disorders		Myocardial infarcation, arrythmia				
Immune system disorders		Anaphylactic type reactions i.e fever, shivering, tachycardia, bronchospasm, dyspnoea, and hypotonia				
Metabolism and nutritiondisorders				Hyperuricemia		
Nervous system disorders		Dizzines	Neuropathy peripheral	Seizure, optic neuritis, cortical blindness transient, neurotoxicities (e.g somnolence, fatigue)		
Eye disorders				Transitory loss of vision, optic neuritis		
Vascular disorders		Transient systolic hypotension following rapid intravenous administration, hypertension				

System Organ Class	Very common	Common	Uncommon	Rare	Very rare	Not known
Respiratory, thoracic and mediastinal disorder				Pulmonary fibrosis, interstitial pneumonitis		
Gastrointestinal disorders	Abdominal pain, constipation, nausea and vomiting, anorexia	Mucositis (including stomatitis and esophagitis), diarrhea		Dysphagia, dysgeusia		
Hepato-biliary disorders	Hepatotoxicity					
Skin and subcutaneous tissue disorder	Alopecia, pigmentation	Rash, urticaria, pruritus		Stevens-johnson syndrome, toxic epidermal necrolysis, radiation recall dermititis		
General disorders and administration conditions site	Asthenia, malaise	Extravasation, phlebitis				

Hematological Toxicity:
The dose-limiting effect of etoposide is myelosuppression. 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 depending on the way of administration and treatment scheme. Nadirs tend to occur earlier with intravenous administration compared to oral administration.

Gastrointestinal Toxicity:
Nausea and vomiting are the main gastrointestinal undesirable effects.

Alopecia:
Reversible alopecia, sometimes progressing to total baldness has been observed.

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 resulting the infusion, a slower administration rate should be used. No delayed hypotension has been noted.

Hypertension:
In clinical studies involving etoposide injection, hypertension has been reported. If clinically significant hypertension occurs in patients receiving etoposide injection, appropriate supportive therapy should be initiated.

Allergic reactions:
Anaphylactic type reactions have also been reported to occure 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. Actual fatal reactions associated with bronchospasm have been reported with etoposide.

Metabolic complications:
Tumour lysis syndroms (sometime fatal) has been reported following the use of etoposide in association with other chemotherapeutic drugs.

Infection:
Including infections seen in patients with a weakened immune system, e.g. a lung infection called pneumocystis jirovecii pneumonia.

OVERDOSE AND TREATMENT
Overdose can lead within one-two weeks to severe myelosuppression. Total doses of 2.4-3.5 g/m^2 of etoposide administered intravenously over 3 days have caused mucositis and myelotoxicity. Metabolic acidosis and severe hepatic toxicity have been reported after the administration of doses that were higher than recommended. There is no specific antidote available. Treatment should therefore be symptomatic and supportive, and patients should be closely monitored.

STORAGE
Store below 30°C.
Diluted solution is stable up to 96 hours when stored at 25°C at specified concentrations.

DOSAGE FORMS AND PACKAGING AVAILABLE
500 mg/25 ml vials: Carton of 1 vial

For further information, please consult your physician or pharmacist.

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Manufactured by:
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