

DBL[®] ETOPOSIDE INJECTION

Injection

Description

DBL[®] Etoposide Injection is a colourless to pale yellow viscous liquid.

Etoposide is a semi-synthetic derivative of podophyllotoxin.

Chemical name: 4'-demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-b-d-glucopyranoside.

Empirical formula: C₂₉H₃₂O₁₃.

MW: = 588.58

DBL[®] Etoposide Injection contains: Etoposide, citric acid, polysorbate 80, Macrogol 300, and ethanol.

Pharmacology

In vitro studies suggest that etoposide initially causes metaphase, however this effect appears to be superseded by interference with cell cycle progression before the cell enters mitosis. Cytofluorometric studies using human lymphoblast cell lines have shown that the major delay in cell cycle progression and the maximum cell killing occurs in the S or G2 phases of the cell cycle. This has been confirmed in several cell lines. The mechanism by which this occurs is unknown but may be related to an inhibition of nucleoside transport demonstrated in HeLa cells. Etoposide does not interfere with microtubule assembly. It is particularly active in human leukaemia cells and a high response rate is also seen in small cell carcinoma of the lung.

Etoposide acts indirectly on cultured HeLa cells and induces single-stranded breaks in DNA. This effect was not demonstrated on DNA *in vitro*.

Pharmacokinetics :

Absorption: Absorption from the oral route of administration is variable and incomplete. Peak blood levels occur about one hour after oral administration.

Bioavailability: While the absolute bioavailability averaged approximately 55.0% there were considerable variations between subjects (17-74%) and in one study within individual subjects.

The standard oral dose is approximately twice the effective intravenous dose.

Distribution : Following intravenous administration of 100 mg etoposide the peak plasma concentration ranged from 2.2-6.1 microgram/mL with an average of 4.7, and time to peak ranged from 0.5-2.0 hours (average 1 hour). Only small levels are found in the cerebrospinal fluid, compared with plasma levels. In a limited number of children, etoposide administered in a dose of 200-250 mg/m² produced a mean plasma clearance of 17.8±11.2 (SD) mL/min/m² based on a model-independent method. The elimination half-life based on a model-dependent method averaged 5.8±3.2 hours.

Etoposide is stored extensively in the tissues and has a volume of distribution during terminal phase of excretion of 28 L.

Protein binding : *In vitro*, etoposide is highly protein bound (97%) to human plasma proteins.

Metabolism: Etoposide is approximately 66% metabolised. One metabolite has been identified but its activity not studied. However, it appears to be extensively distributed and retained. After 72 hours, 44% of

the administered dose of etoposide was recovered in the urine; 29% as unchanged drug and 15% as metabolite. Recovery in the faeces ranged from less than 2% to 16% over three days.

Excretion: Renal clearance 13.6 ± 4.5 mL/min: total body clearance 47 ± 22 mL/min. The one metabolite identified has a renal clearance of 31.3 mL/min and total clearance of 111.7 mL/min.

Half Life: Etoposide shows a biexponential plasma decay curve. The beta phase half life is 11.5 hours.

Clinical Implications of Pharmacokinetic Data : Etoposide and its metabolite are widely distributed within the body and bound to tissue protein. Only about 60% of the administered drug can be accounted for by unchanged or metabolised drug excreted in the urine or faeces, indicating prolonged tissue storage.

The fact that approximately 30% of the administered dose is excreted unchanged by the kidneys indicates that the dosage may need to be adjusted in patients with renal impairment.

Indications

DBL[®] Etoposide Injection is indicated for use in the treatment of:

1. Small cell carcinoma of the lung.
2. Acute monocytic and myelomonocytic leukaemia.
3. Hodgkin's disease.
4. Non-Hodgkin's lymphoma.

Contraindications

Patients with severe hepatic dysfunction. Patients who have a demonstrated hypersensitivity to any of the ingredients. Severe bone marrow failure (WBC less than 2000 cells/mm^3 or platelet count less than $75\,000 \text{ cells/mm}^3$) not due to malignant disease.

Precautions

Etoposide Injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe myelosuppression with resulting infection or bleeding may occur.

In all instances where the use of Etoposide Injection 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 Injection therapy should be carried out with caution, and with adequate consideration of the further need for the drug and alertness as to the possible recurrence of toxicity.

Patients being treated with Etoposide Injection must be observed for myelosuppression carefully and frequently both during and after therapy. Dose limiting bone marrow suppression is the most significant toxicity associated with Etoposide Injection therapy. Therefore the following counts should be obtained at the start of therapy and prior to each subsequent course of Etoposide Injection: platelet count, haemoglobin, white blood cell count and differential. The occurrence of a platelet count below $50,000/\text{mm}^3$ indicates that the patient is at risk of bleeding; the occurrence of a total white cell count below $3,000/\text{mm}^3$ or an absolute neutrophil count below $500/\text{mm}^3$ indicates that the patient is at risk of infection. Therapy should not be commenced if there is a risk of the platelet count, the white cell count or

the neutrophil count falling below these levels. Furthermore, if the counts drops below these levels during therapy, further therapy should be withheld until the blood counts have sufficiently recovered.

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifest by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension. Treatment is symptomatic. Administration of Etoposide Injection should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

There have been reports of cardiac arrest secondary to allergic reactions during infusion with etoposide.

Etoposide Injection 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 infusion.

Infections must be brought under control before using etoposide due to bone marrow suppression following use of the drug and the risk of septicaemia.

Combined chemotherapy may cause increased bone marrow suppression and should be used with caution.

Laboratory Tests: Periodic complete blood counts, hepatic and renal function tests and serum urate should be done during the course of Etoposide Injection treatment. They should be performed prior to therapy and at appropriate periods during therapy. At least one determination should be done to each course of Etoposide Injection.

Patients with Impaired Liver or Renal Function : Etoposide Injection should be given cautiously to individuals with any degree of hepatic or renal dysfunction (see Dosage and Administration with Impaired Liver Function and with Impaired Renal Function).

Carcinogenesis, Mutagenesis, Impairment of Fertility : Six-month chronic studies in rats have shown Etoposide Injection to have oncogenetic potential but two-year carcinogenicity tests with Etoposide Injection have not been conducted in laboratory animals. Given its mechanism of action, it should be considered a possible carcinogen in humans.

Etoposide Injection induced aberrations in chromosome number and structure in embryonic murine cells. (See also Adverse Reactions, Haematological)

Use in Pregnancy:

Category D. Etoposide Injection can cause foetal harm when administered to pregnant women. Etoposide Injection had been shown to be teratogenic in mice and rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be appraised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Etoposide Injection was subjected to a teratology study in SPF rats at doses of 0.13, 0.4, 1.2 and 3.6 mg/kg/day administered intravenously on Days 6 to 15 of gestation. Etoposide Injection caused a dose-related maternal toxicity, embryotoxicity and teratogenicity at dose levels of 0.13 mg/kg/day and higher administered intravenously. Embryonic resorptions were 90 and 100 percent at the two highest dosages. At 0.4 and 1.2 mg/kg, foetal weights were decreased and foetal abnormalities occurred including major skeletal abnormalities, exencephaly and encephalocele and anophthalmia.

Even at the lowest dose tested, 0.13 mg/kg, a significant increase in retarded ossification was observed.

A study in Swiss-Albino mice given a single intraperitoneal injection of Etoposide Injection at dosages of 1.0, 1.5 and 2.0 mg/kg on Days 6, 7 and 8 of gestation showed dose-related embryotoxicity, various cranial abnormalities and major skeletal malformations.

Australian categorisation definition of Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying text above should be consulted for further details.

Use in Lactation:

It is not known whether this drug is excreted in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Etoposide Injection, 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.

Use in Children and Neonates:

Safety and effectiveness in children have not been established.

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

Significant Interactions with Other Drugs:

Single case reports exist of increased bone marrow depression and possible increased risk of anthracycline-induced cardiomyopathy. Etoposide Injection may need to be used with caution in combination chemotherapy.

Adverse Reactions

The incidences of adverse reactions, given below as mean percent, are derived from studies that used single agent Etoposide Injection therapy.

More Common Reactions:

Haematological Toxicity : The principal toxicity of etoposide is dose-related bone marrow suppression, with granulocyte nadirs occurring 7 to 14 days, and platelet nadirs 9 to 16 days, after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. Leucopenia (less than 4,000 cells/mm³) and severe leucopenia (less than 1,000 cells/mm³) were observed in 60 to 91 percent and 7 to 17 percent, respectively, of patients treated with single agent Etoposide Injection. Thrombocytopenia (less than 100,000 platelets/mm³) and severe thrombocytopenia (less than 50,000 platelets/mm³) were seen in 28 to 41 percent and 4 to 20 percent of this same group of patients. Pancytopenia was found in 7% of 340 patients treated with 50-60 mg/m² Etoposide Injection I.V. for 5 days.

The occurrence of acute non-lymphocytic leukaemia with or without preleukaemic phase has been reported in patients treated with Etoposide Injection in association with either antineoplastic agents, in particular, cisplatin.

Alopecia : Reversible alopecia, sometimes progressing to total baldness, has been observed in up to 66 percent of patients.

Gastrointestinal Toxicity: Nausea and vomiting are the major gastrointestinal toxicities. They have been noted in 31-43 percent of patients given intravenous Etoposide Injection. The nausea and vomiting can usually be controlled by anti-emetic therapy. Anorexia was seen in 10 to 13 percent of patients and stomatitis in 1-6 percent of those patients given intravenous Etoposide Injection. Diarrhoea was noted in 1 to 13 percent of these patients.

Hypotension : Temporary hypotension following rapid intravenous administration has been reported. The incidence has been reported between 1 and 2 percent and has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare

occurrence, it is recommended that Etoposide Injection be administered by slow intravenous infusion over a 30 to 60 minute period.

If hypotension occurs, it usually responds to stopping the infusion and administering fluids or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

Less Common Reactions :

Allergic Reactions: Anaphylactic-like reactions characterised by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension have also been reported to occur in 0.7 to 2 percent of patients, occurring during or immediately after intravenous Etoposide Injection administration. Anaphylactic-like reactions have occurred very rarely in patients treated with oral capsules. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate. One fatal acute reaction associated with bronchospasm has been reported. Hypertension and flushing have also been reported. Blood pressure usually normalises with a few hours after cessation of the infusion. Anaphylactic-like reactions can occur with the initial dose of Etoposide Injection. Apnoea has occurred in patients receiving etoposide infusion.

Solutions more concentrated than those recommended (see Dosage and Administration) should not be given intravenously. If such solutions are justifiable, higher rates of anaphylactic-like reactions may occur.

Neuropathy: The use of Etoposide Injection has been reported to cause peripheral neuropathy in 0.7 percent of patients. The associated use of vincristine sulphate can possibly enhance this neuropathy. Caution should be taken when giving etoposide and vincristine combined to older individuals whose performance status is impaired and to patients with pre-existing neurological disease and poor nutritional status.

Other Toxicities: The following reactions have been rarely reported:

Central nervous system toxicity (somnolence and fatigue), liver toxicity (transient jaundice and elevated alkaline phosphatase), renal toxicity (elevated urea; hyperuricaemia), septicaemia during high dose regimens, aftertaste; fever, rash, pigmentation, pruritus, abdominal pain, urticaria, constipation, dysphagia, transient cortical blindness, mucositis, esophagitis and a single report of radiation recall dermatitis. One case of myocardial infarction has been reported in a patient also treated with mediastinal radiation. There is one case report of a possible drug-related life-threatening cardiotoxicity. Cardiac arrest and heart failure, with some fatal outcomes have been reported. Patients with cardiac arrest secondary to acute allergic reactions recovered completely from their episodes.

Occasionally, following extravasation, soft tissue irritation and inflammation has occurred; ulceration is generally not seen.

Dosage and Administration

Biological activity appears to be schedule dependent with multiple dosage over 3 or 5 days showing superiority over single dose administration.

Adult :

Intravenous: Intravenously, 50-60 mg/m²/day for 5 days followed by a treatment-free interval of 2-4 weeks.

Total dose should not exceed 400 mg/m² per course.

DBL[®] Etoposide Injection must be diluted prior to use with either Sodium Chloride Intravenous Infusion (0.9%) or 5% Glucose Injection to give a final concentration of 0.2 to 0.4 mg/mL. More concentrated solutions show crystal formation upon stirring or seeding within 5 minutes and should not be given intravenously.

Note: Hard plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) have been reported to crack and leak when used with UNDILUTED Etoposide Injection.

Hypotension following rapid intravenous administration has been reported, hence, the diluted DBL[®] Etoposide Injection solution should be administered over a period of 30 to 60 minutes. More prolonged infusion lessens the risk of a hypotensive reaction.

DBL[®] ETOPOSIDE INJECTION SHOULD NOT BE GIVEN BY A RAPID INTRAVENOUS PUSH.

Etoposide should not be mixed with other antineoplastic agents in the infusion solution.

Contact with buffered aqueous solutions above pH 8 should be avoided. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

It is important to ascertain that the intravenous catheter is properly positioned during etoposide infusion since extravasation of the drug may cause local irritation.

DBL[®] Etoposide Injection solution should be administered immediately after reconstitution, and certainly within 24 hours, in order to reduce microbiological hazard. DBL[®] Etoposide Injection solution should be stored at room temperature and does not need to be protected from normal room fluorescent light.

DBL[®] Etoposide Injection contains no antimicrobial agent. Use once only and discard any residue.

Paediatric :

Specific paediatric dosages have not been evaluated.

Geriatric :

As for Adults. However see Dosage: With Impaired Liver Function and With Impaired Renal Function.

With Impaired Liver Function :

There are indications that patients with severely impaired liver function (as expressed by an elevation of serum bilirubin above 85 micromoles/L and clinical jaundice) may develop more profound myelotoxicity during etoposide treatment. Its use is contraindicated in patients with severe hepatic dysfunction, and it should be used with caution in patients with mild to moderate hepatic impairment.

With Impaired Renal Function :

Since some etoposide (about 30% of an intravenously administered dose) is excreted unchanged in urine, dosage adjustment may be necessary in patients with impaired renal function.

Compatibility :

- a. Etoposide should not be mixed with other anti neoplastic agents in the infusion solution.
- b. pH range of maximum stability: Contact with buffered aqueous solutions above pH 8 should be avoided.
- c. Special warnings: The stability of the 1:50 dilutions of etoposide in 0.9% sodium chloride is 4 hours. If there is any evidence of crystal formation this dilution should not be administered.

Instructions to be Given to Patient :

The patient should be warned that nausea and reversible alopecia may occur as a result of etoposide therapy.

The patient should advise the clinician if any symptoms of acute reaction develop during DBL[®] Etoposide Injection infusion.

Patients should be advised to use adequate contraceptive measures during treatment with etoposide (see Precautions).

Poisoning and Overdosage:

No information is available relating to etoposide poisoning in humans. No proven antidotes have been established for Etoposide Injection overdose. Treatment will be mainly supportive. Haematologic and gastrointestinal toxic effects are expected to be the principal manifestations of etoposide overdose.

Procedures for Handling and Disposal of Anticancer Drugs :

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published, and should be used appropriately.

Professional staff administering DBL[®] Etoposide Injection infusions should exercise particular care to prevent spillage and self-contact with the drug. Any solution on the skin should be vigorously washed off with soap and cold water. Material used for cleaning accidental spills should be disposed of by incineration.

Storage

Injection: Store below 25°C. Protect from light.

Presentation

DBL[®] Etoposide Injection is available as a clear, colourless to yellow solution, in clear glass vials. Each vial contains 100 mg etoposide in 5 mL solution. DBL[®] Etoposide Injection is supplied in packs of one vial.

Name and Address

Hospira NZ Limited
23 Haining Street
Te Aro
Wellington
New Zealand

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