

NEW ZEALAND DATA SHEET

Name of Medicine

ETOPOPHOS

Etoposide phosphate 113.6mg; 500mg; 1g Vials Powder for Injection

Presentation

Each single use vial contains 113.6mg of **Etoposide phosphate** (equivalent to 100mg etoposide) as a lyophilised powder for injection. In addition each single dose vial contains 32.7mg sodium citrate and 300mg of dextran 40.

ETOPOPHOS injection is also available in pharmacy bulk vials containing either 568mg of etoposide phosphate (equivalent to 500mg etoposide) or 1136mg of etoposide phosphate (equivalent to 1g etoposide). These vials contain 163.5mg and 327.0mg of sodium citrate and 1.5g and 3g of Dextran 40 respectively.

Uses

ETOPOPHOS, a lyophilised powder form of **etoposide** (VP-16-213), a semi-synthetic derivative of podophyllotoxin, is an anti-neoplastic drug for intravenous use, which can be used alone or in combination with other oncolytic drugs.

Actions

Etoposide phosphate is converted *in vivo* to the active moiety, etoposide, by dephosphorylation. The mechanism of action of Etoposide phosphate is believed to be the same as that of etoposide. Etoposide has been shown to cause metaphase arrest in chick fibroblasts. Its main effect, however, appears to be at the G₂ portion of the cell cycle in mammalian cells. Two different dose-dependent responses are seen. At high concentrations (10 µg/mL or more), lysis of cells entering mitosis is observed. At low concentrations (0.3 to 10 µg/mL), cells are inhibited from entering prophase. It does not interfere with micro tubular assembly. The predominant macromolecular effect of etoposide appears to be DNA synthesis inhibition.

Pharmacokinetics

Following intravenous administration of ETOPOPHOS, **Etoposide phosphate** is rapidly and completely converted to **etoposide** in plasma. A direct comparison of the pharmacokinetic parameters (AUC and CMAX) of **etoposide** following intravenous administration of molar equivalent doses of ETOPOPHOS and **etoposide** was made in two randomized cross-over studies in patients with a variety of malignancies. Results from both studies demonstrated no statistically significant differences in the AUC and CMAX for etoposide when administered as ETOPOPHOS or **etoposide**. In addition, there were no statistically significant differences in the pharmacodynamic parameters (haematologic toxicity) after administration of ETOPOPHOS or **etoposide**. Because of the pharmacokinetic and pharmacodynamic bioequivalence of ETOPOPHOS to etoposide, the following information on **etoposide** should be considered:

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 48mL/min or 16 to 36mL/min/m² and, like the terminal elimination half-life, are independent of dose over a range 100-600mg/m². Over the same dose range, the areas under the plasma concentration vs. time curves (AUC) and the maximum plasma concentration (Cmax) values increase linearly with dose. **Etoposide** does not accumulate in the plasma following daily administration of 100mg/m² for 4 to 6 days.

The mean volumes of distribution at steady state fall in the range of 18 to 29 litres or 7 to 17/m². **Etoposide** enters the CSF poorly. Although it is detectable in CSF and intracerebral tumors, the concentrations are lower than in extracerebral tumors and in plasma. **Etoposide** concentrations 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 (97%) to human plasma proteins. Phenyl butazone, sodium salicylate and aspirin at concentrations achieved in vivo displace protein-bound **etoposide**.

After intravenous administration of ³H-etoposide (70-290mg/m²), mean recoveries of radioactivity in the urine range from 42 to 67%, and faecal recoveries range from 0 to 16% of the dose. Less than 50% of an intravenous dose is excreted in the urine as **etoposide** with mean recoveries of 8 to 35% within 24 hours.

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 10mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600mg/m². **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.

Biliary excretion appears to be a minor route of **etoposide** elimination. Only 6% or less of an intravenous dose is recovered in the bile as **etoposide**. Metabolism accounts for most of the

nonrenal clearance of etoposide. In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration, and nonrenal clearance. In adult cancer patients with liver dysfunction, total body clearance of **etoposide** is not reduced. Patients with impaired renal function receiving **etoposide** have exhibited reduced total body clearance, increased AUC and higher steady state volume of distribution (see DOSAGE and ADMINISTRATION). In children, elevated serum 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.

Indications

ETOPOPHOS is indicated in the treatment of:

Small Cell Lung Cancer - ETOPOPHOS Injection in combination with other approved chemotherapeutic agents as first-line treatment in patients with small cell lung cancer.

Hodgkin's Disease

Malignant (non-Hodgkin's) lymphomas, especially of the histiocytic variety

Acute non-lymphocytic leukaemia

Testicular tumors both as first-line combination regimens and for the treatment of refractory testicular tumours.

Dosage and Administration

Etopophos is administered by slow intravenous infusion. ETOPOPHOS SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION. The usual dose for **etoposide** is 50 to 100 mg/m² /day, days 1 to 5 or 100 mg/m²/day, days 1, 3 and 5 every 3 to 4 weeks in combination with other agents approved for use in the disease to be treated. Dosage should be modified to take into account the myelosuppressive effects of other medications in the combination or the effects of prior X-ray therapy or chemotherapy which may have compromised bone marrow reserve.

Etopophos may be infused over 5-210 minutes.

Prior to use, the contents of each vial must be reconstituted with Sterile Water for Injection, 5% Dextrose Injection, 0.9% Sodium Chloride Injection, Bacteriostatic Water for Injection with Benzyl Alcohol, or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol to a concentration equivalent to 20mg/mL or 10mg/mL etoposide (22.7mg/mL or 11.4mg/mL **Etoposide phosphate**), respectively. Use the following quantity of diluent:

Etopophos V3.0

Vial Strength	Volume of Diluent	Final Concentration (Etoposide Equivalent)
113.6mg	5 mL	22.7 mg/mL (20 mg/mL)
	10 mL	11.4 mg/mL (10 mg/mL)
568 mg	25 mL	22.7 mg/mL (20 mg/mL)
	50 mL	11.4 mg/mL (10 mg/mL)
1136 mg	50 mL	22.7 mg/mL (20 mg/mL)
	100 mL	11.4 mg/mL (10 mg/mL)

Following reconstitution the solution may be administered without further dilution or it can be further diluted to concentrations as low as 0.1mg/mL **etoposide** (0.11mg/mL **Etoposide phosphate**) with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection.

The 500- and 1000-mg pharmacy bulk vials are intended for use in a pharmacy admixture service only under a laminar flow hood. The closure should be penetrated only once with a sterile transfer set or other sterile dispensing device, which allows measured distribution of the contents, and the contents dispensed in aliquots using aseptic technique. Following closure puncture, container should be maintained at controlled room temperature, 20° - 25°C (68° - 77°F), under a laminar flow hood until contents are dispensed. Contents should be used as soon as possible following initial closure puncture. Unused portion should be discarded within 24 hours of closure puncture.

Renal Impairment

In patients with impaired renal function, the following initial dose modifications should be considered based on measured creatinine clearance :

Measured Creatinine Clearance	>50mL/min	15-50mL/min
Etoposide	100% of dose	75% of dose

Subsequent **etoposide** dosing should be based on patient tolerance and clinical effect. Equivalent dose adjustments of **Etopophos** should be used.

Data are not available in patients with creatinine clearances <15 mL/min and further dose reduction should be considered in these patients.

Contraindications

ETOPOPHOS is contraindicated in patients with severe hepatic dysfunction or in those patients who have demonstrated a previous hypersensitivity to **etoposide**, **Etoposide phosphate** or any component of the formulation.

Etopophos must not be given by intra-cavity injection.

Warnings and Precautions

ETOPOPHOS 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.

Since etoposide phosphate is rapidly and completely converted to etoposide, the WARNINGS and PRECAUTIONS that are considered when prescribing etoposide should be considered when prescribing ETOPOPHOS[®] (etoposide phosphate).

Fatal myelosuppression has been reported following **etoposide** administration. Patients being treated with ETOPOPHOS 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 ETOPOPHOS therapy. Therefore, the following studies should be obtained at the start of therapy and prior to each subsequent dose of ETOPOPHOS: platelet count, haemoglobin, white blood cell count and differential. The occurrence of a platelet count below $50,000/\text{mm}^3$ or an absolute neutrophil count below $500/\text{mm}^3$ is an indication to withhold further therapy until the blood counts have sufficiently recovered.

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension. Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician; however, the reactions can be fatal.

Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with anaphylactic-type reactions.

Injection site reactions may occur during the administration of ETOPOPHOS (see **Adverse Effects**). Given the possibility of extravasation, it is recommended to closely monitor

the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

General

In all instances where the use of ETOPOPHOS is considered for chemotherapy, the physician must evaluate the need and usefulness of the medicine against the risk of adverse reactions. Most such adverse reactions are reversible if detected early. If severe reactions occur, the medicine should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of ETOPOPHOS therapy should be carried out with caution, and with adequate consideration of the further need for the medicine and alertness as to possible recurrence of toxicity. Patients with low serum albumin may be at increased risk for **etoposide**-associated toxicities.

Carcinogenesis

The carcinogenic potential of ETOPOPHOS has not been studied. However, based upon its pharmacodynamic mechanism of action, ETOPOPHOS is a potential carcinogenic and genotoxic agent. Etoposide has been shown to be mutagenic in mammalian cells and ETOPOPHOS is expected to have similar mutagenic effects.

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

Pregnancy

ETOPOPHOS can cause foetal harm when administered to pregnant women. **Etoposide** has been shown to be teratogenic in mice and rats, and it is therefore assumed the ETOPOPHOS is also teratogenic. There are no adequate and well-controlled studies in pregnant women. If this medicine is used during pregnancy, or if the patient becomes pregnant while receiving this medicine, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Nursing Mothers

It is not known whether this drug is 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 ETOPOPHOS, 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.

Paediatric Use

Safety and effectiveness in children have not been systematically studied.

Adverse Effects

ETOPOPHOS has been found to be well tolerated as a single agent in clinical studies involving 206 patients with a wide variety of malignancies, and in combination with cisplatin in 60 patients with small cell lung cancer. The most frequent clinically significant adverse experiences were leukopenia and neutropenia.

Unless otherwise stated, the following safety data relate to 98 patients administered single agent ETOPOPHOS therapy at or above 450mg/m² on a 5 consecutive day or day 1, 3 and 5 schedule. Adverse events reported were those occurring during or following the first course of therapy.

Acute fatal reactions associated with bronchospasm have been reported.

The most frequent undesirable effect of ETOPOPHOS was leukopenia, occurring in 91% of patients (<4000 cells/mm³). Severe leukopenia (<1000 cells/mm³) in 17% of patients.

Neutropenia (<2000 cells/mm³) occurred in 88% of patients and was severe (<500 cells/mm³) in 37% of patients. Fever and infection have also been reported in patients with neutropenia.

Thrombocytopenia (<100,000 thrombocytes/mm³) was reported in 23% of patients. Nine percent of patients had a platelet count nadir 50,000 thrombocytes/mm³.

Anaemia (Hb<11g/dL) was observed in 72% of patients and was severe (Hb8g/dL) in 19% of patients.

Gastrointestinal adverse events were usually mild to moderate: Nausea and/or vomiting (37% of patients), anorexia (16%), mucositis (11%), constipation (8%), abdominal pain (7%), diarrhoea (6%) and taste alteration (6%) were reported. Treatment discontinuation was required in 1% of patients.

Asthenia or malaise affected 39% of patients and was severe in 3% of patients.

Alopecia was observed in 23% of patients.

In clinical studies involving Etopophos, 151 patients were treated with infusion times ranging from 30 minutes to 3.5 hours, and 63 patients received a 5 minute bolus injection. Four patients experienced one or more episodes of hypertension and 8 patients one or more episodes of hypotension, which may or may not be drug related. Only one of the episodes of hypotension was reported among the patients receiving the 5 minute bolus injection. If clinically significant hyper or hypotension occurs in patients receiving Etopophos, appropriate supportive therapy should be initiated.

Other events reported were: chills and/or fever (24% of patients), dizziness (5%) and extravasation/phlebitis (5%).

Since **Etoposide phosphate** is converted to **etoposide**, the adverse experiences reported below that are associated with **etoposide** can be expected to occur with ETOPOPHOS.

The following data on adverse reactions are based on both oral and intravenous administration of etoposide as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Haematological Toxicity

Myelosuppression with fatal outcome has been reported following etoposide administration (see Warnings and Precautions). Myelosuppression is most often dose-limiting, with leukocyte nadirs occurring 15 to 22 days, granulocyte nadirs occurring 12 to 19 days, and platelet nadirs occurring 10 to 15 days, after administration. Bone marrow recovery is usually complete by day 21, and no cumulative toxicity has been reported. Fever and infection have also been reported in patients with neutropenia.

Leukopenia and severe leukopenia (less than 1,000 cells/mm³) were observed from 60 to 91% and 7 to 17%, respectively, in patients treated with single agent etoposide. Thrombocytopenia and severe thrombocytopenia (less than 50,000 platelets/mm³) were seen in 28 to 41% and 4 to 20%, respectively, with this same group of patients. The occurrence of acute leukaemia with or without a preleukaemic phase has been reported in patients treated with etoposide in association with other antineoplastic agents.

Gastrointestinal Toxicity

Nausea and vomiting are the major gastrointestinal toxicities. They have been noted in 31-43% of patients given intravenous etoposide. The nausea and vomiting can usually be controlled by antiemetic therapy. Anorexia was seen in 10 to 13% of patients and stomatitis in 1-6% of those patients given intravenous etoposide. Mild to severe mucositis/esophagitis may occur. Diarrhoea was noted in 1 to 13% of these patients.

Alopecia

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

Hypotension

Temporary hypotension following rapid intravenous administration has been reported. The incidence has been reported between 1 and 2% of patients and has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. If hypotension occurred with etoposide, it usually responded to stopping the infusion and administering fluid or other supportive therapy as appropriate.

Allergic Reactions

Anaphylactic-like reactions characterized by chills, rigors, fever, tachycardia, bronchospasm, dyspnoea, diaphoresis, fever, pruritis, hypertension or hypotension, loss of consciousness, nausea, and vomiting have also been reported to occur in 3% of patients. These have occurred

Etopophos V3.0

during or immediately after etoposide administration. Higher rates of anaphylactic-like reactions have been reported in children who received infusions at concentrations higher than those recommended. The role that concentration of infusion (or rate of infusion plays in the development of anaphylactic-like reactions) is uncertain.

Anaphylactic-like reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate. However, the reactions can be fatal.

Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions can occur with the initial dose of etoposide. Apnea with spontaneous resumption of breathing following discontinuation of the infusion has been described.

Rash, urticaria, and/or pruritis have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.

Neuropathy

The use of etoposide has been reported to cause peripheral neuropathy in 0.7% of patients. The associated use of vincristine sulphate can possibly enhance this neuropathy.

Other Toxicities

The following reactions have been rarely reported: Interstitial pneumonitis/pulmonary fibrosis, seizures (occasionally associated with allergic reactions), central nervous system toxicity (somnolence and fatigue), liver toxicity, aftertaste, fever, oesophagitis, Stevens Johnson syndrome, toxic epidermal necrolysis (one fatal case has been reported), rash, pigmentation, pruritis, urticaria, abdominal pain, constipation, dysphagia, asthenia, malaise, transient cortical blindness, a single report of radiation recall dermatitis, and optic neuritis. Rarely, hepatic toxicity may be seen.

Hepatic toxicity, generally in patients receiving higher doses of etoposide than those recommended, have been reported. Metabolic acidosis has also been reported in patients receiving higher doses.

Local soft tissue toxicity has been reported following extravasation of ETOPOPHOS. Infiltration of ETOPOPHOS may result in swelling, pain, cellulitis and necrosis including skin necrosis.

Interactions

ETOPOPHOS should not be physically mixed with any other drug.

Caution should be exercised when administering ETOPOPHOS with drugs that are known to inhibit of phosphatase activities (eg, levamisole hydrochloride). High dose cyclosporin, (concentrations >2000 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.

Overdosage

No proven antidotes have been established for ETOPOPHOS overdosage.

Metabolic acidosis and cases of serious hepatic toxicity have been reported in patients receiving higher than recommended intravenous doses of **etoposide**.

Total **etoposide** doses doses of 2.4g/m² to 3.5g/ m² administered intravenously over three days have resulted in severe mucositis and myelotoxicity.

Pharmaceutical Precautions

As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of ETOPOPHOS. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If ETOPOPHOS solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Procedures for proper handling and disposal of anti-cancer agents should be considered. Several guidelines on this subject have been published.

ETOPOPHOS. powder for injection should be stored at 2-8°C (refrigerate). The injection should be protected from light. At these temperatures, ETOPOPHOS will remain stable until expiration date indicated on package.

Preparation for Intravenous Administration: Solutions of ETOPOPHOS should be prepared in an aseptic manner. Prior to use, the contents of each vial must be reconstituted with Sterile Water for Injection, 5% Dextrose Injection, 0.9% Sodium Chloride Injection, Bacteriostatic Water for Injection with Benzyl Alcohol, or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol to a concentration equivalent to 20 mg/mL or 10 mg/mL **etoposide** (22.7 mg/mL or 11.4 mg/mL **Etoposide phosphate**), respectively. Following reconstitution the solution may be administered without further dilution or it can be further diluted to concentrations as low as 0.1 mg/mL **etoposide** (0.14 mg/mL **Etoposide phosphate**) with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection.

When reconstituted as directed, ETOPOPHOS solutions can be stored in glass or plastic containers under refrigeration 2°-8 °C (36 °-46 °F) for 7 days; at controlled room temperature 20°-25 °C (68°-77 °F) for 24 hours following reconstitution with Sterile Water for Injection, USP, 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP; or at controlled room temperature 20°-25 °C (68°-77 °F) for 48 hours following reconstitution with Bacteriostatic Water for Injection with Benzyl Alcohol or Bacteriostatic Sodium chloride for Injection with Benzyl Alcohol. ETOPOPHOS solutions further diluted as directed can be stored under refrigeration 2°-8 °C (36 °-46 °F) or at controlled room temperature 20°-25 °C (68°-77 °F) for 24 hours. Solutions of ETOPOPHOS should be prepared in an aseptic manner.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

The intravenous solution is suitable for infusion in glass or PVC containers.

Expiry Date:

ETOPOPHOS Injection: 36 months when stored at 2-8°C.

Medicine Classification

Prescription Medicine.

Package Quantities

ETOPOPHOS injection is packed in cartons of single vials each vial containing 113.6mg, 568mg or 1136mg **Etoposide phosphate** (equivalent to 100mg, 500mg or 1g **etoposide** respectively).

Name and Address

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