Rx only

ETOPOPHOS®
(etoposide phosphate) for INJECTION

WARNINGS

ETOPOPHOS® (etoposide phosphate) for 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.

DESCRIPTION

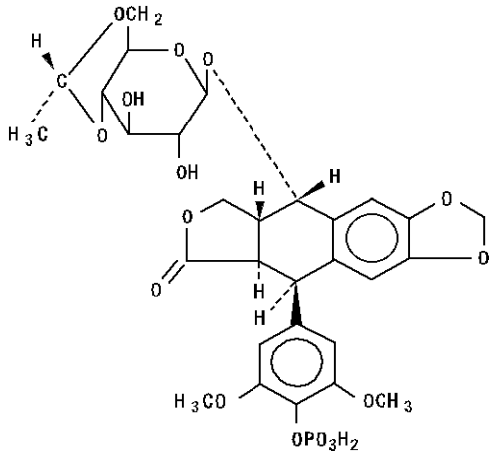
ETOPOPHOS (etoposide phosphate) for Injection is an antineoplastic agent which is available for intravenous infusion as a sterile lyophile in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate USP, and 300 mg dextran 40.

Etoposide phosphate is a water soluble ester of etoposide (commonly known as VP-16), a semi-synthetic derivative of podophyllotoxin. The water solubility of etoposide phosphate lessens the potential for precipitation following dilution and during intravenous administration.

The chemical name for etoposide phosphate is:

4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-β-D-glucopyranoside], 4'-(dihydrogen phosphate).

Etoposide phosphate has the following structure:



CLINICAL PHARMACOLOGY

The *in vitro* cytotoxicity observed for etoposide phosphate is significantly less than that seen with etoposide which is believed due to the necessity for conversion *in vivo* to the active moiety, etoposide, by dephosphorylation. The mechanism of action 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 G_2 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 (0.3-10 µg/mL), cells are inhibited from entering prophase. It does not interfere with microtubular assembly. The predominant macromolecular effect of etoposide appears to be the induction of DNA strand breaks by an interaction with DNA-topoisomerase II or the formation of free radicals.

ETOPOPHOS Bioequivalence

Following intravenous administration of ETOPOPHOS, etoposide phosphate is rapidly and completely converted to etoposide in plasma. A direct comparison of the pharmacokinetic parameters [area under the concentration time curve (AUC) and the maximum plasma concentration (C_{max})] of etoposide following intravenous administration of molar equivalent doses of ETOPOPHOS and VePesid® was made in two randomized crossover studies in patients with a variety of malignancies. In the first study of 41 evaluable patients, the etoposide mean ± S.D. AUC values were 168.3 ± 48.2 µg•hr/mL and 156.7 ± 43.4 µg•hr/mL following administration of molar equivalent doses of 150 mg/m^2 ETOPOPHOS or VePesid

with a 3.5-hour infusion time; the corresponding mean ± S.D. C_{max} values were 20.0 ± 3.7 μg/mL and 19.6 ± 4.2 μg/mL, respectively. The point estimate (90% confidence interval) for the bioavailability of etoposide from ETOPOPHOS, relative to VePesid, was 107% (105%, 110%) for AUC and 103% (99%, 106%) for C_{max}. In the second study of 29 evaluable patients following intravenous administration of 90, 100, and 110 mg/m^2 molar equivalents of ETOPOPHOS or VePesid with a 60-minute infusion time, the etoposide mean ± S.D. AUC values (normalized to the 100 mg/m^2 dose) were 96.1 ± 22.6 μg•hr/mL and 86.5 ± 25.8 μg•hr/mL, respectively; the corresponding mean ± S.D. C_{max} values (normalized to the 100 mg/m^2 dose) were 20.1 ± 4.1 μg/mL and 19.0 ± 5.1 μg/mL, respectively. The point estimate (90% confidence interval) for the bioavailability of etoposide from ETOPOPHOS, relative to VePesid, was 113% (107%, 119%) for AUC and 107% (101%, 113%) for C_{max} indicating bioequivalence. Results from both studies demonstrated no statistically significant differences in the AUC and C_{max} parameters for etoposide when administered as ETOPOPHOS or VePesid. In addition, in the latter study, there were no statistically significant differences in the pharmacodynamic parameters (hematologic toxicity) after administration of ETOPOPHOS or VePesid. Following VePesid administration, the mean nadir values (expressed as percent decrease from baseline) for leukocytes, granulocytes, hemoglobin, and thrombocytes were 67.2 ± 17.0%, 84.1 ± 14.6%, 22.6 ± 9.8%, and 46.4 ± 21.9%, respectively; the corresponding values after administration of ETOPOPHOS were 67.3 ± 14.2%, 81.0 ± 16.5%, 21.4 ± 9.9%, and 44.1 ± 20.7%, respectively.

Because of the similarity of pharmacokinetics and pharmacodynamics of etoposide after administration of either ETOPOPHOS or VePesid, the following information on VePesid should be considered:

VePesid Pharmacokinetics

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 48 mL/min or 16 to 36 mL/min/m^2 and, like the terminal elimination half-life, are independent of dose over a range 100 to 600 mg/m^2. Over the same dose range, the AUC and the C_{max} 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. After intravenous infusion the C_{max} and AUC values exhibit marked intra- and inter-subject variability.

The mean volumes of distribution at steady state fall in the range of 18 to 29 liters or 7 to 17 L/m^2. 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. An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children. In a study determining the effect of other therapeutic agents on the *in vitro* binding of carbon-14 labeled etoposide to human serum proteins, only phenylbutazone, sodium salicylate, and aspirin displaced protein-bound etoposide at concentrations achieved *in vivo*.

Etoposide binding ratio correlates directly with serum albumin in patients with cancer and in normal volunteers. The unbound fraction of etoposide significantly correlated with bilirubin in a population of cancer patients. Data have suggested a significant inverse correlation between serum albumin concentration and free fraction of etoposide (see **PRECAUTIONS**).

After intravenous administration of ^{14}C-etoposide (100-124 mg/m^2), mean recovery of radioactivity in the urine was 56% of the dose at 120 hours, 45% of which was excreted as etoposide; fecal recovery of radioactivity was 44% of the dose at 120 hours.

In children, approximately 55% of the dose of VePesid is excreted in the urine as etoposide in 24 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. 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 of unchanged drug and/or metabolites is an important route of etoposide elimination as fecal recovery of radioactivity is 44% of the intravenous dose. The hydroxy acid metabolite [4'-demethylepipodophyllic acid-9-(4,6-O-(R)-ethylidene-β-D-gluco-pyranoside)], formed by opening of the lactone ring, is found in the urine of adults and children. It is also present in human plasma, presumably as the *trans* isomer. Glucuronide and/or sulfate conjugates of etoposide are also excreted in human urine. Only 8% or less of an intravenous dose is excreted in the urine as radiolabeled metabolites of ^{14}C-etoposide. In addition, O-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration, and nonrenal clearance. Patients with impaired renal function

receiving etoposide have exhibited reduced total body clearance, increased AUC, and a lower volume of distribution at steady state (see **PRECAUTIONS**). Use of cisplatin therapy is associated with reduced total body clearance. 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.

Although some minor differences in pharmacokinetic parameters between age and gender have been observed, these differences were not considered clinically significant.

Clinical Studies

A total of seven clinical trials with 365 patients treated (368 entered) provide the database for the human experience summarized in this insert. Five phase I trials evaluated etoposide phosphate given on a days 1, 3, and 5 or days 1 through 5 schedule. In two trials the drug was given over 5 minutes and in three over 30 minutes. The following table summarizes the doses, schedules, infusion times, and numbers of patients entered in the phase I experience.

Dose Escalation (Phase I) Trials of Etoposide Phosphate

Study	Schedule Q 21 days	Infusion Time	Dose Range (mg/m^2)	Number of Patients Entered
002	Days 1-5	30 minutes	25-110	68
005	Days 1,3,5	30 minutes	50-175	39
006	Days 1-5	30 minutes	50-125	28
008	Days 1,3,5	5 minutes	50-200	36
009	Days 1-5	5 minutes	50-125	27

Two trials evaluated the pharmacokinetic equivalence of etoposide and etoposide phosphate. A phase I study (002) was expanded at the higher doses to compare the pharmacokinetic profile of etoposide following administration of etoposide or etoposide phosphate. Another multi-institutional trial (012) was conducted at a dose of 150 mg/m^2 using a day 1, 3, and 5 schedule and a crossover design.

The seventh trial (011) was a randomized study in which patients with limited or extensive small cell lung cancer and no prior therapy were treated with either cisplatin plus etoposide or cisplatin plus etoposide phosphate. Patients received 20 mg/m^2/day of cisplatin for 5 days and 80 mg/m^2/day of etoposide or etoposide phosphate. A total of 121 patients were randomized and 120 treated (60 per group). Response rates, time to response, duration of response, time to progression, time to worsening performance status, and survival were

similar in the two groups whether the analysis was done for patients with limited or extensive disease or for the entire population. The following table summarizes the results regardless of disease extent.

Response to Treatment for All Patients			
	Etoposide Phosphate plus Cisplatin	**Etoposide plus Cisplatin**	**P-value**
Complete Responses:	15%	15%	1.000*
Partial Responses:	46%	43%	0.855*
Overall Response Rate:	61%	58%	0.854*
Median Time to Response:	48 days	46 days	0.596**
Median Response Duration:	273 days	241 days	0.141***
Median Time to Progression:	211 days	213 days	0.500***
Median Time to Worsening Performance Status:	210 days	149 days	0.472***
Median Survival:	348 days	318 days	0.780***
*Fisher's Exact test **Wilcoxon Rank Sum test ***Logrank test			

The most prominent side effects were myelosuppression and GI toxicity. Sixty-eight percent of patients treated with etoposide phosphate plus cisplatin had neutrophils less than 500/mm^3 at some time during treatment as did 88% of those getting etoposide and cisplatin. Over 85% in each group had nausea and/or vomiting. No differences in the pattern or severity of side effects were observed.

INDICATIONS AND USAGE

ETOPOPHOS for Injection is indicated in the management of the following neoplasms:

Refractory Testicular Tumors-ETOPOPHOS for Injection in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic, and radiotherapeutic therapy.

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

CONTRAINDICATIONS

ETOPOPHOS for Injection is contraindicated in patients who have demonstrated a previous hypersensitivity to etoposide, etoposide phosphate, or any other component of the formulations.

WARNINGS

Patients being treated with ETOPOPHOS must be frequently observed for myelosuppression both during and after therapy. Myelosuppression resulting in death has been reported following etoposide administration. 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 cycle of ETOPOPHOS: platelet count, hemoglobin, white blood cell count, and differential. The occurrence of a platelet count below 50,000/mm^3 or an absolute neutrophil count below 500/mm^3 is an indication to withhold further therapy until the blood counts have sufficiently recovered. The toxicity of rapidly infused ETOPOPHOS in patients with impaired renal or hepatic function has not been adequately evaluated. The toxicity profile of ETOPOPHOS when infused at doses >175 mg/m^2 has not been delineated.

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension. Higher rates of anaphylactic-like reactions have been reported in children who received infusions of etoposide 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. (See **ADVERSE REACTIONS**.) 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.

Injection site reactions may occur during the administration of ETOPOPHOS (see **ADVERSE REACTIONS**). Closely monitor the infusion site for possible infiltration during drug administration. No specific treatment for extravasation reactions is known.

ETOPOPHOS can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats, and it is therefore likely that ETOPOPHOS is also teratogenic.

In rats, an intravenous etoposide dose of 0.4 mg/kg/day (about 1/20 of the human dose on a mg/m^2 basis) during organogenesis caused maternal toxicity, embryotoxicity, and teratogenicity (skeletal abnormalities, exencephaly, encephalocele, and anophthalmia); higher doses of 1.2 and 3.6 mg/kg/day (about 1/7 and 1/2 of the human dose on a mg/m^2 basis) resulted in 90% and 100% embryonic resorptions. In mice, a single 1.0 mg/kg (1/16 of the human dose on a mg/m^2 basis) dose of etoposide administered intraperitoneally on days

6, 7, or 8 of gestation caused embryotoxicity, cranial abnormalities, and major skeletal malformations. An intraperitoneal dose of 1.5 mg/kg (about 1/10 of the human dose on a mg/m^2 basis) on day 7 of gestation caused an increase in the incidence of intrauterine death and fetal malformations and a significant decrease in the average fetal body weight.

If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be warned of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

ETOPOPHOS should be considered a potential carcinogen in humans. The occurrence of acute leukemia with or without a preleukemic phase has been reported in rare instances in patients treated with etoposide alone or in association with other neoplastic agents. The risk of development of a preleukemic or leukemic syndrome is unclear. Carcinogenicity tests with ETOPOPHOS have not been conducted in laboratory animals.

PRECAUTIONS

General

In all instances where the use of ETOPOPHOS 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 ETOPOPHOS 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.

Patients with low serum albumin may be at an increased risk for etoposide associated toxicities.

Drug Interactions

Caution should be exercised when administering ETOPOPHOS with drugs that are known to inhibit phosphatase activities (e.g., levamisole hydrochloride). High-dose cyclosporin A resulting in concentrations above 2000 ng/mL administered with oral etoposide has led to an 80% increase in etoposide exposure with a 38% decrease in total body clearance of etoposide compared to etoposide alone.

Laboratory Tests

Periodic complete blood counts should be done during the course of ETOPOPHOS treatment. They should be performed prior to each cycle of therapy and at appropriate intervals during and after therapy.

Renal Impairment

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

Measured Creatinine Clearance	>50 mL/min	15-50 mL/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.

Carcinogenesis (see WARNINGS), Mutagenesis, Impairment of Fertility

ETOPOPHOS was non-mutagenic in *in vitro* Ames microbial mutagenicity assay and the *E. coli* WP2 uvrA reverse mutation assay. Since ETOPOPHOS is rapidly and completely converted to etoposide *in vivo* and etoposide has been shown to be mutagenic in Ames assay, ETOPOPHOS should be considered as a potential mutagen *in vivo*.

In rats, an oral dose of ETOPOPHOS at 86.0 mg/kg/day (about 10 times the human dose on a mg/m^2 basis) or above administered for 5 consecutive days resulted in irreversible testicular atrophy. Irreversible testicular atrophy was also present in rats treated with ETOPOPHOS intravenously for 30 days at 5.11 mg/kg/day (about 1/2 of the human dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category D. (See **WARNINGS**.)

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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Anaphylactic reactions have been reported in pediatric patients who received etoposide (see **WARNINGS**).

Geriatric Use

Clinical studies of etoposide for the treatment of refractory testicular tumors did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Of more than 600 patients in four clinical studies in the NDA databases who received ETOPOPHOS or etoposide in combination with other chemotherapeutic agents for the treatment of small cell lung cancer, about one third were older than 65 years. When advanced age was determined to be a prognostic factor for response or survival in these studies, comparisons between treatment groups were performed for the elderly subset. In the one study (etoposide in combination with cyclophosphamide and vincristine compared with cyclophosphamide and vincristine or cyclophosphamide, vincristine, and doxorubicin) where age was a significant prognostic factor for survival, a survival benefit for elderly patients was observed for the etoposide regimen compared with the control regimens. No differences in myelosuppression were seen between elderly and younger patients in these studies except for an increased frequency of WHO Grade III or IV leukopenia among elderly patients in a study of etoposide phosphate or etoposide in combination with cisplatin. Elderly patients in this study also had more anorexia, mucositis, dehydration, somnolence, and elevated BUN levels than younger patients.

In five single-agent studies of etoposide phosphate in patients with a variety of tumor types, 34% of patients were aged 65 years or more. WHO Grade III or IV leukopenia, granulocytopenia, and asthenia were more frequent among elderly patients.

Postmarketing experience also suggests that elderly patients may be more sensitive to some of the known adverse effects of etoposide, including myelosuppression, gastrointestinal effects, infectious complications, and alopecia.

Although some minor differences in pharmacokinetic parameters between elderly and non-elderly patients have been observed, these differences were not considered clinically significant.

Etoposide and its metabolites are known to be substantially excreted by the kidney, and the risk of adverse reactions to ETOPOPHOS may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **PRECAUTIONS: Renal Impairment**, for recommended dosing adjustments in patients with renal impairment).

ADVERSE REACTIONS

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.

The incidences of adverse experiences in the table that follows are derived from studies in which ETOPOPHOS was administered as a single agent. A total of 98 patients received total doses at or above 450 mg/m^2 on a 5 consecutive day or day 1, 3, and 5 schedule during the first course of therapy.

Summary of Adverse Events Reported With Single-Agent ETOPOPHOS Following Course 1 at Total Five Day Doses of ≥450 mg/m^2		
		Percent of Patients
Hematologic toxicity		
Leukopenia	<4000/mm^3	91
	<1000/mm^3	17
Neutropenia	<2000/mm^3	88
	<500/mm^3	37
Thrombocytopenia	<100,000/mm^3	23
	<50,000/mm^3	9
Anemia	<11 g/dL	72
	<8 g/dL	19
Gastrointestinal toxicity		
Nausea and/or vomiting		37
Anorexia		16
Mucositis		11
Constipation		8
Abdominal Pain		7
Diarrhea		6
Taste Alteration		6
Asthenia/Malaise		39
Alopecia		33
Chills and/or Fever		24
Dizziness		5
Extravasation/Phlebitis		5

Since etoposide phosphate is converted to etoposide, those adverse experiences that are associated with VePesid can be expected to occur with ETOPOPHOS.

Hematologic Toxicity

Myelosuppression after ETOPOPHOS administration is dose related and dose limiting with the leukocyte nadir counts occurring from day 15 to day 22 after initiation of drug therapy, granulocyte nadir counts occurring day 12 to 19 after initiation of drug therapy, and platelet nadirs occurring from day 10 to 15. Bone marrow recovery usually occurs by day 21 but may be delayed, and no cumulative toxicity has been reported. Fever and infection have also been reported in patients with neutropenia. Death associated with myelosuppression has been reported following etoposide administration.

Gastrointestinal Toxicity

Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy.

Blood Pressure Changes

In clinical studies, 151 patients were treated with ETOPOPHOS with infusion times ranging from 30 minutes to 3.5 hours. Sixty-three patients received ETOPOPHOS as a 5-minute bolus infusion. Four patients experienced one or more episodes of hypertension and eight patients experienced one or more episodes of hypotension, which may or may not be drug related. One episode of hypotension was reported among those patients who received a 5-minute bolus infusion. If clinically significant hypotension or hypertension occurs with ETOPOPHOS, appropriate supportive therapy should be initiated.

Allergic Reactions

Anaphylactic-type reactions characterized by chills, rigors, tachycardia, bronchospasm, dyspnea, diaphoresis, fever, pruritus, hypertension or hypotension, loss of consciousness, nausea, and vomiting have been reported to occur in 3% (7/245) of all patients treated with ETOPOPHOS. Facial flushing was reported in 2% and skin rashes in 3% of patients receiving ETOPOPHOS. These 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 initial infusion.

Anaphylactic-like reactions have occurred during the initial infusion of ETOPOPHOS (see **WARNINGS**). Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported.

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

Alopecia

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

Other Toxicities

The following adverse reactions have been reported: abdominal pain, aftertaste, constipation, dysphagia, fever, transient cortical blindness, interstitial pneumonitis/pulmonary fibrosis, optic neuritis, pigmentation, seizure (occasionally associated with allergic reactions), Stevens-Johnson syndrome, toxic epidermal necrolysis, and radiation recall dermatitis. Hepatic toxicity may be seen.

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.

The incidences of adverse reactions in the table that follows are derived from multiple databases from studies in 2081 patients when VePesid was used either orally or by injection as a single agent.

Adverse Drug Effects Observed With Single-Agent VePesid	Percent Range of Reported Incidence
Hematologic toxicity	
Leukopenia (<1000/mm^3)	3-17
Leukopenia (<4000/mm^3)	60-91
Thrombocytopenia (<50,000/mm^3)	1-20
Thrombocytopenia (<100,000/mm^3)	22-41
Anemia	0-33
Gastrointestinal toxicity	
Nausea and vomiting	31-43
Abdominal pain	0-2
Anorexia	10-13
Diarrhea	1-13
Stomatitis	1-6
Hepatic	0-3
Alopecia	8-66
Peripheral neurotoxicity	1-2
Hypotension	1-2
Allergic Reaction	1-2

OVERDOSAGE

No proven antidotes have been established for ETOPOPHOS overdosage in humans. In mice, a single intravenous dose of rapidly administered ETOPOPHOS was lethal at or above 120 mg/kg (about 7 times human dose on a mg/m^2 basis) and was associated with clinical signs of neurotoxicity.

DOSAGE AND ADMINISTRATION

The usual dose of VePesid for Injection in testicular cancer in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m^2/day on days 1 through 5 to 100 mg/m^2/day on days 1, 3, and 5. Equivalent doses of ETOPOPHOS should be used.

In small cell lung cancer, the VePesid for Injection dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m^2/day for 4 days to 50 mg/m^2/day for 5 days. Equivalent doses of ETOPOPHOS should be used.

For recommended dosing adjustments in patients with renal impairment, see **PRECAUTIONS**.

ETOPOPHOS SHOULD NOT BE GIVEN BY BOLUS INTRAVENOUS INJECTION. ETOPOPHOS solutions may be administered at infusion rates from 5 to 210 minutes. Chemotherapy courses are repeated at 3- to 4-week intervals after adequate recovery from any toxicity.

The dosage should be modified to take into account the myelosuppressive effect of other drugs in the combination or the effects of prior x-ray therapy or chemotherapy which may have compromised bone marrow reserve.

Administration 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 ETOPOPHOS may occur. The use of gloves is recommended. If ETOPOPHOS solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

Preparation for Intravenous Administration

Prior to use, the content of each vial must be reconstituted with Sterile Water for Injection, USP; 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; 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 or 11.4 mg/mL etoposide phosphate, respectively). Use the quantity of diluent shown below to reconstitute the product.

Vial Strength	Volume of Diluent	Final Concentration
100 mg	5 mL	20 mg/mL
	10 mL	10 mg/mL

Following reconstitution, ETOPOPHOS can be further diluted to concentrations as low as 0.1 mg/mL etoposide with either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP.

Solutions of ETOPOPHOS should be prepared in an aseptic manner. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Stability

Unopened vials of ETOPOPHOS for Injection are stable until the date indicated on the package when stored under refrigeration 2° to 8°C (36°-46°F) in the original package. When reconstituted as directed, ETOPOPHOS solutions can be stored in glass or plastic containers under refrigeration 2° to 8°C (36°-46°F) for 7 days; at controlled room temperature 20° to 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° to 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° to 8°C (36°-46°F) or at controlled room temperature 20° to 25°C (68°-77°F) for 24 hours.

HOW SUPPLIED

ETOPOPHOS® (etoposide phosphate) for Injection is supplied as individual cartoned vials with white flip-off seals containing etoposide phosphate equivalent to 100 mg etoposide:

NDC 0015-3404-20 100 mg single-dose vial

Storage

Store the unopened vials under refrigeration 2° to 8°C (36°-46°F). Retain in original package to protect from light.

Handling and Disposal

Caution should be exercised when handling ETOPOPHOS for Injection. Procedures for proper handling and disposal of anticancer drugs should be utilized. Several guidelines on this subject have been published.[1-4]

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing ETOPOPHOS for Injection. More information is available in the references listed below.

REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

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