

ETOPOPHOS- etoposide phosphate injection, powder, lyophilized, for solution

H2-Pharma, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ETOPOPHOS safely and effectively. See full prescribing information for ETOPOPHOS.

**ETOPOPHOS® (etoposide phosphate) for injection, for intravenous use
Initial U.S. Approval: 1983**

INDICATIONS AND USAGE

ETOPOPHOS is a topoisomerase inhibitor indicated for the treatment of patients with:

- Refractory testicular tumors, in combination with other chemotherapeutic drugs. (1)
- Small cell lung cancer, in combination with cisplatin, as first-line treatment. (1)

DOSAGE AND ADMINISTRATION

- Refractory testicular tumors: 50 to 100 mg/m² per day administered intravenously over 5 minutes to 3.5 hours on days 1 through 5, or 100 mg/m² administered intravenously over 5 minutes to 3.5 hours on days 1, 3, and 5. (2.1)
- Small cell lung cancer: 35 mg/m² per day administered intravenously over 5 minutes to 3.5 hours for 4 days or 50 mg/m² per day administered intravenously over 5 minutes to 3.5 hours for 5 days. (2.2)
- Do not give by bolus injection. (2.4)
- Renal impairment: Reduce the recommended dose to 75% in patients with creatinine clearance 15 to 50 mL/min. (2.3)

DOSAGE FORMS AND STRENGTHS

For injection: 114 mg etoposide phosphate (equivalent to 100 mg etoposide), white to off-white, lyophilized powder in single-dose vial for reconstitution. (3, 11)

CONTRAINDICATIONS

Hypersensitivity to etoposide products. (4, 5.3)

WARNINGS AND PRECAUTIONS

- Myelosuppression: Obtain complete blood counts prior to each cycle and more frequently as clinically indicated. (5.1)
- Secondary leukemias: Can occur with long-term use. (5.2)
- Hypersensitivity reactions: Hypersensitivity reactions including anaphylaxis may occur. (5.3)
- Embryo-fetal toxicity: ETOPOPHOS can cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception during treatment with ETOPOPHOS and for 6 months after final dose. Advise males to use effective contraception for 4 months, after the last dose of ETOPOPHOS. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reaction is neutropenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact the Safety Call Center at 1-866-885-0690 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Warfarin: Co-administration can result in elevated international normalized ratio (INR). Measure INR frequently. (7)

USE IN SPECIFIC POPULATIONS

Lactation: Do not breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Refractory Testicular Tumors
- 1.2 Small Cell Lung Cancer

2 DOSAGE AND ADMINISTRATION

- 2.1 Refractory Testicular Tumors
- 2.2 Small Cell Lung Cancer
- 2.3 Dosage Modification
- 2.4 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Myelosuppression
- 5.2 Secondary Leukemias
- 5.3 Hypersensitivity Reactions
- 5.4 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Refractory Testicular Tumors

ETOPOPHOS is indicated, in combination with other chemotherapeutic drugs, for treatment of patients with refractory testicular tumors.

1.2 Small Cell Lung Cancer

ETOPOPHOS is indicated, in combination with cisplatin, for first-line treatment of patients with small cell lung cancer.

2 DOSAGE AND ADMINISTRATION

2.1 Refractory Testicular Tumors

The recommended dose of ETOPOPHOS is:

- 50 to 100 mg/m² per day administered intravenously over 5 minutes to 3.5 hours on days 1 through 5 of each 21-day (or 28-day cycle), or
- 100 mg/m² administered intravenously over 5 minutes to 3.5 hours on days 1, 3, and 5 of each 21-day (or 28-day cycle).

2.2 Small Cell Lung Cancer

The recommended dose of ETOPOPHOS is:

- 35 mg/m² per day administered intravenously over 5 minutes to 3.5 hours for 4 days, or
- 50 mg/m² per day administered intravenously over 5 minutes to 3.5 hours for 5 days.

2.3 Dosage Modification

In patients with a creatinine clearance (CL_{cr}) 15-50 mL/min, administer 75% of the recommended dose.

Data are not available in patients with CL_{cr} less than 15 mL/min. Consider further dose reduction in these patients.

2.4 Preparation and Administration

Preparation

- Reconstitute 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, using the quantity of diluent shown below:

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 with either 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Storage

After reconstitution, store under the following conditions:

- Refrigerated 2° to 8°C (36° to 46°F) for 7 days;
- Room temperature at 20° to 25°C (68° to 77°F) for 24 hours following reconstitution with Sterile Water for Injection, USP, 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP;
- Room temperature 20° to 25°C (68° to 77°F) for 48 hours following reconstitution with Bacteriostatic Water for Injection with benzyl alcohol or Bacteriostatic Sodium Chloride for Injection with benzyl alcohol.

Reconstituted ETOPOPHOS solutions further diluted as directed can be stored under refrigeration 2° to 8°C (36° to 46°F) or at room temperature 20° to 25°C (68° to 77°F) for 24 hours.

Administration

DO NOT GIVE ETOPOPHOS BY BOLUS INTRAVENOUS INJECTION. ETOPOPHOS solutions may be administered at infusion rates up to 3.5 hours. Extravasation of ETOPOPHOS may result in swelling, pain, cellulitis, and necrosis including skin necrosis.

ETOPOPHOS is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹ To minimize the risk of dermal exposure, use of gloves is recommended. If dermal contact occurs, immediately and thoroughly wash areas of skin contact with soap and water and flush mucosa with water.

3 DOSAGE FORMS AND STRENGTHS

For injection: 114 mg etoposide phosphate (equivalent to 100 mg etoposide), white to off-white, lyophilized powder in single-dose vial for reconstitution [see *Description (11)*].

4 CONTRAINDICATIONS

ETOPOPHOS is contraindicated in patients with a history of a severe hypersensitivity reaction to etoposide products [see *Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

ETOPOPHOS causes myelosuppression that results in thrombocytopenia and neutropenia. Fatal infections and bleeding have occurred. Obtain complete blood counts prior to each cycle of ETOPOPHOS and more frequently as clinically indicated [see

Adverse Reactions (6.1)].

5.2 Secondary Leukemias

Secondary leukemias have occurred with long term use of ETOPOPHOS.

5.3 Hypersensitivity Reactions

ETOPOPHOS can cause hypersensitivity reactions, including rash, urticaria, pruritus, and anaphylaxis [*see Adverse Reactions (6.1)]*. If hypersensitivity reactions occur, immediately interrupt ETOPOPHOS and institute supportive management. Permanently discontinue ETOPOPHOS in patients who experience a severe hypersensitivity reaction.

5.4 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, ETOPOPHOS can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential hazard to the fetus [*see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with ETOPOPHOS and for at least 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose [*see Use in Specific Populations (8.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Myelosuppression [*see Warnings and Precautions (5.1)]*
- Secondary leukemias [*see Warnings and Precautions (5.2)]*
- Hypersensitivity reactions [*see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates, observed in the clinical trials of a drug, cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ETOPOPHOS has been used as a single agent in clinical studies involving 206 patients with a variety of malignancies (including one non-Hodgkin's lymphoma) and in combination with cisplatin in 60 patients with small cell lung cancer. The most common adverse reaction was neutropenia.

Other Important Adverse Reactions

Gastrointestinal Toxicity

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

Other Toxicities

Other clinically important adverse reactions in clinical trials were:

Gastrointestinal: abdominal pain, constipation, dysphagia

General: fever

Ocular: transient cortical blindness, optic neuritis

Respiratory: interstitial pneumonitis/pulmonary fibrosis

Skin: pigmentation, radiation recall dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Neurologic: seizure, aftertaste

Hepatobiliary disorder: hepatotoxicity

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ETOPOPHOS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Extravasation

Extravasation, resulting in local soft tissue toxicity. Extravasation of ETOPOPHOS can result in swelling, pain, cellulitis, and necrosis, including skin necrosis.

Acute Renal Failure

Reversible cases of acute renal failure have been reported with administration of high dose (2220 mg/m²) ETOPOPHOS with total body irradiation used for hematopoietic stem cell transplantation. The ETOPOPHOS formulation contains dextran 40, which has been associated with acute renal failure when administered in high doses.

7 DRUG INTERACTIONS

Warfarin: Co-administration of ETOPOPHOS with warfarin can result in elevated international normalized ratio (INR). Measure INR frequently.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action, ETOPOPHOS can cause fetal harm when administered to a pregnant woman. Etoposide, the active moiety of etoposide phosphate is teratogenic in mice and rats (*see Data*). Advise pregnant women of the potential hazard to a fetus.

Advise women of childbearing potential to avoid becoming pregnant.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In rats, an intravenous etoposide dose of 0.4 mg/kg/day (about 0.05 times of the 50 mg/m² human dose based on body surface area [BSA]) 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 0.14 and 0.5 times the 50 mg/m² human dose based on BSA) resulted in 90%

and 100% embryonic resorptions. In mice, a single etoposide dose of 1.0 mg/kg (approximately 0.06 times the 50 mg/m² human dose based on BSA) 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 0.1 times the 50 mg/m² human based on BSA) 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 [see *Nonclinical Toxicology (13.1)*].

8.2 Lactation

There is no information regarding the presence of etoposide in human milk or its effects on breastfed infant milk production. Because of the potential for serious adverse reactions in nursing infants from ETOPOPHOS, advise women not to breastfeed during treatment with ETOPOPHOS.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with ETOPOPHOS and for 6 months after the final dose.

Males

ETOPOPHOS may damage spermatozoa and testicular tissue, resulting in possible genetic fetal abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during treatment with ETOPOPHOS and for 4 months after the final dose.

Infertility

Females

In females of reproductive potential, ETOPOPHOS may cause infertility and result in amenorrhea. Premature menopause can occur with ETOPOPHOS. Recovery of menses and ovulation is related to age at treatment.

Males

In male patients, ETOPOPHOS may result in oligospermia, azoospermia, and permanent loss of fertility. Sperm counts have been reported to return to normal levels in some men, and in some cases, have occurred several years after the end of therapy [See *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of etoposide did not include sufficient numbers (n=71) of patients aged 65 years and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

10 OVERDOSAGE

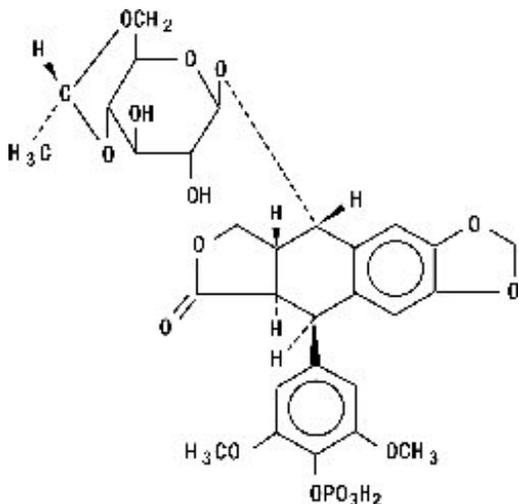
No antidote has been established for ETOPOPHOS overdose in humans. Based on

animal studies, overdose may result in neurotoxicity.

11 DESCRIPTION

ETOPOPHOS (etoposide phosphate) is a topoisomerase inhibitor. 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:



Etoposide phosphate is a phosphate ester of etoposide, a semi-synthetic derivative of podophyllotoxin. ETOPOPHOS is available for intravenous infusion as a sterile lyophilized powder in single-dose vials for reconstitution containing 114 mg etoposide phosphate, equivalent to 100 mg etoposide, 32.7 mg sodium citrate USP, and 300 mg dextran 40.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Etoposide phosphate is a prodrug that is converted to its active moiety, etoposide, by dephosphorylation. Etoposide causes the induction of DNA strand breaks by an interaction with DNA-topoisomerase II or the formation of free radicals, leading to cell cycle arrest, primarily at the G2 stage of the cell cycle, and cell death.

12.2 Pharmacodynamics

Following intravenous administration of 90, 100, and 110 mg/m² dose of ETOPOPHOS over 60 minutes, mean nadir values (expressed as percent decrease from baseline) for granulocytes, hemoglobin, and thrombocytes were 81.0 ± 16.5%, 21.4 ± 9.9%, and 44.1 ± 20.7%, respectively.

12.3 Pharmacokinetics

Following intravenous administration of an etoposide formulation, the area under the concentration time curve (AUC) and maximum plasma concentration (C_{max}) values increased linearly and etoposide did not accumulate in the plasma following daily administration for 4 to 5 days.

Distribution

Following administration of an injectable etoposide formulation, the mean volume of distribution of etoposide at steady state was 18 to 29 liters.

Etoposide enters the CSF poorly.

In vitro, etoposide is 97% bound to human plasma proteins, primarily albumin.

Elimination

The terminal elimination half-life of etoposide ranges from 4 to 11 hours. Total body clearance values range from 33 to 48 mL/min.

Metabolism

Following intravenous administration of ETOPOPHOS, etoposide phosphate is completely converted to etoposide in plasma. Etoposide is metabolized by opening of the lactone ring, O-demethylation, and conjugation (i.e., glucuronidation and sulfation). O-demethylation occurs through the CYP450 3A4 isoenzyme pathway to produce the active catechol metabolite.

Excretion

At 120 hours after intravenous administration of radiolabeled etoposide formulation, the mean recovery of radioactivity in the urine was 56% of the dose, 45% of which was excreted as etoposide and 8% or less as metabolites. Fecal recovery of radioactivity was 44% of the dose.

Specific Populations

Following intravenous administration of etoposide in adults, the total body clearance of etoposide was correlated with creatinine clearance, serum albumin concentration, and non-renal clearance. No clinically significant differences in the pharmacokinetics of etoposide were observed based on age and sex.

Drug Interaction Studies

Cisplatin: Co-administration of cisplatin may increase exposure to etoposide.

Highly protein-bound drugs: Phenylbutazone, sodium salicylate, and aspirin displaced protein-bound etoposide in vitro.

Select antiepileptic medications: Co-administration with antiepileptic medications including phenytoin, phenobarbital, carbamazepine, and valproic acid may increase etoposide clearance.

Etoposide may be a substrate of the P-glycoprotein (P-gp) transporter system based upon in vitro studies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ETOPOPHOS was non-mutagenic in an in vitro Ames microbial mutagenicity assay; however, ETOPOPHOS is rapidly and completely converted to etoposide in vivo. Therefore, as etoposide is mutagenic in the Ames assay, ETOPOPHOS is considered mutagenic in vivo.

In rats, oral dosing of ETOPOPHOS for 5 consecutive days at doses greater than or equal to 86 mg/kg/day (about 10 times the 50 mg/m² human dose based on BSA) 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 0.5

times the 50 mg/m² human dose based on BSA).

14 CLINICAL STUDIES

Study 1 was a multicenter trial in patients, with previously untreated, small cell lung cancer, randomized (1:1) to receive either etoposide phosphate (80 mg/m²/day) plus cisplatin (20 mg/m²/day) for 5 days, or etoposide (80 mg/m²/day) plus cisplatin (20 mg/m²/day). The major efficacy outcome measure was objective response rate (ORR). Among the 121 patients enrolled, the median age was 64 years, 65% of patients were male, 89% were White, and ECOG performance score was 0 to 2. Study 1 demonstrated an overall response rate of 61% (95% confidence interval [CI] 47, 73) for patients treated with etoposide phosphate plus cisplatin, and 58% (95% CI: 45, 71) for those receiving etoposide plus cisplatin.

15 REFERENCES

1. "OSHA Hazardous Drugs." *OSHA*.
<http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied/Storage

ETOPOPHOS is supplied as a single-dose vial containing etoposide phosphate equivalent to 100 mg etoposide as a lyophilized powder for reconstitution, individually packaged in a carton:

NDC 61269-410-20

Store unopened vials at 2° to 8°C (36°-46°F). Keep vial in outer carton to protect from light.

Handling

ETOPOPHOS is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Myelosuppression

- Advise patients that periodic monitoring of their blood counts is required. Advise patients to contact their healthcare provider for new onset of bleeding, fever, or symptoms of infection [see *Warnings and Precautions* (5.1)].

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.4) and *Use in Specific Populations* (8.1, 8.3)].
- Advise females of reproductive potential to use effective contraception during and 6 months after treatment with ETOPOPHOS [see *Warnings and Precautions* (5.4) and *Use in Specific Populations* (8.1, 8.3)].
- Advise males with female sexual partners of reproductive potential to use condoms during treatment with ETOPOPHOS and for at least 4 months after the final dose [see

Warnings and Precautions (5.4) and Use in Specific Populations (8.3)].

Licensed by:

CHEPLAPHARM Arzneimittel GmbH

17489 Greifswald, Germany

Product of Germany

Distributed by:

H2-Pharma, LLC

Montgomery, AL 36117

ETOPOPHOS 100 mg for Injection Representative Packaging

See **How Supplied** section for a complete list of available packages of ETOPOPHOS.

NDC 61269-410-20

Single-Dose Vial

ETOPOPHOS®

(etoposide phosphate) for Injection

For IV use

Etoposide phosphate equivalent to

100 mg etoposide

Rx only



ETOPOPHOS

etoposide phosphate injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:61269-410
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
etoposide phosphate (UNII: 528XYJ8L1N) (etoposide - UNII:6PLQ3CP4P3)	etoposide	100 mg

Inactive Ingredients

Ingredient Name	Strength
SODIUM CITRATE, UNSPECIFIED FORM (UNII: 1Q73Q2JULR)	32.7 mg
DEXTRAN 40 (UNII: K3R6ZDH4DU)	300 mg

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61269-410-20	1 in 1 CARTON	06/01/2009	
1		1 in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020457	06/01/2009	

Labeler - H2-Pharma, LLC (028473634)**Registrant** - CHEPLAPHARM Arzneimittel GmbH (329834878)

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H2-Pharma, LLC