

ETOPÓSIDO SERVYCAL

ETOPOSIDE 100 mg

Solution for Injection

Sale under filed prescription

Made in Argentina

Quali-quantitative composition:

Each ampoule of Etopósido Servycal 100 mg contains:

Etoposide	0.100 g
Citric acid	0.010 g
Benzyl alcohol	0.150 g
Polysorbate 80	0.400 g
Polyethylene glycol 300	3.250 g
Absolute alcohol q.s. to	5.000 ml

CATEGORY:

Cytostatic.

INDICATIONS AND USAGE

Etoposide is indicated in the management of the following neoplasms:

Refractory testicular tumors: it is used in combination with other chemotherapeutic agents, in patients who received surgical and/or radiotherapeutic therapy.

Small cell lung cancer: it is used in combination with other chemotherapeutic agents.

PHARMACOLOGICAL ACTION:

PHARMACOKINETICS: following intravenous administration of etoposide, the disposition etoposide is described as a biphasic process with a distribution half-life of about 1.5 hours and a terminal elimination half-life of about 4 to 11 hours. Total body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min; both these values and terminal elimination half-life are independent of dose whenever it ranges over 100 – 600 mg/m².

Over the same dose range, the values of areas under the plasma concentration-time curve (AUC) and the values of peak plasma concentrations increase linearly with dose. Etoposide does not accumulate in the plasma if 100 mg/m² doses are administered for 4 to 5 days. The volumes of distribution in steady state fall in a range of 18 to 29 liters or 7 to 17 L/m².

Mechanism of action/effect: etoposide is a topoisomerase II inhibitor. It acts in the pre-mitotic phase of cell division to inhibit the DNA synthesis; it is cell-cycle dependent and phase-specific, and its maximum effect occurs in S and G2 phases of cell division.

Absorption: oral bioavailability is variable; average 50 % (ranges between 25% and 75%)

Distribution: low and variable into the cerebrospinal fluid (CSF). Concentrations are higher in normal lungs than in lung metastases, and are similar in primary tumors and normal tissues of the myometrium.

Protein binding: in vitro, highly protein bound (97%). The binding ratio correlates directly with serum albumin in cancer patients and normal individuals. The unbound fraction was found to be significantly correlated with bilirubin in a population of cancer patients. Phenylbutazone, sodium salicylate, and aspirin displace protein-bound etoposide in vitro.

Metabolism: hepatic.

Half-life: terminal half-life (biphasic) 7 hours; range: 4 to 11 hours.

Elimination: In urine = 44 to 60% (67% unchanged). In feces = up to 16% (as unchanged drug and metabolites). In bile = 6% or less.

DOSAGE AND ADMINISTRATION:

* **Note:** according to certain reports, plastic devices made of acrylic or “ABS” (a polymer composed of acrylonitrile, butadiene and styrene) may crack or leak when undiluted etoposide for injection is introduced.

ETOPÓSIDO SERVICAL for Injection: the usual dose in combination with other chemotherapeutic agents for testicular cancer therapy ranges from 75 to 100 mg/m² a day, during the days 1 through 5, to 100 mg/m² a day on days 1, 3 and 5. In small cell lung cancer therapy, the etoposide dose in combination with other approved chemotherapeutic agents, as well as with radiotherapy, ranges from 35 mg/m² a day, for 3 to 5 days, to 50 mg/m² a day for 5 days.

The chemotherapy courses are repeated at intervals of 3 to 4 weeks after achieving adequate recovery from general toxicity.

The dosage should be modified taking into account the myelosuppressive effect produced by other drugs in the combination or the effects caused by radiotherapy or chemotherapy, which may have compromise the cell reserve of the bone marrow.

Administration precautions: as other potentially toxic compounds, etoposide solution must be handled and prepared with caution. Skin reactions may occur, associated with accidental exposure to etoposide solution. The use of protecting gloves is recommended. If etoposide solution contacts the skin or mucosa, wash immediately with plenty of soap and water.

Preparation for intravenous administration: before use, etoposide for injection must be diluted with 5% dextrose injection, or with 0.9% sodium chloride solution, in either case sterile and nonpyrogenic, to a final concentration of 0.2 to 0.4 mg/mL.

Concentrations over 0.4 mg/mL may precipitate.

As some cases of hypotension have been reported due to rapid intravenous administration, etoposide solution for injection is recommended to be infused over a period of 60 minutes. Infusion time may be extended if the volume of liquid to be injected may involve any risk.

Etoposide solution for injection should not be administered by rapid intravenous infusion: All drugs for parenteral administration should be inspected carefully for foreign particles or discoloration prior to use whenever container and solution allow doing so.

Stability: etoposide ampoules are stable for 24 months when stored at room temperature below 30° C. Once the solution is diluted to recommended concentration of 0.2 to 0.4 mg/mL, they are stable for 96 and 24 hours respectively, at room temperature (25° C), under normal light conditions, inside glass or plastic containers.

Procedures for proper handling and disposal of anticancer drugs should be taken into account. Several documents with informative purposes have been published on this subject. However, there is no absolute agreement on how necessary or appropriate these procedural guidelines may be.

CONTRAINDICATIONS: hypersensitivity to active ingredient. Severe liver dysfunction.

PRECAUTIONS

General: in all cases where etoposide administration is considered necessary for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions.

Most of these adverse reactions are reversible if detected from the beginning.

If such reactions occur, the administered dose should be reduced or interrupted. In this sense, proper corrective measures should be taken, in accordance with the physician's judgment.

Reinstitution of etoposide therapy should be carried out very carefully, considering the further need for the drug as well as possible toxicity recurrence.

Laboratory tests: during the course of etoposide treatment, a periodic and continued blood count should be carried out.

They should be done prior to the beginning of therapy, and at adequate intervals during and after therapy.

Before each etoposide dose, at least one determination of hematimetric indexes should be performed.

Carcinogenesis. Mutagenesis. Fertility impairment: carcinogenesis tests with etoposide have not been conducted in laboratory animals.

Etoposide should be considered a potential carcinogen in humans.

The occurrence of acute leukemia, with or without pre-leukemic phase, has been rarely reported in humans treated with etoposide along with other antineoplastic agents.

Etoposide was tested to determine its mutagenic and genotoxic potential on mammary cells.

Etoposide cause abnormalities in the number and structure of chromosomes in embryonic murine cells and human blood-forming cells; mutations of gens in Chinese hamsters' ovarian cells; and DNA damage due to DNA-protein crosslink break and DNA strand break in mice's cells with leukemia.

Etoposide also produced an increase in sister chromatide exchange of the Chinese hamster's ovarian cells.

Treatment of Swiss-Albino mice with 1.5 mg/kg I.P. of etoposide on day 7 of gestation increased the incidence of intrauterine death and fetal malformations, and significantly increased the average fetal body weight. Maternal weight increase was not affected.

Treatment of pregnant SPF rats with 1.2 mg/kg I.V. of etoposide a day, for 10 days, led to a prenatal mortality rate of 92%; 50 % of the fetuses were abnormal.

Pregnancy: (See WARNINGS)

Breastfeeding: it is unknown whether this drug is excreted in breast milk. Because many drugs are excreted in breast milk and due to the potential for adverse reactions in nursing babies after etoposide, the patient should choose to discontinue breastfeeding or to discontinue the drug administration, considering the importance of the drug to the breastfeeding mother.

Pediatric use: Safety and efficacy of etoposide in children have not been determined.

To be used as an injection, etoposide contains polysorbate 80. In premature babies, a syndrome has been detected that risks patient's life. This syndrome has caused renal and hepatic disorders, pulmonary deterioration, thrombocytopenia, and ascites, associated with a product containing polysorbate 80. Also, anaphylactic reactions have been reported in pediatric patients. (See WARNINGS)

WARNINGS: patients receiving etoposide may develop myelosuppression during and after therapy. Cases of myelosuppression resulting in death have been reported.

Dose-limiting myelosuppression has been the most significant toxicity associated with etoposide therapy.

Consequently, the following studies should be performed before etoposide treatment or before each cycle of etoposide: platelet count, hemoglobin, white blood cell count and differential, and erythrocytes count.

When platelet count is below 100,000/mm³, or absolute neutrophil count is below 1500/mm³, etoposide therapy must be discontinued until these counts return to their normal values.

Physicians should also be aware of reported anaphylactic reactions, which are manifested by: chills, fever, tachycardia, bronchospasm, dyspnea and hypotension.

A significant number of minor anaphylactic reactions have been reported in children receiving etoposide at higher doses than those recommended. Treatment of these reactions is symptomatic. Whenever these reactions occur, infusion must be immediately terminated, and, administration of pressor agents, corticosteroids, antihistamines, or plasma volume expanders should be determined at treating physician's discretion.

Etoposide must be infused over a period of 60 minutes. Hypotension episodes have been reported, probably related to rapid intravenous administration.

Pregnancy: etoposide causes fetal harm in pregnant women. It has been shown to be teratogenic in rats and mice.

A dose of 0.4 mg/kg a day (about 1/20 of the human dose on a mg/m² basis) was administered during organogenesis and it caused maternal toxicity, embryotoxicity and teratogenicity (skeletal abnormalities, encephalocele and anophthalmia).

Women who are old enough to become pregnant and who have childbearing potential should be advised to avoid becoming pregnant. If this drug is administered during pregnancy, or if the woman becomes pregnant during etoposide treatment, she should be informed of the potential hazard to the fetus.

Etoposide should be considered a potential carcinogen in humans. The occurrence of acute leukemia, with or without pre-leukemic phase, has been reported in humans treated with etoposide along with other antineoplastic agents.

The risk of developing a leukemic or preleukemic syndrome has not been clearly determined yet.

ADVERSE REACTIONS: the following information about adverse reactions is based on etoposide as single agent, administered either orally or intravenously, using different dosing schedules, for the treatment of a wide range of malignancies.

Hematologic toxicity: it was found that myelosuppression was closely related to dose and its limitations; the granulocyte nadirs occur from 7 to 14 days after drug administration, while the platelet nadirs occur from 9 to 16 days following drug administration. Bone marrow recovery is usually complete by the 20th day, and no cumulative toxicity has been reported. Fever and infection have been reported in patients with neutropenia.

Acute leukemia occurrence with or without preleukemic phase has rarely been reported in humans being treated with etoposide in combination with other antineoplastic agents. (See WARNINGS)

Gastrointestinal toxicity: main gastrointestinal toxicities are nausea and vomiting. The severity of these reactions is generally mild to moderate; treatment discontinuation was required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Gastrointestinal toxicities usually occur more frequently after oral administration than after intravenous administration.

Hypotension: transitory hypotension episodes have been reported in 1 to 2% of tested patients after rapid intravenous administration. This reaction is not associated with any cardiac toxicity or electrocardiographic changes. No delayed hypotension episode has been reported. In order to avoid this rather unusual adverse effect, it is recommended to infuse etoposide slowly, over a period of 60 minutes. If hypotension occurs, infusion must be interrupted and fluids should be given or any other adequate supportive therapy should be initiated. Infusion may be resumed, but more slowly.

Allergic reactions: anaphylactic-type reactions, characterized by chills, fever, tachycardia, bronchospasm, dyspnea and/ or hypotension, have been reported in 0.7 to 2% of patients receiving etoposide intravenously, and in less than 1% of patients receiving etoposide orally and in capsules. These reactions have promptly responded to the interruption of the infusion and administration of pressor agents, corticosteroids, antihistamines or other volume expanders, at physician 's discretion. However, these reactions can be fatal. Hypertension and flushing have also been reported. Blood pressure generally normalizes within a couple of hours after infusion interruption. These anaphylactic-type reactions occurred during the initial infusion of etoposide.

In association with the above mentioned reactions, facial and tongue swelling, coughing, diaphoresis, cyanosis, throat tightness, laryngospasm, back pain and/or loss of consciousness sometimes occurs. Besides, few cases of apparent hypersensitivity-related apnea have been reported.

Rash, urticaria and or itching have been unusually reported at recommended doses.

At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.

Alopecia: in more than 66% of patients, reversible alopecia was observed, sometimes progressing to total alopecia.

Other toxicities: the following adverse reactions have been rarely reported: taste alterations, fever, pigmentation, abdominal pain, constipation, dysphagia, transient cortical blindness and optic neuritis. One single case of dermatitis due to radiation was reported.

At much higher doses than those recommended, hepatic toxicity was reported. In addition, metabolic acidosis was observed when etoposide is administered at considerably high doses.

The incidences of adverse reactions included in the following table were obtained from studies in 2,081 patients treated with etoposide, used as single agent and by injection.

ADVERSE EFFECT CAUSED BY ETOPOSIDE	PERCENTAGE (%) RANGE OF REPORTED INCIDENCE
Hematologic toxicity	
Leukopenia ($< 1,000$ WBC (*) / mm^3)	3 - 17
Leukopenia ($< 4,000$ WBC (*) / mm^3)	60 - 91
Thrombocytopenia ($< 50,000$ platelets/ mm^3)	1 - 20
Thrombocytopenia ($< 100,000$ platelets/ 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 toxicity	0 - 3
Alopecia	8 - 66
Peripheral neurotoxicity	1 - 2
Hypotension	1 - 2
Allergic reactions	1 - 2

(*) WBC White blood cells

OVERDOSAGE: no proven antidote has been established for etoposide overdose.

If an overdose occurs, go to the nearest Hospital or contact Toxicology Centers:

Hospital de Niños Dr. Ricardo Gutiérrez: Ph: + 54 (11) 4962-6666 / 2247

Hospital Dr. Juan P. Garrahan: Ph: + 54 (11) 4941-6191 / 6012

Hospital Dr. Juan A. Fernández: Ph: + 54 (11) 4801-5555

Hospital A. Posadas: Ph: + 54 (11) 4654-6648 / 4658-7777

PRESENTATION

ETOPOSIDO SERVYCAL FOR INJECTION: cartons containing 1 ampoule for sale to the public.

KEEP BETWEEN 15° C AND 30° C, PROTECTED FROM LIGHT.

THIS MEDICINE SHALL BE USED UNDER MEDICAL PRESCRIPTION AND SURVEILLANCE, AND IT SHALL NOT BE REPEATED WITHOUT A NEW PRESCRIPTION.

KEEP OUT OF THE REACH OF CHILDREN

Medicinal Specialty Authorized by the Argentine Ministry Of Health (A.N.M.A.T.)
Certificate No. 50052

Technical Director: Pamela Carla Marcuzzi – Pharmacist- Biochemist

SERVYCAL S.A.

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Manufactured at:
Palpa 2870 – (C1426DPB) - C.A.B.A. - Argentina

Revision date: 08/2005

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Polyethylene glycol 300	3.250 g
Absolute alcohol q.s. to	5.000 mL

DOSAGE AND ADMINISTRATION:

See patient package insert inside carton.

Batch no.:

Expiration date:

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