

CNS toxicity	12
Infection	8
Renal deterioration	6
Liver Dysfunction	3
Phlebitis	2
Fever	1
Allergic reaction	<1
Anorexia	<1
Cardiotoxicity	<1
Coagulopathy	<1
Constipation	<1
Dermatitis	<1
Diarrhea	<1
Fatigue	<1
Hypertension	<1
Malaise	<1
Polyneuropathy	<1
Lung Symptoms	<1
Salivation	<1
Estomatitis	<1

HEMATOLOGICAL TOXICITY:

Myelosuppression depended on the dose and at the same time limited the dose. It consisted mainly in leukopenia and to a lesser degree thrombocytopenia. A WBC<3,000/micro/l count is expected in 50% of the patients treated with simple agent Ifosfamide with a daily 1.2 g/m² dose during 5 running days At this dose level, thrombocytopenia (platelets<100,000/micro/l) occurred in approx 20% of the patients. At higher doses, leukopenia was practically universal and at total doses of 10-12 g/m²/cycle, half of the patients had a WBC count lower than 1,000/micro/l and 8% of the patients had a platelet count lower than 50,000/micro/l. Myelosuppression was generally reversible and the treatment can be administered every 3 or 4 weeks. When Ifosfamide is used combined with other myelosuppressive agents dosage adjustments may be needed. Those patients that experience severe myelosuppression run a higher infection risk .

Digestive System: Nausea and vomiting occurred in 58% of the patients that were administered sterile Ifosfamide. Both symptoms were usually controlled with standard anti-vomiting therapy. Other gastrointestinal side effects include anorexia, diarrhea and in some cases constipation.

Urinary System: Urotoxicity included hemorrhagic cystitis, dysuria, urinary frequency and other symptoms of bladder irritation. Hematuria occurred in 6% to 92% of the patients treated with Ifosfamide. The incidence and seriousness of hematuria can be significantly reduced through vigorous hydration, a fractioned dose program and a protector such as

mesma. With a daily dose of 1.2 gr /m² during 5 running days without a protector microscopic hematuria is expected in approx half of the patients and macroscopic hematuria in approx 8%. Renal toxicity occurred in 6% of the patients treated with Ifosfamide as simple agent. Clinical symptoms such as BUN increase or creatinine in serum or creatinine clearance diminishing were usually temporary. These symptoms were more likely associated with tubular damage. A case of tubular acidosis that developed into chronic insufficiency was reported. Proteinuria and acidosis rarely occurred. Metabolic acidosis was also reported in 31% of the patients in a study carried out using Ifosfamide at a daily 2.0 to 2.5 gr/m² during 4 days. Renal tubular acidosis , Fanconi Syndrome and renal rickets were also reported. Close clinical monitoring of urine chemistry is recommended. The laboratory tests proposed are phosphorus, potassium, alkaline phosphatase and others. Replacement therapy should be administered as indicated.

Central Nervous system: CNS side effects were observed in 12% of the patients treated with Ifosfamide. The effects most commonly observed were somnolence, depression, depressive psychosis and hallucinations. Other less frequent symptoms are vertigo, disorientation and cranial nerve dysfunction. Attacks and coma were occasionally reported. The central nervous system toxicity incidence can be higher in patients with altered renal function.

Others: Alopecia occurred in approx. 83% of the patients treated with Ifosfamide as a simple agent. Combined, this incidence can reach as high as 100% depending on other agents present in the chemotherapy regime. Liver and/or bilirubin enzyme increases were observed in 3% of the patients. Other less frequent side effects include phlebitis, pulmonary symptoms, fever of unknown origin, allergic reactions, stomatitis, cardiotoxicity and polyneuropathy.

OVERDOSE

No specific antidote for Ifosfamide is known. The overdose procedure should include general measures to support the patient during possible toxicity period.

This medicine must be used under medical prescription and supervision, and it must not be repeated without a new prescription.

CONTENT

Ifosfamide Servycal 1 g x 1 vial.
Ifosfamide Servycal 2 g x 1 vial.
Ifosfamide Servycal 3 g x 1 vial.

Conservation:

Keep at room temperature not higher than 25 °C, away from light.

Keep away from children.

In case of overdose, go to the nearest Hospital.

Medicinal Specialty authorized by Argentine Ministry of Health (ANMAT). N°49.841

SERVYCAL S.A.

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**QUALI-QUANTITATIVE COMPOSITION:**

Ifosfamide Servycal 1 g

Each vial contains: Ifosfamide 1.0 g, Mannitol 0.5 g

Ifosfamide Servycal 2 g

Each vial contains: Ifosfamide 2.0 g, Mannitol 1.0 g

Ifosfamide Servycal 3 g

Each vial contains: Ifosfamide 3.0 g, Mannitol 1.5 g

TYPE OF AGENT:

Antineoplastic agent, ATC code: L01AA06

INSTRUCTIONS AND USE:

Ifosfamide is used in combination with other approved antineoplastic agents. It is indicated in second and third line chemotherapy of germinal cell testicular cancer.

It must be used in combination with a prophylactic agent for hemorrhagic cystitis such as mesna.

PHARMACOLOGICAL ACTION:

Ifosfamide needs metabolic activation through microsomic liver enzymes to produce biologically active metabolites. Activation occurs through hydroxylation in the ring of carbon 4 atom to form the hydroxylphosphamide-4 unstable intermediate. This metabolite degrades to the urinary stable 4-ketoifosfamide rapidly. The opening of the ring results in the urinary stable metabolite 4-carboxifosfamide formation. There is no evidence that said metabolites are cytotoxic. N, N-bis (2 - chloride ethyl) phosphoric acid diamide (isophosphoramidate). The enzymatic oxidation of the chloride ethyl lateral chains and the subsequent alkylation produces the main urinary metabolites, ifosfamide chloride ethyl and cyclophosphamide chloride ethyl. The ifosfamide alkylated metabolites interact with DNA. In vitro incubation has produced phosphotriesters.

Pharmacokinetics

Ifosfamide shows pharmacokinetics depending on the dosage in humans. At simple 3.8-5.0 g/m² doses, concentrations in plasma fall in two phases and the terminal elimination average life is around 15 hours. At 1.6-2.4 g/m²/day doses, plasma decrease is mono-exponential and the terminal elimination average life is

around 7 hours. Ifosfamide is widely metabolized in humans and metabolic stages seem to saturate at high doses.

After the administration of 5 g/m² doses of labeled 14C ifosfamide, 70% to 86% of dosed radioactivity was recovered in the urine, with nearly 61% of the dose excreted as parent compound. At 1.6-2.4 g/m² doses, only 12% to 18% of the dose was excreted in urine as unaltered drug within 72 hours. Two different ifosfamide dechloride ethyl derivatives, 4-carboxifosfamide, thydialcetic acid, and conjugated chloroacetic acid cistein have been identified, as the main ifosfamide metabolites in humans and only small amounts of 4-hidroxiifosfamide, and acrolein are present. Small amounts(nmol/ml) of ifosfamide mustard and 4-hidroxiifosfamide have been detected in human plasma. Ifosfamide metabolism is required for the generation of biologically active species and even if the metabolism is extensive, it also varies among the patients.

DOSAGE AND ADMINISTRATION:

Servycal Ifosfamide should be intravenously administered at a daily 1.2 g/m² dose during 5 consecutive days. The treatment is repeated every three weeks or after recovery from hematological toxicity (Platelets ?100,000/micro/l, WBC

?4,000/micro/l). In order to prevent bladder toxicity, SERVYCAL Ifosfamide should be administered with extensive hydration consisting at least of two liter oral or intravenous fluid a day. A protector, such as mesna, should be used to prevent hemorrhagic cystitis. Ifosfamide should be administered as a slow intravenous infusion during at least 30 minutes. Even though Ifosfamide has been administered to a small group of patients with compromise in their hepatic and/or renal function, no research has been done to set optimal Ifosfamide dose schedules for such patients.

PREPARING FOR INTRAVENOUS ADMINISTRATION / STABILITY

Injections are prepared for parenteral use by adding USP injection Sterile Water, USP injection Bacteriostatic Water to the flask and shaking to dissolve. Use the amount of diluent shown below to reconstitute the product:

Dosage	Concentration	Amount of diluent	Final concentration
1 g		20 ml	50 mg/ml
2 g		40 ml	50 mg/ml
3 g		60 ml	50 mg/ml

Ifosfamide solutions may be additionally diluted to reach 0.6 to 20 mg/ml concentrations in the following fluids:

USP 5% Dextrose injection.
USP 0.9% Sodium Chloride injection.
USP Ringer Injection with Lactate.
USP Sterile Water for Injection.

Since basically identical stability results were obtained for mixes with Sterile Water for Injection and for other mixes (5% Dextrose Injection, 0.9% Sodium Chloride Injection, and Ringer Injection with Lactate), the use of greater volume parenteral glass bottles, Vialflex bags or PABTM bags containing intermediate concentrations or excipient mixes (e.g., 2.5% Dextrose injection, 0.45% Sodium Chloride injection or 5% dextrose and 0.9% Sodium Chloride injection) are also acceptable.

Ifosfamide solutions and additionally diluted solutions should be kept in the refrigerator and used within 24 hours. Parenteral drug products should be visually checked for particles or discoloration prior to administration.

Special recommendations:

Do not intravenously administer in a direct way. Do not mix with any other medicine.

Any reconstituted solution showing signs of precipitation must be discarded.

Usage and handling instructions:

Adequate material handling and discard procedures shall be followed with Ifosfamide and all objects which are in contact with the drug. Said procedures shall adapt to current recommendations on the treatment of cytotoxic residuum.

CONTRAINDICATIONS

Sustained use of Ifosfamide is contraindicated for patients suffering from severely depressed bone marrow function. Ifosfamide is also contraindicated in patients evidencing previous hypersensitivity to the drug.

PRECAUTIONS

General: Ifosfamide should be carefully administered to patients with impaired renal function, as well as to those with compromised bone marrow reserve, as shown by leukopenia, granulocytopenia, extensive bone marrow metastasis, previous radiation therapy or previous therapy with other cytotoxic agents.

Laboratory tests: During the treatment, the patient's hematological profile (particularly neutrophils and platelets) should be regularly monitored in order to establish the degree of hematopoietic suppression. Urine should also be regularly checked for possible red cells which could evidence hemorrhagic cystitis.

Drug Interactions: Physicians should be on the alert to detect possible combined drug actions, whether or

not expected, which might involve Ifosfamide, even when ifosfamide has been successfully used together with other drugs, including cytotoxic drugs.

Injury healing: Ifosfamide may interfere with the normal healing of injuries.

Pregnancy: "Category D" pregnancy

Nursing mothers: Ifosfamide is excreted in breast milk. Due to its potential severe adverse effects and the carcinogenesis shown by Ifosfamide in animal research, a decision should be taken on whether to discontinue drug or suspend lactation, considering the importance of the drug to the mother.

Carcinogenesis, Mutagenesis, fertility impairment: Ifosfamide has proved to be carcinogenic in rats, with female rats showing a significant incidence of mammary fibroadenomas and leiomyosarcomas.

Ifosfamide mutagenic potential has been documented in in-vitro bacterial systems and in-vivo mammal cells. In vivo, Ifosfamide has induced mutagenic effects in mice and Drosophila melanogaster germinal cells, and has induced a significant increase in dominant lethal mutations in male mice as well as lethal mutations linked to recessive sex in drosophila. Pregnant mice showed an increase in reabsorptions and anomalies on day 19 after a 30 mg/m² ifosfamide dose was administered on day 11 of pregnancy.

Embryo lethal effects were observed in rats after a 54 mg/m² ifosfamide dose was administered from day 6 to day 15 of pregnancy. Ifosfamide is embryotoxic in rabbits receiving 88 mg/m²/day doses from day 6 to day 18 after mating. The number of abnormalities was also significantly increased in the control group.

PEDIATRIC USE:

Safety and efficiency in children has not been established.

Usage precautions:

IFOSFAMIDE SERVYCAL should not be handled by pregnant women. In order to prevent nausea and vomiting, an associate treatment may be prescribed. Your physician should be contacted about any question.

WARNINGS:

Urinary system: Urotoxic side effects, especially hemorrhagic cystitis, have been frequently associated with ifosfamide use.

An urine test should be made prior to each ifosfamide dose. Should there be microscopic hematuria (higher than 10 RBCs per high power field) the subsequent administration should be stopped until complete resolution.

Additional ifosfamide administration must be accompanied by a vigorous oral or parenteral hydration.

Hematopoietic system: When ifosfamide is administered in combination with other chemotherapeutic agents, severe myelosuppression is frequently observed. Close hematological monitoring is recommended. White blood cell count (WBC) under 2,000/micro/l and platelet count under 50,000/micro/l.

Central nervous system: After ifosfamide therapy, neurological manifestations have been reported consisting in somnolency, dizziness, hallucinations and in some cases, coma. These symptoms occurrence demands the suspension of ifosfamide therapy. The symptoms have usually been reversible, and the support measures should be maintained until complete resolution.

Pregnancy: Animal research suggests that the drug may cause genetic mutations and chromosomal impairment in vitro. Embryotoxic and teratogenic effects have been observed in mice, rats and rabbits at 0.05 to 0.075 times the human dose. Ifosfamide may be lethal when administered to a pregnant woman. Should Ifosfamide be used during pregnancy, or should the patient become pregnant while using the drug, the patient should be warned against the potential risk for the fetus. The procedures for correct handling and placing of anti-cancer drugs should be considered. Skin reactions may occur due to accidental exposure to ifosfamide. Using gloves is recommended. Should ifosfamide solution be in contact with the skin or mucosa , the skin should be thoroughly washed with water and soap, and the mucosa should be washed with abundant water. Several standards have been published regarding this topic. There is no general agreement on whether the recommended procedures are necessary or adequate.

ADVERSE EFFECTS:

In patients undergoing treatment with Ifosfamide as simple agent, the dose limiting toxicities are myelosuppression and urotoxicity. The fractioning of the dose, vigorous hydration and a protector such as mesna can significantly reduce the hematuria incidence, particularly macroscopic hematuria associated with hemorrhagic cystitis. With a 1.2 g/m² daily dose during 5 running days when leukopenia appears it is from mild to moderate. Other relevant side effects are alopecia, nausea, vomiting and central nervous system toxicity.

ADVERSE REACTION	INCIDENCE
Alopecia	83
Nausea-Vomiting	58
Hematuria	46
macroscopic hematuria	12