Fosfa Injection

Ifosfamide USP
Lyophilized Powder

DRUG INTERNATIONAL LTD.

COMPOSITION : Each vial contains Ifosfamide USP 2 gm Injection.

CLINICAL PHARMACOLOGY :

Mechanism of Action : Ifosfamide is a prodrug that requires metabolic activation by hepatic cytochrome P450 isoenzymes to exert its cytotoxic activity. Activation occurs by hydroxylation at the ring carbon atom forming the unstable intermediate 4-hydroxyifosfamide and its ring-opened aldo tautomer, which decomposes to yield the cytotoxic and urotoxic compound acrolein and an alkylating isophosphoramide mustard as well as multiple other nontoxic products. The exact mechanism of action of ifosfamide has not been determined, but its cytotoxic action is primarily through DNA crosslinks caused by alkylation by the isophosphoramide mustard at guanine N-7 positions. The formation of inter- and intra-strand cross-links in the DNA results in cell death. Ifosfamide exhibits dose-dependent pharmacokinetics in humans. At single doses of 3.8 to 5 g/m^2, the plasma concentrations decay biphasically and the mean terminal elimination half-life is about 15 hours. At doses of 1.6 to 2.4 g/m^2/day, the plasma decay is monoexponential and the terminal elimination half-life is about 7 hours. Ifosfamide exhibits time-dependent pharmacokinetics in humans. Following intravenous administration of 1.5 g/m^2 over 0.5 hours once daily for 5 days to 15 patients with neoplastic disease, a decrease in the median elimination half-life from 7.2 hours on Day 1 to 4.6 hours on Day 5 occurred with a concomitant increase in the median clearance from 66 mL/min on Day 1 to 115 mL/min on Day 5. There was no significant change in the volume of distribution on Day 5 compared with Day 1.

Distribution : Ifosfamide volume of distribution (Vd) approximates the total body water volume, suggesting that distribution takes place with minimal tissue binding. Following intravenous administration of 1.5 g/m^2 over 0.5 hours once daily for 5 days to 15 patients with neoplastic disease, the median Vd of ifosfamide was 0.64 L/kg on Day 1 and 0.72 L/kg on Day 5. Ifosfamide shows little plasma protein binding. Ifosfamide and its active metabolites are extensively bound by red blood cells. Ifosfamide is not a substrate for P-glycoprotein.

Metabolism : Ifosfamide is extensively metabolized in humans through two metabolic pathways: ring oxidation ("activation") to form the active metabolite, 4-hydroxy-ifosfamide and side-chain oxidation to form the inactive metabolites, 3-dechloro-ethylifosfamide or 2-dechloroethylifosfamide with liberation of the toxic metabolite, chloroacetaldehyde. Small quantities (nmol/mL) of ifosfamide mustard and 4-hydroxyifosfamide are detectable in human plasma. Metabolism of ifosfamide is required for the generation of the biologically active species and while metabolism is extensive, it is also quite variable among patients.
Excretion : After administration of doses of 5 g/m^2 of 14C-labeled ifosfamide, from 70% to 86% of the dosed radioactivity was recovered in urine as metabolites, with about 61% of the dose excreted as parent compound. At doses of 1.6 to 2.4 g/m^2 only 12% to 18% of the dose was excreted in the urine as unchanged drug within 72 hours.

INDICATIONS AND USAGE : Ifosfamide Injection is indicated for use in combination with certain other approved antineoplastic agents for third-line chemotherapy of germ cell testicular cancer. It should be used in combination with mesna for prophylaxis of hemorrhagic cystitis.

DOSAGE AND ADMINISTRATION : Ifosfamide should be administrated intravenously at a dose of 1.2 g/m^2 per day for 5 consecutive days. Treatment is repeated every 3 weeks or after recovery from hematologic toxicity (Platelets ≥100,000/mL, WBC ≥ 4,000/mL). In order to prevent bladder toxicity, ifosfamide should be given with extensive hydration consisting of at least 2 liters of oral or intravenous fluid per day. A protector, such as Mesna (Mes-D), should also be used to prevent hemorrhagic cystitis. Ifosfamide should be administrated as a slow intravenous infusion lasting a minimum of 30 minutes. Although Ifosfamide has been administrated to a small number of patients with compromised hepatic and/.or renal function, studies to establish optimal dose schedules of Ifosfamide in such patients have not been conducted.

CONTRAINDICATIONS : Ifosfamide is contraindicated in patients with known hypersensitivity to administration of ifosfamide and urinary outflow obstruction.

WARNINGS AND PRECAUTIONS : Myelosuppression, Immunosuppression, and Infections Treatment with ifosfamide may cause myelosuppression and significant suppression of immune responses, which can lead to severe infections. Fatal outcomes of ifosfamide-associated myelosuppression have been reported. Ifosfamide-induced myelosuppression can cause leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding events), and anemia. The nadir of the leukocyte count tends to be reached approximately during the second week after administration. When ifosfamide is given in combination with other chemotherapeutic/hematotoxic agents and/or radiation therapy, severe myelosuppression is frequently observed. The risk of myelosuppression is dose-dependent and is increased with administration of a single high dose compared with fractionated administration. The risk of myelosuppression is also increased in patients with reduced renal function. Severe immunosuppression has led to serious, sometimes fatal, infections. Sepsis and septic shock also have been reported. Infections reported with ifosfamide include pneumonias, as well as other bacterial, fungal, viral, and parasitic infections. Latent infections can be reactivated. In patients treated with ifosfamide, reactivation has been reported for various viral infections. Infections must be treated appropriately. Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician. In case of neutropenic fever, antibiotics and/or antimycotics must be given. Close hematologic monitoring is recommended. White blood cell (WBC) count, platelet count and hemoglobin should be obtained prior to each administration and at appropriate intervals after administration. Unless clinically essential, ifosfamide should not be given to patients with a WBC count below 2000/microliter and/or a platelet count below 50,000/microliter. Ifosfamide should be given cautiously, if at all, to patients with presence of an infection, severe immunosuppression or compromised bone marrow reserve, as indicated by leukopenia, granulocytopenia, extensive bone marrow metastases, prior radiation therapy, or prior therapy with other cytotoxic agents.Central Nervous System Toxicity, Neurotoxicity Administration of ifosfamide can cause CNS toxicity and other neurotoxic effects. The risk of CNS oxicity and other neurotoxic effects necessitates careful monitoring of the patient. Neurologic manifestations consisting of somnolence, confusion, hallucinations, blurred vision, psychotic ehavior, extrapyramidal symptoms, urinary incontinence, seizures, and in some instances, coma, ave been reported following ifosfamide therapy. There have also been reports of peripheral europathy associated with ifosfamide use. fosfamide neurotoxicity may become manifest within a few hours to a few days after first dministration and in most cases resolves within 48 to 72 hours of ifosfamide discontinuation. Symptoms may persist for longer periods of time. Supportive therapy should be maintained until heir complete resolution. Occasionally, recovery has been incomplete. Fatal outcomes of CNS oxicity have been reported. Recurrence of CNS toxicity after several uneventful treatment courses as been reported. If encephalopathy develops, administration of ifosfamide should be discontinued. Due to the potential for additive effects, drugs acting on the CNS (such as antiemetics, sedatives, arcotics, or antihistamines) must be used with particular caution or, if necessary, be discontinued n case of ifosfamide-induced encephalopathy. Manifestations of CNS toxicity may impair a patient's ability to operate an automobile or other eavy machinery. Renal and Urothelial Toxicity and Effects fosfamide is both nephrotoxic and urotoxic. Women should not become pregnant and men should not father a child during therapy with osfamide. Further, men should not father a child for up to 6 months after the end of therapy. If his drug is used during pregnancy, or if the patient becomes pregnant while taking this drug or fter treatment, the patient should be apprised of the potential hazard to a fetus. Effects on Fertility fosfamide interferes with oogenesis and spermatogenesis. Amenorrhea, azoospermia, and sterility n both sexes have been reported.

ADVERSE REACTIONS : Adverse Reactions from Clinical Trials Because clinical trials are conducted from 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 clinical practice. The adverse reactions and frequencies below are based on 30 publications describing clinical experience with fractionated administration of ifosfamide as monotherapy with a total dose of 4 to 12 g/m^2 per course.

DRUG INTERACTIONS : Ifosfamide is a substrate for both CYP3A4 and CYP2B6. Inducers of CYP3A4 CYP3A4 inducers (e.g., carbamazepine, phenytoin, fosphenytoin, phenobarbital, rifampin, St. John's Wort) may increase the metabolism of ifosfamide to its active alkylating metabolites. CYP3A4 inducers may increase the formation of the neurotoxic/nephrotoxic ifosfamide metabolite, chloroacetaldehyde. Closely monitor patients taking ifosfamide with CYP3A4 inducers for toxicities and consider dose adjustment.Inhibitors of CYP3A4 CYP3A4 inhibitors (e.g., ketoconazole, fluconazole, itraconazole, sorafenib, aprepitant, fosaprepitant, grapefruit, grape fruit juice) may decrease the metabolism of ifosfamide to its active alkylating metabolites, perhaps decreasing the effectiveness of ifosfamide treatment.

USE IN PREGNANCY AND LACTATION : Pregnancy Category D. Ifosfamide can cause fetal harm when administered to a pregnant woman. Fetal growth retardation and neonatal anemia have been reported following exposure to ifosfamide-containing chemotherapy regimens during pregnancy. Animal studies indicate that ifosfamide is capable of causing gene mutations and chromosomal damage in vivo. In pregnant mice, resorptions increased and anomalies were present at day 19 after a 30 mg/m2 dose of ifosfamide was administered on day 11 of gestation. Embryo-lethal effects were observed in rats following the administration of 54 mg/m^2 doses of ifosfamide from the 6th through the 15th day of gestation and embryotoxic effects were apparent after dams received 18 mg/m2 doses over the same dosing period. Ifosfamide is embryotoxic to rabbits receiving 88 mg/m^2/day doses from the 6th through the 18th day after mating. The number of anomalies was also significantly increased over the control group. Women should not become pregnant and men should not father a child during therapy with ifosfamide. Further, men should not father a child for up to 6 months after the end of therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug or after treatment, the patient should be apprised of the potential hazard to a fetus. Nursing Mothers: Ifosfamide is excreted in breast milk. Because of the potential for serious adverse events and the tumorigenicity shown for ifosfamide in animal studies, 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. Women must not breastfeed during treatment with ifosfamide. Pediatric Use: Safety and effectiveness have not been established in pediatric patients. 8.5 Geriatric Use In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. A study of patients 40 to 71 years of age indicated that elimination half-life appears to increase with advancing age. This apparent increase in half-life appeared to be related to increases in volume of distribution of ifosfamide with age. No significant changes in total plasma clearance or renal or non-renal clearance with age were reported. Ifosfamide and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug 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. 8.6 Use in Patients with Renal Impairment.

OVERDOSAGE : No specific antidote for ifosfamide is known. Patients who receive an overdose should be closely monitored for the development of toxicities. Serious consequences of overdosage include manifestations of dose-dependent toxicities such as CNS toxicity, nephrotoxicity, myelosuppression, and mucositis. Management of overdosage would include general supportive measures to sustain the patient through any period of toxicity that might occur, including appropriate state-of-the-art treatment for any concurrent infection, myelosuppression, or other toxicity. Ifosfamide as well as ifosfamide metabolites are dialyzable. Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with overdose.

PREPARATION FOR INTRAVENOUS ADMINISTRATION/STABILITY : Injections are prepared for parenteral use by adding Sterile Water for Injection or Sterile Bacteriostatic Water for Injection (benzyl alcohol or parabens preserved), to the vial and shaking to dissolve. Use the quantity of diluent shown below to constitute the product.

Dosage Strength	Quantity of Diluent	Final Concentration
2 gram	40 mL	50 mg/mL

Solutions of Ifosfamide may be diluted further to achieve concentrations of 0.6 to 20 mg/mL in the following fluids: 5% Dextrose Injection, 0.9% Sodium Chloride Injection. Lactated Ringer's Injection, Sterle Water for Injection. Because essentially identical stabillity results were obtained for Sterile Water admixtures as for the other admixtures (5% Dextrose Injection, 0.9% Sodium Chioride Injection and Lactated Ringer's Injection). Constituted or constituted and further diluted solutions of Xifos should be refrigerated and used within 24 hours. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Ifosfamide should be administered as a slow intravenous infusion lasting a minimum of 30 minutes.

For IV administration Ifomes Injection can de biluted by adding the Ifomes Injection solution to any of the following fluids obtaining final concentrations of 20 mg Ifomes/mL; 5% Dextrose Injection, 5% Dextrose and 0.2% Sodium Chloride Injection, 5% Dextrose and 0.33% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, 0.92% Sodium Chloride Injection, Lactated Ringer's Injection. Ifomes is usually administered through a vein over at least five minutes.

STORAGE : Store the vial in original carton at 2° - 8° C. Protect from light. Keep out of reach of children.

PACKAGING : Each box contains one vial of Ifosfamide 2 gm Lyophilized Powder.