xifos

Ifosfamide

COMPOSITION

Xifos 1 Injection : Each vial contains Ifosfamide USP 1 gm as lyophilized powder.
Xifos 2 Injection : Each vial contains Ifosfamide USP 2 gm as lyophilized powder.

DESCRIPTION

Xifos (Ifosfamide for Injection) single-dose vials for constitution and administration by intravenous infusion each contain 1 gram or 2 grams of sterile Ifosfamide.

CLINICAL PHARMACOLOGY

Mode of Action

Ifosfamide has been shown to require metabolic activation by microsomal liver enzymes to produce biologically active metabolites. Activation occurs by hydroxylation at the ring carbon atom 4 to form the unstable intermediate 4-hydroxyIfosfamide. This metabolite rapidly degrades to the stable urinary metabolite 4-ketoIfosfamide. Opening of the ring results in formation of the stable urinary metabolite, 4-carboxyIfosfamide. These urinary metabolites have not been found to be cytotoxic. N, N-*bis* (2-chloroethyl)-phosphoric acid diamide (ifosphoramide) and acrolein are also found. Enzymatic oxidation of the chloroethyl side chains and subsequent dealkylation produces the major urinary metabolites, dechloroethyl Ifosfamide and dechloroethyl cyclophosphamide. The alkylated metabolites of Ifosfamide have been shown to interact with DNA. *In vitro* incubation of DNA with activated Ifosfamide has produced phosphotriesters. The treatment of intact cell nuclei may also result in the formation of DNA-DNA cross-links. DNA repair most likely occurs in G-1 and G-2 stage cells.

Pharmacokinetics/Dynamics

Ifosfamide exhibits dose-dependent pharmacokinetics in humans. At single doses of 3.8- 5.0 g/m^2, the plasma concentrations decay biphasically and the mean terminal elimination half-life is about 15 hours. At doses of 1.6-2.4 g/m^2/day, the plasma decay is monoexponential and the terminal elimination half-life is about 7 hours. Ifosfamide is extensively metabolized in humans and the metabolic pathways appear to be saturated at high doses. After administration of doses of 5 g/m^2 of 14C-labeled Ifosfamide, from 70% to 86% of the dosed radioactivity was recovered in the urine, with about 61% of the dose excreted as parent compound. At doses of 1.6-2.4 g/m^2 only 12% to 18% of the dose was excreted in the urine as unchanged drug within 72 hours.

INDICATION AND USAGE

Xifos, used in combination with certain other approved antineoplastic agents, is indicated for third line chemotherapy of germ cell testicular cancer. It should ordinarily be used in combination with a prophylactic agent for hemorrhagic cystitis, such as Mesna.

DOSAGE AND ADMINISTRATION

Xifos should be administered 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 $\geq$100,000/μL, WBC $\geq$ 4,000/μL). In order to prevent bladder toxicity, Xifos should be given with extensive hydration consisting of at least 2 liters of oral or intravenous fluid per day. A protector, such as Mesna, should also be used to prevent hemorrhagic cystitis. Xifos should be administered as a slow intravenous infusion lasting a minimum of 30 minutes. Although Xifos has been administered to a small number of patients with compromised hepatic and/or renal function, studies to establish optimal dose schedules of Xifos in such patients have not been conducted.

CONTRAINDICATIONS

Continued use of Xifos is contraindicated in patients with severely depressed bone marrow function. Xifos is also contraindicated in patients who have demonstrated a previous hypersensitivity to it.

WARNINGS

Urinary System

Urotoxic side effects, especially hemorrhagic cystitis, have been frequently associated with the use of Xifos. It is recommended that a urinalysis should be obtained prior to each dose of Xifos. If microscopic hematuria (greater than 10 RBCs per high power field), is present, then subsequent administration should be withheld until complete resolution.
Further administration of Xifos should be given with vigorous oral or parenteral hydration.

Hematopoietic System

When Xifos is given in combination with other chemotherapeutic agents, severe myelosuppression is frequently observed. 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. Unless clinically essential, Xifos should not be given to patients with a WBC count below 2000/μL and/or a platelet count below 50,000/μL.

Central Nervous System

Neurologic manifestations consisting of somnolence, confusion, hallucinations and in some instances, coma, have been reported following Xifos therapy. The occurrence of these symptoms requires discontinuing Xifos therapy. The symptoms have usually been reversible and supportive therapy should be maintained until their complete resolution.

Pregnancy

Animal studies indicate that the drug is capable of causing gene mutations and chromosomal damage in vivo. Embryotoxic and teratogenic effects have been observed in mice, rats and rabbits at doses 0.05 to 0.075 times the human dose. Ifosfamide can cause fetal damage when administered to a pregnant woman. If Xifos is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General

Xifos should be given cautiously to patients with impaired renal function as well as to those with compromised bone marrow reserve, as indicated by: leukopenia, granulocytopenia, extensive bone marrow metastases, prior radiation therapy or prior therapy with other cytotoxic agents.

Laboratory Tests

During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression. Urine should also be examined regularly for red cells which may precede hemorrhagic cystitis.

Drug Interactions

The physician should be alert for possible combined drug actions, desirable or undesirable, involving Ifosfamide even though Ifosfamide has been used successfully concurrently with other drugs, including other cytotoxic drugs.

Wound Healing

Ifosfamide may interfere with normal wound healing.

Pregnancy

Pregnancy "Category D"

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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In patients receiving Xifos as a single agent, the dose-limiting toxicities are myelosuppression and urotoxicity. Dose fractionation, vigorous hydration and a protector such as Mesna can significantly reduce the incidence of hematuria, especially gross hematuria, associated with hemorrhagic cystitis. At a dose of 1.2 g/m^2 daily for 5 consecutive days, leukopenia, when it occurs, is usually mild to moderate. Other significant side effects include alopecia, nausea, vomiting and central nervous system toxicities.

Hematologic Toxicity

Myelosuppression was dose related and dose limiting. It consisted mainly of leucopenia and to a lesser extent, thrombocytopenia. A WBC count <3000/μL is expected in 50% of the patients treated with Xifos single agent at doses of 1.2 g/m2 per day for 5 consecutive days. At this dose level, thrombocytopenia (platelets <100,000/μL) occurred in about 20% of the patients. At higher dosages, leukopenia was almost universal, and at total dosages of 10-12 g/m^2/cycle, one half of the patients had a WBC count below 1000/μL and 8% of patients had platelet counts less than 50,000/μL. Myelosuppression was usually reversible and treatment can be given every 3 to 4 weeks. When Xifos is used in combination with other myelosuppressive agents, adjustments in dosing may be necessary. Patients who experience severe myelosuppression are potentially at increased risk for infection. Anemia has been reported as part of postmarketing surveillance.

Digestive System

Nausea and vomiting occurred in 58% of the patients who received Xifos. They were usually controlled by standard antiemetic therapy. Other gastrointestinal side effects include anorexia, diarrhea and in some cases, constipation.

Urinary System

Urotoxicity consisted of hemorrhagic cystitis, dysuria, urinary frequency and other symptoms of bladder irritation. Hematuria occurred in 6% to 92% of patients treated with Xifos. The incidence and severity of hematuria can be significantly reduced by using vigorous hydration, a fractionated dose schedule and a protector such as Ifomes. At daily doses of 1.2 g/m^2 for 5 consecutive days without a protector, microscopic hematuria is expected in about one half of the patients and gross hematuria in about 8% of patients. Renal toxicity occurred in 6% of the patients treated with Ifosfamide as a single agent. Clinical signs, such as elevation in BUN or serum creatinine or decrease in creatinine clearance, were usually transient. They were most likely to be related to tubular damage. One episode of renal tubular acidosis which progressed into chronic renal failure was reported. Proteinuria and acidosis also occurred in rare instances. Metabolic acidosis was reported in 31% of patients in one study when Xifos was administered at doses of 2.0 to 2.5 g/m^2/day for 4 days. Renal tubular acidosis, Fanconi syndrome, renal rickets and acute renal failure have been reported. Close clinical monitoring of serum and urine chemistries including phosphorus, potassium, alkaline phosphatase and other appropriate laboratory studies is recommended. Appropriate replacement therapy should be administered as indicated.

Central Nervous System

CNS side effects were observed in 12% of patients treated with Xifos. Those most commonly seen were somnolence, confusion, depressive psychosis and hallucinations. Other less frequent symptoms include dizziness, disorientation and cranial nerve dysfunction. Seizures and coma with death were occasionally reported. The incidence of CNS toxicity may be higher in patients with altered renal function.

Other

Alopecia occurred in approximately 83% of the patients treated with Xifos as a single agent. In combination, this incidence may be as high as 100%, depending on the other 9 agents included in the chemotherapy regimen. Increases in liver enzymes and/or bilirubin were noted in 3% of the patients. Other less frequent side effects included phlebitis, pulmonary symptoms, fever of unknown origin, allergic reactions, stomatitis, cardiotoxicity and polyneuropathy.

OVERDOSAGE

No specific antidote for Xifos is known. Management of overdosage would include general supportive measures to sustain the patient through any period of toxicity that might occur.

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
1 gram	20 mL	50 mg/mL
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, Sterile Water for Injection. Because essentially identical stability results were obtained for Sterile Water admixtures as for the other admixtures (5% Dextrose Injection, 0.9% Sodium Chloride 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 be diluted 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.

PHARMACEUTICAL INFORMATION

Storage Condition

Store the vial in original carton at 2ºC to 8ºC, away from light. Keep out of the reach of children.

HOW SUPPLIED

Xifos (Ifosfamide) Injection is available in combination packages with the uroprotective agent Ifomes (Mesna) injection or as single-dose vials as follows:

Presentation & Packaging

Xifos 1 Injection: Each combipack contains 1 vial of Ifosfamide USP 1 gm Injection as lyophilized powder & 2 ampoules of 4 ml Ifomes (Mesna BP 400 mg) Injection.
Xifos 2 Injection: Each combipack contains 1 vial of Ifosfamide USP 2 gm Injection as lyophilized powder & 3 ampoules of 4 ml Ifomes (Mesna BP 400 mg) Injection.

Manufactured By
BEACON
Pharmaceuticals Limited
Mymensingh, Bangladesh

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