INJECTION
IFOSFAMIN 1gm & 2gm

U.S.P Specs.
(IFOSFAMIDE U.S.P)
Antineoplastic Agent

انجکشن

آئی فوسفامن 1 گرام، 2 گرام

(آئی فوسفامائیڈ) یو۔ایس۔پی

CAUTION: Ifosfamide is a potent drug and should be used only by physicians experienced with cancer chemotherapeutic drugs. In those patients who develop bacterial, fungal or viral infections, interruption or modification of dosage should be considered. Blood counts should be taken at regular intervals. Due to the urotoxic effect of oxazaphosphorines, ifosfamide should not be administered without the use of a uroprotective agent.

Action and Clinical Pharmacology: Ifosfamide is activated by metabolism in the liver by the mixed-function oxidase system of the smooth endoplasmic reticulum. The activation is induced by hydroxylation at the ring carbon atom 4. Opening of the ring results in the formation of aldo-ifosfamide, the tautomer of 4-hydroxy-ifosfamide. Two stable metabolites, 4-keto-ifosfamide and 4-carboxyifosfamide, appear in the urine However, they have no cytotoxic activity. N, Ne-bis (2-chlooethyl)-phosphoric acid diamide and acrolein are also found. The enzymatic oxidation of the chloroethyl side chains and subsequent dealkylation may produce further metabolites. DNA is one of the main target sites of ifosfamide. In vitro, incubation of DNA with activated ifosfamide produces phosphotriesters as the predominant reaction products. The treatment of intact cell nuclei may also result in the formation of DNA-DNA crosslinks. DNA repair occurs in G-1 and G-2 stage cells. Repair capacity is more marked in less sensitive tumors. An accumulation of cells in the G-1 phase is found in tumors that respond well.

Indications And Clinical Uses: Soft Tissue Sarcoma: First-line single agent therapy, second-line single agent therapy in patients who have failed to respond or who have relapsed on other chemotherapeutic regimens.

Pancreatic Carcinoma: Second-line single agent therapy in patients who have failed to respond or who have relapsed on other chemotherapeutic regimens.

Cervical Carcinoma: As a single agent or in combination with cisplatin and bleomycin in advanced or recurrent disease.

Contra-Indications: In individuals with a known hypersensitivity to it. It is also contraindicated in patients having severe leukopenia, thrombocytopenia, severe renal and/or hepatic impairment, cystitis, obstructions to the urine flow, or active infections. Ifosfamide should not be administered to patients with advanced cerebral arteriosclerosis.

Warnings In Clinical States: Urotoxic side effects, especially hemorrhagic cystitis, have been demonstrated in that the incidence of urinary tract complications was reduced from 40 to 3.5%. Thus ifosfamide should always be accompanied by uroprotective treatment with mesna. Patients, male or female, during the reproductive period of life, should be advised of the mutagenic potential of ifosfamide. Adequate methods of contraception are recommended for such patients.

Pregnancy and Lactation: Ifosfamide can be teratogenic or cause fetal resorption in experimental animals. It should not be used in pregnancy, particularly in early pregnancy, unless in the judgment of the physician the potential benefits outweigh the possible risks. As is the case with the oxazaphosphorine class of alkylatig agents, ifosfamide is excreted in breast milk and breast-feeding should be terminated prior to institution of drug therapy. Since the possibility of interference with normal wound healing has been reported with other oxazaphosphorines, therapy should not be initiated for at least 10 to 14 days after surgery. Ifosfamide, like other alkylating agents, has been reported to have oncogenic activity in animals. Thus the possibility that it may have oncogenic potential in humans should be considered.

Precautions: Ifosfamide should be given cautiously to patients with any of the following conditions: leukopenia, thrombocytopenia, tumor-cell infiltration of the bone marrow, prior radiotherapy, prior treatment with other antineoplastic agents, brain metastases and advanced cerebral arteriosclerosis, impaired renal function, impaired hepatic function, in the presence of known infections, abnormal serum creatinine and serum albumin levels. Because ifosfamide may exert a suppressive action in immune mechanisms, the interruption or modification of dosage should be considered for patients who develop bacterial, fungal or viral infections. This is especially true for patients receiving concomitant steroid therapy, since infections in some of these patients have been fatal. Ifosfamide may cause significant neurologic, renal and hematologic toxicities which may prove fatal despite careful monitoring prior to and during therapy. Prior to initiating treatment, it is necessary to exclude or correct any obstruction of the efferent urinary tract, cystitis, infections, and electrolyte imbalances. Urinary sediment should be examined at regular intervals. Extra care is required in unilaterally nephrectomized patients, in patients with impaired renal function, and in patients pretreated with nephrotoxic drugs (e.g., cisplatin) who obviously tolerate high-doses of ifosfamide less well. Ifosfamide should not be given until 3 months after the nephrectomy. Additional caution is also advisable in patients treated concomitantly with drugs having nephrotoxic potential (e.g., aminoglycoisdes and amphotericin B). Careful monitoring is also required for patients with cerebral metastases, as ifosfamide has been associated with several CNS symptoms. Leukocyte, erythrocyte and platelet counts should be carried out at regular intervals. There is normally a reduction in the leukocyte count beginning on approximately day 5. The nadir, depending on dosage and baseline count, tends to be reached after 8 to 10 days. Recovery occurs after 10 to 14 days and is usually complete after 2 to 3 weeks. Neurologic manifestations consisting of somnolence, confusion, hallucinations and in some instances, coma have been reported following ifosfamide therapy. In the case of ifosfamide induced CNS symptoms, drugs acting on the CNS (e.g., antiemetics and narcotics) should be discontinued, if possible, or used with caution. The occurrence of these symtoms requires discontinuing ifosfamide therapy. These symptoms have usually been reversible and supporting therapy should be maintained until their resolution.

Drug Interactions: The concurrent use of ifosfamide may enhance the anticoagulant effect of warfarin and thus raise the risk of hemorrhages.

Adverse Reactions: Urinary: Hemorrhagic cystitis, manifested by the occurrence of hematuria, dysuria, urinary frequency and occasionally urinary incontinence or retention, develops frequently in patients treated with ifosfamide. The incidence, severity and persistence of ifosfamide-induced hemorrhagic cystitis increase as the dose of the drug increases. In most instances, the hematuria resolves spontaneously upon cesation of therapy. The urinary tract toxicity of ifosfamide can be minimized by administering a uroprotective agent such as mesna, and ensuring adequate hydration and maintenance of fluid balance. Granular casts in the urinary sediment have occurred mainly after high doses of ifosfamide. The cylinduria generally resolves spontaneously a few days after the last injection. Renal parenchymal and tubular necrosis, which could lead to death, have been reported. Disorders of glomerular renal function with an increase in serum creatinine, a decrease in creatinine clearance and proteinuria occasionally occur, more frequently, disorders of tubular renal function with hyperaminoaciduria, phosphaturia, acidosis, or proteinuria occur. Severe nephropathies are rare. Predisposing factors for nephrotoxicity include the presence of renal tumors, pre-existing renal impairment, prior treatment with platinum containing drugs, and concomitant treatment with potentially nephrotoxic agents.

Metabolic acidosis was reported in 31% of patients in one study when ifosfamide was administered at doses of 2 to 2.5 g/m day for 4 days. Renal tubular acidosis, Fanconi Syndrome and renal rickets have also 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. Increases and decreases in creatinine clearance are usually reversible.

Hematopoietic: Leukopenia with the risk of life-threatening infection is an expected effect and ordinarily is used as a guide to therapy. Thrombocytopenia with the risk of hemorrhage and anemia have been known to occur in a few patients. These effects are almost always reversible when therapy is interrupted. Episodes of petechial bleeding due to severe thrombocytopenia have been reported. When ifosfamide is used in combination with other myelosuppressive agents, adjustments in dosing may be necessary.

Gastrointestinal: Nausea and vomiting are dose-related and also depend on individual sensitivity. Other gastrointestinal adverse events include anorexia, diarrhea, constipation, and stomatitis.

Effects on Gonads: Gonadal suppression, resulting in amenorrhea or azoospermia, has been reported with other oxazaphos phorines and thus may occur with ifosfamide.

Integumentary: It is ordinarily advisable to inform patients in advance of possible alopecia, a frequent complication of ifosfamide therapy. Regrowth of hair can be expected although occasionally the new hair may be of a different color or texture. Nonspecific dermatitis and inflammation of mucous membranes have been reported to occur with ifosfamide.

CNS: Cerebral side effects consist mainly of somnolence, confusion, hallucinations and depressive psychosis. Other less frequent symptoms included dizziness, disorientation, cranial nerve dysfunction, and cerebellar symptoms. Seizures of the tonic-clonic type have been reported occasionally. Isolated cases of encephalitis, generalized seizure and seizures resulting in coma have also been observed. It is possible that the severity ad incidence of cerebral effects increase with the administration of high doses, the presence of brain metastases, or advanced cerebral arteriosclerosis. The incidence and extent of cerebral effects due to ifosfamide may also be affected by the age of the patient, impaired renal clearance, pretreatment with nephrotoxic drugs, and postrenal obstructions (e.g., pelvic tumors). Other possible risk factors may include decreased levels of serum albumin or hydrogen carbonate, or concurrent high-dose treatment with antiemetic drugs.

Cardiotoxicity: Although cardiotoxicity is rarely encountered, there have been reported cases of supraventricular or ventricular arrhythmias, ST segment changes and heart failure at high doses of ifosfamide, or after pretreatment or concomitant treatment with anthracyclines. Hypertension and hypotension have been reported rarely.

Respiratory: Interstitial pulmonary fibrosis has been reported in patients treated with large doses of alkylating agents for prolonged periods. Although not reported in patients treated with ifosfamide, physicians should be aware of its possible occurrence. Pulmonary toxicities, including reports of interstitial pneumonitis and pulmonary edema, have been reported from fewer than 1% of patients.

Other: Adverse reactions in addition to those mentioned above have been noted with ifosfamide. They include infection with or without fever, hematemesis, asthenia, thrombophlebitis, increase in liver enzymes and/or bilirubin, allergic reactions, polyneuropathy, impaired or blurred vision, and increased sensitivity to irradiation. In addition, in isolated cases, syndrome of inappropriate of antidiuretic hormone (SIADH) has been reported. Pancreatitis has been reported in isolated cases.

Symptoms and Treatment Of Overdose: Symptoms and Treatment: No specific antidote is known. Management of overdosage would include general supportive measures to sustain the patients through any period of toxicity that might occur.

Dosage And Administration: Chemotherapy with ifosfamide, as with other drugs used in cancer chemotherapy, is potentially hazardous and fatal complications can occur. It is recommended that it be administered only by physicians aware of the associated risks. Total dosage of 250 to 300 mg/kg per cycle is the usual standard. As a rule, 50 to 60 mg/kg are administered i.v., over a period of a minimum of 30 minutes, each day for 5 consecutive days. If the calculation of the dosage is based on body surface area, the recommended dosage is 2000 to 2400 mg/m daily on 5 consecutive days. If a lower daily dosage or the total dosage over a longer period is indicated, ifosfamide can be given every other day (days 1, 3, 5, 7 and 9) or on 10 consecutive days in lower doses. A treatment series should be repeated after an interval of not less than 3 to 4 weeks. The therapeutic administration should invariably be accompanied by uroprotective treatment with mesna. Alternately, the administration of high single dose infusions is now feasible up to 5 to 8 g/m 24 h under protection of continuous mesna infusion. The optimal use of ifosfamide in combination with other myelosuppressive agents requires dosage adjustments according to the regimen and schedule to be adopted.

Prevention of Cystitis: The concomitant administration of mesna helps to prevent the urotoxic side effects of ifosfamide which had perviously limited the drug's therapeutic use. Every ifosfamide regimen should be accompanied by uroprotective treatment with mesna. Mesna is usually given by i.v. injection concurrently with ifosfamide and 4 and 8 hours afterwards, each dose being 20% of the ifosfamide dose. Even with the administration of the uroprotector mesna, the daily fluid intake should be at least 2 L. If urinary excretion appears insufficient, a fast-acting diuretic such as furosemide may be administered.

Reconstitution: Preparation for I.V. Use: Reconstitute with Sterile Water for Injection. Shake well until dissolved. The prepared solution may be further diluted to achieve concentratios of 0.6 to 20 mg/mL with any of the solutions for i.v. infusion.

Solutions for I.V. Infusion: 5% Dextrose Injection USP, 0.9% Sodium Chloride USP, Lactated Ringer's Injection USP.

Stability of Solutions: Reconstituted and further diluted solutions should be used within 24 hours from the time of the initial constitution or within 72 hours when refrigerated, when stored in glass bottles, viaflex bags or PAB bags.

Note: Product should be inspected visually for particulate matter and discoloration prior to administration.

Handling and Disposal: Preparation of ifosfamide should be done in a vertical laminar flow hood. Personnel preparing ifosfamide should wear PVC gloves, safety glasses, disposable gowns and masks. All needles, syringes, vials and other materials which have come in contact with ifosfamide should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport. Personnel regularly involved in the preparation and handling of ifosfamide should have bi-annual blood examinations.

Availability and Storage:
Ifosfamin - 1g Injection:
Each vial contains Ifosfamide U.S.P 1gm
Ifosfamin - 2g Injection:
Each vial contains Ifosfamide U.S.P 2gm
Dosage:
As directed by the physician.
Instruction:
Store at 2 - 8°C. Protect from heat, light and moisture as melting of drug may occur. Keep all medicines out of the reach of children. To be sold on prescription of registered medical practitioner only.

خوراک: ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
ہدایات: 2 سے 8 ڈگری سینٹی گریڈ پر رکھیں۔
گرمی، نمی اور روشنی سے بچائیں، ورنہ دوا پگھل سکتی ہے۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
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