Ifosfamide for Injection, USP should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Urotoxic side effects, especially hemorrhagic cystitis, as well as CNS toxicities such as confusion and coma have been associated with the use of ifosfamide. When they occur, they may require cessation of ifosfamide therapy. Severe myelosuppression has been reported (see "ADVERSE REACTIONS").

Metabolism of ifosfamide is required for the generation of alkylated metabolites of 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 phosphorimesters. 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.

The occurrence of these symptoms requires discontinuing ifosfamide therapy. The symptoms have usually been reversible and supportive therapy should be maintained until their complete resolution.

Ifosfamide for Injection, USP should be given cautiously to patients with severely depressed bone marrow function (see WARNINGS and PRECAUTIONS sections). Ifosfamide for Injection is also contraindicated in patients who have demonstrated a previous hypersensitivity to it.

Ifosfamide is a white crystalline powder that is soluble in water.

Ifosfamide exhibits dose-dependent pharmacokinetics in humans. At single doses of 3.8 to 5 g/m², the plasma concentrations decay biexponentially and the mean terminal elimination half-life is about 15 hours. At doses of 1.6 to 2.4 g/m²/day, the plasma decay is monoeponential 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/m² of [14C]-labeled ifosfamide, from 70% to 86% of the dose was recovered in the urine with about 61% of the dose excreted as parent compound. At doses of 1.6 to 2.4 g/m² only 12% to 18% of the dose was excreted in the urine as unchanged drug within 72 hours.

Two different dechloroethylated derivatives of ifosfamide, 4-carboxy ifosfamide, thiodiacetic acid and cysteine conjugates of chloroacetid acid have been identified as the major urinary metabolites of ifosfamide in humans and only small amounts of 4-hydroxy ifosfamide and acrolein are present. Small quantities (nmole/mL) of ifosfamide mustard and 4-hydroxy ifosfamide 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.

In a study at Indiana University, 50 fully evaluable patients with germ cell testicular cancer were treated with ifosfamide for Inphills and platelet count. Ifosfamide therapy was given in combination with cisplatin and either vinblastine or etopoide after failing (47 of 50 patients) at least two prior chemotherapy regimens consisting of cisplatin/vinblastine/bleomycin, (PVB), cisplatin/vinblastine/actinomycin D/bleomycin/ cyclophosphamide, (VAB6), or the combination of cisplatin and etoposide. Patients were selected for remaining cisplatin sensitivity because they had previously responded to a cisplatin containing regimen and had not progressed while on the cisplatin containing regimen or within 3 weeks of stopping it. Patients served as their own controls based on the premise that long term complete responses could not be achieved by retreatment with a regimen to which they had previously responded and subsequently relapsed.

Ten of 50 fully evaluable patients were still alive 2 to 5 years after treatment. Four of the 10 long term survivors were rendered free of cancer by surgical resection after treatment with the ifosfamide regimen; median survival for the entire group of 50 fully evaluable patients was 53 weeks.

INDICATIONS AND USAGE:

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

CONTRAINdications:

Continued use of ifosfamide for Injection is contraindicated in patients with severely depressed bone marrow function (see WARNINGS and PRECAUTIONS sections). Ifosfamide for Injection is also contraindicated in patients who have demonstrated a previous hypersensitivity to it.

WARNINGS:

Urotoxic side effects, especially hemorrhagic cystitis, have been frequently associated with the use of ifosfamide. It is recommended that a urinalysis be obtained prior to each dose of ifosfamide. 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 ifosfamide should be given with vigorous oral or parenteral hydration.

Hematopoietic System

When ifosfamide 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, ifosfamide 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 ifosfamide therapy. The occurrence of these symptoms requires discontinuing ifosfamide 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 0.1 times the human dose. Ifosfamide can cause fetal damage when administered to a pregnant woman. If ifosfamide 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

Ifosfamide 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) 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
Teratogenic Effects: Pregnancy Category D. See WARNINGS.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Ifosfamide has been shown to be carcinogenic in rats, with female rats showing a significant incidence of leiomyosarcomas and mammary fibroadenomas. The mutagenic potential of ifosfamide has been demonstrated in bacterial systems and in mammalian cells in vivo. In vivo, ifosfamide has induced mutagenic effects in mice and Drosophila melanogaster germ cells, and has induced a significant increase in dominant lethal mutations in male mice as well as recessive sex-linked lethal mutations in Drosophila. In pregnant mice, resorptions increased and anomalies were present at day 19 after 30 minute/day doses of ifosfamide administered on day 11 of gestation. Embryolethal effects were observed in rats following the administration of 18 mg/m²/day doses over the same dosing period. Ifosfamide is embryotoxic to rabbits receiving 88 mg/m²/day doses from the 6th through the 15th day of gestation and embryotoxic effects were apparent after doses reached 16 mg/m²/day over the same dosing period. Ifosfamide is embryotoxic to rabbits receiving 88 mg/m²/day doses from the 6th through the 15th day after mating. The number of anomalies was also significantly increased over the control group.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:
In patients receiving ifosfamide as a single agent, the dose-limiting toxicities are myelosuppression and urotoxicity. Dose fractionation, veno-occlusive disease, and a protector such as mesna can significantly reduce the incidence of hematotoxic and gastrointestinal toxicity. At a dose of 2.2 g/m² daily for 5 consecutive days, leukopenia, when it occurs, is usually mild to moderate. Other significant effects include anemia, nausea, vomiting, and central nervous system toxicities.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>93</td>
</tr>
<tr>
<td>Nausea-Vomiting</td>
<td>58</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>36</td>
</tr>
<tr>
<td>Gross Hematuria</td>
<td>12</td>
</tr>
<tr>
<td>CNS Toxicity</td>
<td>12</td>
</tr>
<tr>
<td>Infertility</td>
<td>8</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>6</td>
</tr>
<tr>
<td>Liver Dysfunction</td>
<td>3</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Constipation</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypotension</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Malaise</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Polynuropathy</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pulmonary Symptoms</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Salivation</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
*Based upon 2,070 patients from the published literature and 30 single agent studies.

Hematologic Toxicity
Myelosuppression was dose related and dose limiting. It consisted mainly of leukopenia and, to a lesser extent, thrombocytopenia. A WBC count <3,000/µL is expected in 50% of the patients treated with ifosfamide 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 to 12 g/m²/day, cycle 1, one half of the patients had a WBC count below 1000/µL and 8% of patients had platelet counts less than 100,000/µL. Myelosuppression was usually reversible and treatment can be given every 3 to 4 weeks. If ifosfamide 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.

Dermatologic Toxicity
Nausea and vomiting occurred in 58% of the patients who received ifosfamide. They were usually controlled with 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 ifosfamide. The incidence and severity of hematuria can be significantly reduced by using vigorous hydration, a fractionated dose schedule and a protector such as mesna. At daily doses of 1.2 g/m² for 5 consecutive days without a protector, microscopic hematuria is expected in about one third of patients and gross hematuria in about 8% of patients.

Renal toxicity occurred in 8% of the patients treated with IFOS single agent 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 series. When ifosfamide was administered at doses of 2 to 2.5 g/m²/day for 4 days. Renal tubular acidosis, Fanconi syndrome, renal tubular acidosis and chronic renal failure have been reported. Close clinical monitoring of serum and urine chemistries including phosphorus, potassium, creatinine, and phosphate and other appropriate laboratory studies is recommended. Appropriate clinical or biopsies may be indicated under these circumstances.

Other
Allopurinol administered in approximately 83% of the patients treated with ifosfamide as a single agent. In combination, this incidence may be as high as 100%, depending on the other 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, myalgias, cardiotoxicity, and polynuropathy.

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

DOSEAGING AND ADMINISTRATION:
Ifosfamide for Injection should be administered as a slow intravenous infusion lasting a minimum of 30 minutes. Although ifosfamide for injection has been administered to a small number of patients with compromised hepatic and/or renal function, studies to establish optimal dose schedules of ifosfamide for Injection in such patients have not been conducted.

Preparation for Intravenous Administration/ Stability
Injections are prepared for parenteral use by adding Sterile Water for Injection, USP, or Bacteriostatic Water for Injection, USP (benzyl alcohol or parabens preserved) to prevent bacterial contamination and shaking to dissolve. Use the quantity of diluent shown below to constitute the product:

<table>
<thead>
<tr>
<th>Dosage Strength</th>
<th>Diluent Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 gram</td>
<td>20 mL 50 mg/mL</td>
</tr>
<tr>
<td>3 grams</td>
<td>60 mL 50 mg/mL</td>
</tr>
</tbody>
</table>

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), the use of large volume parenteral glass bottles, Viaflex bags or PAB™ bags that contain intermediate concentrations of vasoactive agents (e.g., Dextrose Injection, 0.45% Sodium Chloride Injection, or 5% Dextrose and 0.9% Sodium Chloride Injection) is also acceptable. Constituted or constituted and further diluted solutions of ifosfamide for injection should be refrigerated and used within 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED:
Ifosfamide for Injection, USP, lyophilized is available as:

Product No. No. No.
104210 63323-142-10 Ifosfamide for Injection, USP, 1 gram single-dose vial, pack-aged individually.
104300 63323-143-00 Ifosfamide for Injection, USP, 3 gram single-dose vial, pack-aged individually.

Vial stoppers do not contain natural rubber latex.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from temperatures above 30°C (86°F).

Procedures for proper handling and disposal of anticancer drugs should be considered. Solutions and preparations associated with the handling of ifosfamide must be used with care to avoid exposure to the skin or mucous membranes. Ifosfamide for Injection solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of sterile water before rinsing with soap and water. Ifosfamide solution, or mixtures of excipients (e.g., Dextrose Injection, Sodium Chloride Injection, or Lactated Ringer’s Injection), may contain latex. A decision should be made prior to injection as to whether the patient is sensitive to latex.

REFERENCES: