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September 15, 2020; December 30, 2020; June 19, 2023,
September 2, 2025

Package Insert for Ifosfamide for Injection

Please read this package insert carefully and use under the guidance of a physician.

[Drug Name]

Generic Name: Ifosfamide for Injection

English Name: Ifosfamide for Injection

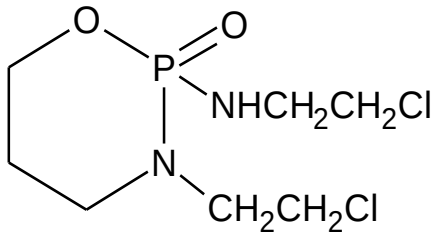
Pinyin: Zhusheyong Yihuanlinxian'an

[Ingredients]

Main Ingredients: The main ingredient of this product is ifosfamide. Excipients include glycine and mannitol.

Chemical Name: 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

Chemical Structural Formula:



Molecular Formula: $C_7H_{15}Cl_2N_2O_2P$

Molecular Weight: 261.08

[Description]

This product is a white or off-white loose mass or powder.

[Indications**]**

Indicated for testicular cancer, ovarian cancer, breast cancer, sarcoma, malignant lymphoma, and lung cancer.

[Strength] (1) 0.5 g; (2) 1.0 g

[Dosage and Administration**]**

This product should be reconstituted in sterile water for injection, then further diluted with 500 to 1000 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection, and

administered by slow intravenous infusion over at least 30 minutes.

Single-drug therapy: Administer intravenously at a dose of 1.2–2.5 g/m^2 per body surface area for 5 consecutive days as one cycle.

Combination therapy: Administer intravenously at a dose of 1.2–2.0 g/m^2 per body surface area for 5 consecutive days as one cycle.

The next cycle should be initiated after an interval of 3 o 4 weeks or once hematologic toxicity has recovered (platelet count 100,000/μL and white blood cell count 4,000/μL). To prevent bladder toxicity, adequate hydration is required, with a daily fluid intake of 2 L via oral or intravenous route. A protective agent against hemorrhagic cystitis, such as Mesna, should be co-administered. Mesna dissolved in normal saline should be given intravenously concurrently with ifosfamide administration and again at 4 and 8 hours post-administration. The usual dose of Mesna is 20% of the total daily dose of ifosfamide. Dosage adjustment for patients with hepatic or renal impairment has not been established.

[Adverse Reactions**]**

In patients treated with ifosfamide as single-drug therapy, the dose-limiting toxicities are myelosuppression and urinary toxicity. Fractionated dosing, adequate fluid intake, and the use of protective agents such as Mesna can significantly reduce the incidence of hemorrhagic cystitis complicated by hematuria, particularly gross hematuria. At a daily dose of 1.2 g/m^2, administered for 5 consecutive days, leukopenia, if it occurs, is typically mild to moderate. Other notable adverse effects include alopecia, nausea, vomiting, and neurologic toxicity.

Based on data from single-drug studies involving 2,070 patients reported in 30 foreign publications, the incidence rates of various adverse reactions are presented in the following table:

Adverse Reactions	Incidence (%)	Adverse Reactions	Incidence (%)
Alopecia	83	Coagulopathy	<1
Nausea and vomiting	58	Constipation	<1
Hematuria	46	Dermatitis	<1
Gross hematuria	12	Diarrhoea	<1
Neurologic toxicity	12	Fatigue	<1
Infection	8	Hypertension	<1
Renal impairment	6	Hypotension	<1
Hepatic dysfunction	3	Malaise	<1
Phlebitis	2	Polyneuropathy	<1

Pyrexia	1	Pulmonary symptoms	<1
Allergic reaction	<1	Sialorrhea	<1
Anorexia	<1	Stomatitis	<1
Cardiotoxicity	<1		

1. Hematologic Toxicity: Myelosuppression is a dose-related and dose-limiting toxicity, primarily manifesting as leukopenia, followed by thrombocytopenia. In patients receiving ifosfamide as a single drug at 1.2 g/m^2 daily for 5 consecutive days, 50% develop a white blood cell count below 3,000/μL. At this dosage, approximately 20% of patients experience thrombocytopenia (<100,000/μL). With higher doses, leukopenia occurs in nearly all cases. For total cumulative doses of 10–12 g/m^2 per cycle, 50% of patients have a white blood cell count below 1,000/μL, and 8% have a platelet count below 50,000/μL. Myelosuppression is typically reversible, allowing treatment to be resumed every 3 to 4 weeks. When ifosfamide is combined with other myelosuppressive agents, dosage modification is required. Patients experiencing severe myelosuppression may be at increased risk of infection.

2. Digestive System: Nausea and vomiting occurred in 58% of patients receiving this drug and were typically controlled with standard antiemetic therapy. Other gastrointestinal adverse effects include anorexia, diarrhoea, and constipation in some cases.

3. Urinary System: Urotoxicity includes hemorrhagic cystitis, dysuria, urinary frequency, and other bladder irritation symptoms. Hematuria occurs in 6% to 92% of patients receiving this drug. The incidence and severity of hematuria can be significantly reduced through adequate fluid intake, fractionated dosing, and the use of protective agents such as Mesna. At a daily dose of 1.2 g/m^2 administered for 5 consecutive days without a protective agent, approximately half of the patients develop microscopic hematuria, and about 8% exhibit gross hematuria.

6% of patients treated with ifosfamide as a single drug develop nephrotoxicity. Clinical manifestations include elevated blood urea nitrogen (BUN) or serum creatinine, or reduced creatinine clearance, which are usually transient. These may be associated with renal tubular injury. There have been reports of an isolated case of renal tubular acidosis progressing to chronic renal failure, proteinuria and acidosis have also occurred in very rare cases. One study reported that at daily doses of 2–2.5 g/m^2 for 4 days, 31% of patients developed metabolic acidosis. Cases of renal tubular acidosis, Fanconi syndrome, and nephrogenic rickets have also been reported. Therefore, close monitoring of serum and urinary

biochemical parameters is recommended, including phosphorus, potassium, alkaline phosphatase, and other appropriate laboratory tests. Appropriate replacement therapy should be administered.

4. Central Nervous System: Central nervous system adverse effects occurred in 12% of patients receiving this drug. The most common manifestations include somnolence, confusion, depressive psychosis, and hallucinations. Other rare symptoms include dizziness, disorientation, and cranial nerve dysfunction. Seizures and fatal coma have been rarely reported. Patients with altered renal function exhibit a higher frequency of neurologic toxicity.

5. Other: Alopecia occurred in approximately 83% of patients treated with ifosfamide as single-drug therapy. When used in combination with other agents, the incidence may reach 100%, depending on the concomitant chemotherapy regimen. Elevated liver enzymes and/or bilirubin levels were observed in 3% of patients. Other rare adverse effects include phlebitis, pulmonary symptoms, fever of unknown origin, allergic reaction, stomatitis, cardiac toxicity, and polyneuropathy.

Long-term use may result in immunosuppression, hypopituitarism, infertility, and secondary malignancies.

[Contraindications**]**

Contraindicated in patients with severe myelosuppression, hypersensitivity to this product, bilateral ureteral obstruction, pregnancy, and nursing mothers.

[Precautions**]**

1. Urinary system: The use of ifosfamide is frequently associated with urinary tract adverse effects, particularly hemorrhagic cystitis. Therefore, a urinalysis should be performed prior to each dose. If microscopic hematuria is detected (more than 10 red blood cells per high-power field), the drug should be discontinued until hematuria has completely resolved. Subsequent administration of this drug should be accompanied by adequate fluid, either orally or via intravenous infusion of large volumes of aqueous solution.

2. Hematologic system: When ifosfamide is used in combination with other chemotherapeutic agents, severe myelosuppression frequently occurs; therefore, close monitoring of hematologic parameters is recommended. White blood cell count, platelet count, and hemoglobin levels should be assessed prior to each dose and at appropriate intervals thereafter. Ifosfamide should not be administered to patients with a white blood cell count below 2,000/μL and/or a platelet count below 50,000/μL unless clinically necessary.

3. Central Nervous System: Neurological symptoms reported following ifosfamide therapy include somnolence, confusion, and hallucinations; in some cases, coma has occurred. Discontinue the drug upon occurrence of these symptoms. These effects are typically reversible and can be managed with symptomatic supportive care until complete resolution.

4. Ifosfamide should be used with caution in the following situations: patients with impaired hepatic or renal function; patients with compromised bone marrow function, such as leukopenia or granulocytopenia; extensive bone marrow metastases; patients who have previously undergone radiotherapy or received other cytotoxic agents; hypoproteinemia; and women of childbearing potential.

5. Laboratory tests: During treatment, hematologic parameters (particularly neutrophils and platelets) should be monitored regularly to assess the degree of myelosuppression. Urinary red blood cells should also be checked periodically, as they may appear prior to the onset of hemorrhagic cystitis.

6. The aqueous solution of this product is unstable and must be prepared immediately before use. Gloves should be worn during dispensing. In case of accidental skin contact, cutaneous reactions may cause, the area should be thoroughly washed immediately with soap and water.

【Use in Pregnancy and Lactation】

Animal studies have shown that this product is mutagenic and teratogenic, capable of causing fetal death or congenital malformations. It is contraindicated in pregnant women. Ifosfamine is excreted in breast milk, breastfeeding must be discontinued upon initiation of therapy.

【Pediatric Use】

Safety and effectiveness have not been established in pediatric patients.

【Geriatric Use】

Safety and effectiveness have not been established in geriatric patients.

【Drug Interactions】

(1) Prior administration of cisplatin exacerbate ifosfamide-induced myelosuppression, neurotoxicity, and nephrotoxicity.

(2) Concomitant use with anticoagulants cause bleeding.

(3) Concomitant use with hypoglycemic agents potentiate hypoglycemic effects.

(4) Dose reduction should be considered as appropriate when used in combination with other cytotoxic agents.

(5) Administration of live vaccines (e.g., rotavirus vaccine) during therapy increases the risk of infection from the live vaccine; live vaccines should not be administered to patients receiving immunosuppressive chemotherapy.

(6) Concomitant radiotherapy exacerbate radiation-induced cutaneous reactions.

【Overdosage】

No specific antidote for ifosfamide is known.

Management of overdosage primarily involves general supportive measures to alleviate potential toxic reactions in patients.

【Pharmacology and Toxicology】

Pharmacological Effects

This product exhibits no anticancer activity in vitro. Upon entering the body, it is hydrolyzed by phosphoamidase or phosphatase present in the liver or tumors into active phosphoramide mustard, which exerts its therapeutic effect. Its mechanism of action may involve DNA crosslinks, inhibiting DNA synthesis, and interfering with RNA function; it belongs to cell cycle non-specific drugs. This product is a broad-spectrum antitumor agent and demonstrates inhibitory effects on various types of tumors.

Toxicological Studies

Genotoxicity: In vitro bacterial mutation assays and tests conducted in mammalian cells have shown that this product possesses mutagenic properties. In vivo, it can induce mutations in germ cells of mice and Drosophila melanogaster, and significantly increase dominant lethal mutations in male mice as well as recessive sex-linked lethal mutations in Drosophila.

Reproductive Toxicity: In pregnant mice, embryonic resorption increase at day 19 after a 30 mg/m^2 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 of ifosfamide from the 6^{th} through the 15^{th} day of gestation. Ifosfamide is embryotoxic to rabbits receiving 88 mg/m^2 doses from the 6th through the 18th day after mating. The number of anomalies was also significantly increased over the control group.

Carcinogenicity: Studies in rats have demonstrated carcinogenicity of this product, with female rats showing a notably higher incidence of leiomyosarcoma and mammary fibroadenoma.

【Pharmacokinetics】

After entering the body, this product is extensively metabolized, primarily activated in the

liver to produce active metabolites; the metabolites may vary among individuals. The active metabolite crosses the blood-brain barrier only to a limited extent, with cerebrospinal fluid drug concentrations reaching 20% of plasma concentration. Metabolic saturation occurs at high doses. Following a single intravenous injection of 3.8–5.0 g/m^2 based on body surface area, plasma concentration exhibits biphasic decline, with a terminal elimination half-life of approximately 15 hours; following a single intravenous injection of 1.6–2.4 g/m^2, plasma concentration shows monophasic decline, with a terminal elimination half-life of approximately 7 hours. Approximately 70%–80% is excreted via the kidneys; when administered as a single intravenous dose of 5.0 g/m^2, 61% is excreted unchanged, whereas at doses of 1.2–2.4 g/m^2, only 12%–18% is excreted unchanged. Plasma protein binding of this product is less than 20%.

【Storage】

Protect from light, seal, and store in a cold place.

【Packaging】

Ifosfamide for injection is available in single-dose vials. 5 vials per carton.

【Shelf Life】

36 months.

【Standard Executed】 Chinese Pharmacopoeia 2025 Edition, Part II; YBH00732009

【Approval Number】 (1) GYZZ H20093077; (2) GYZZ H20093079

【Marketing Authorization Holder】

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【Manufacturer】

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