





## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ifosfamide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### INFECTIONS AND INFESTATIONS:

The following manifestations have been associated with myelosuppression and immunosuppression caused by ifosfamide: increased risk for and severity of infections<sup>†</sup>, pneumonia<sup>†</sup>, sepsis and septic shock (including fatal outcomes), as well as reactivation of latent infections, including viral hepatitis<sup>†</sup>, *Pneumocystis jiroveci*<sup>†</sup>, herpes zoster, *Strongyloides*, progressive multifocal leukoencephalopathy<sup>†</sup>, and other viral and fungal infections.

† Severe immunosuppression has led to serious, sometimes fatal, infections.

### NEOPLASMS, BENIGN AND MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS):

As treatment-related secondary malignancy\*, Acute leukemia\* (Acute myeloid leukemia)\*, Acute promyelocytic leukemia\*, Acute lymphocytic leukemia\*, Myelodysplastic syndrome, Lymphoma (Non-Hodgkin's lymphoma), Sarcomas\*, Renal cell carcinoma, Thyroid cancer

### BLOOD AND LYMPHATIC SYSTEM DISORDERS:

Hematotoxicity\*, Myelosuppression manifested as Bone marrow failure, Agranulocytosis; Febrile bone marrow aplasia; Disseminated intravascular coagulation, Hemolytic uremic syndrome, Hemolytic anemia, Neonatal anemia, Methemoglobinemia

### IMMUNE SYSTEM DISORDERS:

Angioedema\*, Anaphylactic reaction, Immunosuppression, Urticaria, Hypersensitivity reaction

### ENDOCRINE DISORDERS:

Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

### METABOLISM AND NUTRITION DISORDERS:

Tumor lysis syndrome, Metabolic acidosis, Hypokalemia, Hypocalcemia, Hypophosphatemia, Hyperglycemia, Polydipsia

### PSYCHIATRIC DISORDERS:

Panic attack, Catatonia, Mania, Paranoia, Delusion, Delirium, Bradyphrenia, Mutism, Mental state change, Echolalia, Logorrhea, Perseveration, Amnesia

### NERVOUS SYSTEM DISORDERS:

Convulsion\*, Status epilepticus (convulsive and nonconvulsive), reversible posterior leukoencephalopathy syndrome, Leukoencephalopathy, Extrapyramidal disorder, Asterixis, Movement disorder, Polyneuropathy, Dysesthesia, Hypothesia, Paresthesia, Neuralgia, Gait disturbance, Fecal incontinence, Dysarthria

### EYE DISORDERS:

Visual impairment, Vision blurred, Conjunctivitis, Eye irritation

### EAR AND LABYRINTH DISORDERS:

Deafness, Hypoacusis, Vertigo, Tinnitus

### CARDIAC DISORDERS:

Cardiotoxicity\*, Cardiac arrest\*, Ventricular fibrillation\*, Ventricular tachycardia\*, Cardiogenic shock\*, Myocardial infarction\*, Cardiac failure\*, Bundle branch block left, Bundle branch block right, Pericardial effusion, Myocardial hemorrhage, Angina pectoris, Left ventricular failure, Cardiomyopathy\*, Congestive cardiomyopathy, Myocarditis\*, Arrhythmia\*, Pericarditis, Atrial fibrillation, Atrial flutter, Bradycardia, Supraventricular extrasystoles, Premature atrial contractions, Ventricular extrasystoles, Myocardial depression, Palpitations, Ejection fraction decreased\*, Electrocardiogram ST-segment abnormal, Electrocardiogram T-wave inversion, Electrocardiogram QRS complex abnormal

### VASCULAR DISORDERS:

Pulmonary embolism, Deep vein thrombosis, Capillary leak syndrome, Vasculitis, Hypertension, Flushing, Blood pressure decreased

### RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS:

Respiratory failure\*, Acute respiratory distress syndrome\*, Pulmonary hypertension\*, Interstitial lung disease\* as manifested by Pulmonary fibrosis\*, Alveolitis allergic, Interstitial pneumonitis, Pneumonitis\*, Pulmonary edema\*, Pleural effusion, Bronchospasm, Dyspnea, Hypoxia, Cough

### GASTROINTESTINAL DISORDERS:

Cecitis, Colitis, Enterocolitis, Pancreatitis, Ileus, Gastrointestinal hemorrhage, Mucosal ulceration, Constipation, Abdominal pain, Salivary hypersecretion

### HEPATOBIILIARY DISORDERS:

Hepatic failure\*, Hepatitis fulminant\*, Veno-occlusive liver disease, Portal vein thrombosis, Cytolytic hepatitis, Cholestasis

### SKIN AND SUBCUTANEOUS TISSUE DISORDERS:

Toxic epidermal necrolysis, Stevens-Johnson syndrome, Palmar-plantar erythrodysesthesia syndrome, Radiation recall dermatitis, Skin necrosis, Facial swelling, Petchiae,

Macular rash, Rash, Pruritus, Erythema, Skin hyperpigmentation, Hyperhidrosis, nail disorder

### MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER:

Rhabdomyolysis, Osteomalacia, Rickets, Growth retardation, Myalgia, Arthralgia, Pain in extremity, Muscle twitching

### RENAL AND URINARY DISORDERS:

Fanconi syndrome, Tubulointerstitial nephritis, Nephrogenic diabetes insipidus, Phosphaturia, Aminoaciduria, Polyuria, Enuresis, Feeling of residual urine

Fatal outcomes from acute and chronic renal failure have been documented.

### REPRODUCTIVE SYSTEM AND BREAST DISORDERS:

Infertility, Ovarian failure, Premature menopause, Amenorrhea, Ovarian disorder, Ovulation disorder, Azospermia, Oligospermia, Impairment of spermatogenesis, Blood estrogen decreased, Blood gonadotrophin increased

### CONGENITAL, FAMILIAL AND GENETIC DISORDERS:

Fetal growth retardation

### GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS:

Multi-organ failure\*, General physical deterioration, Injection/Infusion site reactions including swelling, inflammation, pain, erythema, tenderness, pruritus; Chest pain, Edema, Mucosal inflammation, Pain, Pyrexia, Chills

\* Including fatal outcomes

### 7 DRUG INTERACTIONS

Ifosfamide is a substrate for both CYP3A4 and CYP2B6.

### 7.1 Inducers of CYP3A4

CYP3A4 inducers (e.g., carbamazepine, phenytoin, fosphenytoin, phenobarbital, rifampin, St. John 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.

### 7.2 Inhibitors of CYP3A4

CYP3A4 inhibitors (e.g., ketoconazole, fluconazole, itraconazole, sorafenib, aprepitant, fosaprepitant, grapefruit, grapefruit juice) may decrease the metabolism of ifosfamide to its active alkylating metabolites, perhaps decreasing the effectiveness of ifosfamide treatment.

### 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.8)]*.

Ifosfamide for Injection 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/m<sup>2</sup> dose of ifosfamide was administered on day 11 of gestation. Embryo-lethal effects were observed in rats following the administration of 54 mg/m<sup>2</sup> doses of ifosfamide from the 6th through the 15th day of gestation and embryotoxic effects were apparent after dams received 18 mg/m<sup>2</sup> doses over the same dosing period. Ifosfamide is embryotoxic to rabbits receiving 88 mg/m<sup>2</sup>/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.

### 8.3 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.

### 8.4 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 *[see Pharmacokinetics (12.3)]*. 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

No formal studies were conducted in patients with renal impairment. Ifosfamide and its metabolites are known to be excreted by the kidneys and may accumulate in plasma with decreased renal function. Patients with renal impairment should be closely monitored for toxicity and dose reduction may be considered. Ifosfamide and its metabolites are dialyzable.

### 8.7 Use in Patients with Hepatic Impairment

No formal studies were conducted in patients with hepatic impairment. Ifosfamide is extensively metabolized in the liver and forms both efficacious and toxic metabolites. Ifosfamide for Injection should be given cautiously to patients with impaired hepatic function.

### 10 OVERDOSAGE

No specific antidote for Ifosfamide for Injection 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 *[see Warnings and Precautions (5)]*.

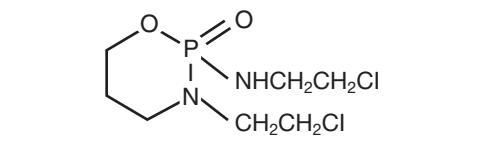
Management of overdosage would include general supportive measures to sustain the patient through any period of toxicity that might occur, including appropriate state-of-the-art treatment for any concurrent infection, myelosuppression, or other toxicity. Ifosfamide as well as ifosfamide metabolites are dialyzable.

Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with overdose.

### 11 DESCRIPTION

Ifosfamide for Injection, USP single-dose vials for constitution and administration by intravenous infusion each contain 1 gram or 3 grams of sterile ifosfamide. Ifosfamide is a chemotherapeutic agent chemically related to the nitrogen mustards and a synthetic analog of cyclophosphamide. Ifosfamide is 3-[(2-chloroethyl)-2-[(2-chloroethyl)amino] tetrahydro-2H-1,3,2 oxazaphosphorine 2-oxide. The molecular formula is C<sub>7</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>P and its molecular weight is 261.1. Ifosfamide is a white crystalline powder soluble in water. There are no excipients in the formulation. Each vial contains 1 gram or 3 grams of sterile ifosfamide alone.

Its structural formula is:



### 12 CLINICAL PHARMACOLOGY

### 12.1 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.

### 12.3 Pharmacokinetics

Ifosfamide exhibits dose-dependent pharmacokinetics in humans. At single doses of 3.8 to 5.0 g/m<sup>2</sup>, 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<sup>2</sup>/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<sup>2</sup> over 0.5 hour once daily for 5 days to 15 patients with neoplastic disease, a decrease in the median elimination half-life from 7.2 hour 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<sup>2</sup> over 0.5 hour 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-dechloroethylifosfamide 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<sup>2</sup> of <sup>14</sup>C-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<sup>2</sup> 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 chloroacetic acid have been identified as the major urinary metabolites of ifosfamide in humans and only small amounts of 4-hydroxyifosfamide and acrolein are present.

### Pediatrics

Population PK analysis was performed on plasma data from 32 pediatric patients various malignant diseases aged between 1 and 18 years. Patients received a total of 45 courses of ifosfamide at doses of 1.2, 2.0 and 3.0 g/m<sup>2</sup> given intravenously over 1 or 3 hours on 1, 2, or 3 days. The mean±standard error population estimates for the initial clearance and volume of distribution of ifosfamide were 2.4±0.33 L/h/m<sup>2</sup> and 21±1.6 L/m<sup>2</sup> with an interindividual variability of 43% and 32%, respectively.

### Effect of Age

A study of 20 patients between 40 to 71 years of age receiving 1.5 g/m<sup>2</sup> of ifosfamide daily for 3 or 5 days indicated that elimination half-life appears to increase with age. The elimination half-life increase appeared to be related to the increase in ifosfamide volume of distribution with age. No significant changes in total plasma clearance or renal clearance with age were reported.

### 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ifosfamide has been shown to be carcinogenic in rats when administered by intraperitoneal injection at 6 mg/kg (37 mg/m<sup>2</sup>, or about 3% of the daily human dose on a mg/m<sup>2</sup> basis) 3 times a week for 52 weeks. Female rats had a significantly higher incidence of uterine leiomyosarcomas and mammary fibroadenomas than vehicle controls.

The mutagenic potential of ifosfamide has been documented in bacterial systems *in vitro* and 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*.

Ifosfamide was administered to male and female beagle dogs at doses of 1.00 or 4.64 mg/kg/day (20 or 93 mg/m<sup>2</sup>) orally 6 days a week for 26 weeks. Male dogs at 4.64 mg/kg (about 7.7% of the daily clinical dose on a mg/m<sup>2</sup> basis) had testicular atrophy with degeneration of the seminiferous tubular epithelium. In a second study, male and female rats were given 0, 25, 50, or 100 mg/kg (0, 150, 300, or 600 mg/m<sup>2</sup>) ifosfamide intraperitoneally once every 3 weeks for 6 months. Decreased spermatogenesis was observed in most male rats given 100 mg/kg (about half the daily clinical dose on a mg/m<sup>2</sup> basis).

## 14 CLINICAL STUDIES

Patients with refractory testicular cancer (n=59) received a combination of ifosfamide, cisplatin, and either etoposide (VePesid) or vinblastine (VIP) as third-line therapy or later. The selection of etoposide or vinblastine ("V" in the VIP regimen) was guided by the therapeutic effect achieved with prior regimens. The contribution of ifosfamide to the VIP combination was determined in patients treated with cisplatin etoposide prior to ifosfamide-cisplatin-etoposide or those who received cisplatin-vinblastine prior to ifosfamide-cisplatin-vinblastine.

A total of 59 patients received a third-line salvage regimen which consisted of ifosfamide 1.2 g/m<sup>2</sup>/day intravenously on days 1 to 5, cisplatin 20 mg/m<sup>2</sup>/day intravenously on days 1 to 5, and either etoposide 75 mg/m<sup>2</sup>/day intravenously on days 1 to 5 or vinblastine 0.22 mg/kg intravenously on day 1. Efficacy results with the VIP regimen were compared to data pooled from six single agent phase II trials conducted between August 1980 and October 1985 including a total of 90 patients of whom 65 were eligible as controls of this study. Twenty-three patients in the VIP regimen became free of disease with VIP alone or VIP plus surgery, whereas a single patient in the historical control group achieved complete response. The median survival time exceeded two years in the VIP group versus less than one year in the control group.

Performance status ≥ 80, embryonal carcinoma and minimal disease were favorable prognostic factors for survival. In all prognostic categories, the difference between VIP and historical controls remained highly significant.

### Table 1. Efficacy Results

	Number. (%) of Patients		p-value
	VIP	Control	
Total Patients	59 (100)	65 (100)	
Disease-free	23 (39)	1 (2)	< 0.001
Chemotherapy alone	15 (25)	1 (2)	< 0.001
Chemotherapy plus surgery	8 (14)	0	
Overall Response	32 (54)	2 (3)	< 0.001
Time to progression (weeks)			
Median	19	4	< 0.001 <sup>a</sup>
Range	1 – 205+	1 – 29	
Disease-free interval (weeks)			
Median	114	29	
Range	13 – 205+	-	
Survival (weeks)			
Median	53	10	< 0.001 <sup>a</sup>
Range	1 – 205+	1 – 123+	

a: Gehan-Breslow and Mantel-Cox tests

In a study, 50 fully evaluable patients with germ cell testicular cancer were treated with ifosfamide for Injection in combination with cisplatin and either vinblastine or etoposide 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 control 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.

### 15 REFERENCES

- NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
- OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling occupational exposure to hazardous drugs. OSHA, 1999. [http://www.osha.gov/dts/osta/otm/otm\\_vi/otm\\_vi\\_2.html](http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html)
- American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.
- Polovich M, White JM, Kelleher LO, (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice. (2<sup>nd</sup> ed.) Pittsburgh, PA: Oncology Nursing Society.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

Ifosfamide for Injection, USP, is available in single-dose vials as follows:

Product No.	NDC No.	
104210	63323-142-10	1 gram single dose vial, packaged individually.
104300	63323-143-00	3 grams single dose vial, packaged individually.

The container closure is not made with natural rubber latex.

Store at controlled room temperature 20°C to 25°C (68°F to 77°F). Protect from temperatures above 30°C (86°F).

Exercise caution when handling Ifosfamide for Injection. The handling and preparation of ifosfamide should always be in accordance with current guidelines on safe handling of cytotoxic agents. Several guidelines on this subject have been published.<sup>1-4</sup> Skin reactions associated with accidental exposure to Ifosfamide for Injection may occur. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and solutions containing Ifosfamide for Injection. If 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 water.

### 17 PATIENT COUNSELING INFORMATION

Inform patients of the risks associated with the use of ifosfamide for Injection as well as the plan for regular blood monitoring during therapy.

Specifically inform patients of the following:

- Treatment with ifosfamide may cause myelosuppression which can be severe and lead to fatal outcome. Significant suppression of immune responses can also occur which can lead to severe infections. Latent infections can be reactivated. Patients should report fever or other symptoms of an infection.

- The risk of bleeding and anemia.
- The risk of CNS toxicity and other neurotoxic effects with fatal outcome.
- The risk of bladder and kidney toxicity. Patients should be aware of the need to increase fluid intake and frequent voiding to prevent accumulation in the bladder.

- The risk of cardiotoxicity and fatal outcome. Patients should report preexisting cardiac disease.
- The risk of pulmonary toxicity leading to respiratory failure with fatal outcome.
- The risk of secondary malignancies due to therapy.
- The risk of veno-occlusive liver disease.
- The potential hazard to a fetus if a patient becomes pregnant or fathers a child during therapy and for up to 6 months after therapy. Effective methods of contraception should be used during therapy and for up to 6 months after therapy.
- The potential for serious adverse reactions and tumorigenicity when children are breastfed during therapy.
- The risk of amenorrhea, premature menopause, and sterility.
- The risk of alopecia, wound healing, and other serious skin and subcutaneous tissue disorders.
- Therapy may cause gastrointestinal disorders and alcohol may increase nausea and vomiting.
- The risk of stomatitis and the importance of proper oral hygiene.
- The risk of eye disorders such as visual impairment, blurred vision, and eye irritation.
- The risk of ear and labyrinth disorders such as deafness, vertigo, and tinnitus.

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