Ifosfamide Injection is indicated for use in combination with certain other approved antineoplastic agents. Close hematologic monitoring is recommended. White blood cell counts, platelet counts, and serum electrolytes should be performed regularly during treatment. Latent infections can be reactivated. In patients undergoing therapy, the risk of infection may be increased, and severe infections can occur. Fatal outcomes of ifosfamide-associated myelosuppression have been reported. Treatment should be withheld or discontinued if the platelet count falls below 50,000/mm³ or the white blood cell count falls below 1000/mm³. If thrombocytopenia or neutropenia develops, treatment should be withheld until the platelet count and white blood cell count have recovered to at least 50,000/mm³ and 1000/mm³, respectively. Monitoring of the hematologic system is recommended. If anemia develops, treatment should be withheld until the hematocrit is recovered to at least 25%. Ifosfamide injection should be adminstered without concomitant chemotherapy at doses higher than 500 mg/m² to patients receiving bladder cancer chemotherapy. Treatment should be withheld if the hematocrit falls below 30% or the hemoglobin falls below 10 g/dL. Ifosfamide injection should be administered with extensive hydration. Ifosfamide injection should be prepared and administered in a manner consistent with regulatory and institutional guidelines for the safe administration of cytotoxic drugs. Ifosfamide injection should be stored at or below 30°C (86°F) in a refrigerated environment. Ifosfamide injection should be administered with extensive hydration. Ifosfamide injection should be stored at or below 30°C (86°F) in a refrigerated environment. Ifosfamide injection should be administered with extensive hydration. Ifosfamide injection should be stored at or below 30°C (86°F) in a refrigerated environment. Ifosfamide injection should be administered with extensive hydration. Ifosfamide injection should be stored at or below 30°C (86°F) in a refrigerated environment. Ifosfamide injection should be administered with extensive hydration. Ifosfamide injection should be stored at or below 30°C (86°F) in a refrigerated environment.
At doses of 1.6 to 2.4 g/m² only 12% to 18% of the dose was excreted in the urine. Radioactivity was recovered in urine as metabolites, with about 61% of the dose excreted as parent dose on a mg/m² basis.

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In male and female rats, ifosfamide produced a dose-dependent increase in the number of mammary fibroadenomas than vehicle controls. Ifosfamide also increased the incidence of uterine leiomyosarcomas and mammary gland tumors in female rats. Ifosfamide was administered to rats, hamsters, mice, and dogs at total daily doses of 1.5 to 24 g/m² for up to 28 weeks. Ifosfamide was given either alone or in combination with cyclophosphamide. Ifosfamide caused a statistically significant increase in the incidence of uterine tumors in female rats. The number of uterine leiomyosarcomas and mammary gland tumors increased in a dose-dependent manner. The mutagenic potential of ifosfamide has been documented in bacterial systems.

### 8.4 Pediatric Use

Ifosfamide is extensively metabolized in humans through two metabolic pathways: ring oxidation to the unstable intermediate 4-hydroxyifosfamide and its ring-opened aldo tautomer, which decomposes 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 exert its cytotoxic activity. Upon administration of doses of 1.5 g/m² or greater, 4-hydroxyifosfamide is detectable in human plasma. Metabolism of ifosfamide is required for the elimination of the parent drug within 72 hours. Two different dechloroethylated derivatives of ifosfamide, 4-carboxyifosfamide, thiodiacetic acid and cysteine conjugates of chloroacetic acid have been identified in urine and plasma of patients treated with ifosfamide. Ifosfamide USP is 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2H-pyrimidine-4,6 (1H, 3H)-dione. Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with ifosfamide.

### 12.3 Pharmacokinetics

Ifosfamide is extensively metabolized in humans through two metabolic pathways: ring oxidation to the unstable intermediate 4-hydroxyifosfamide and its ring-opened aldo tautomer, which decomposes 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 exert its cytotoxic activity. Upon administration of doses of 1.5 g/m² or greater, 4-hydroxyifosfamide is detectable in human plasma. Metabolism of ifosfamide is required for the elimination of the parent drug within 72 hours. Two different dechloroethylated derivatives of ifosfamide, 4-carboxyifosfamide, thiodiacetic acid and cysteine conjugates of chloroacetic acid have been identified in urine and plasma of patients treated with ifosfamide.

### 12 PHARMACODYNAMICS