Intravenous Dosing Schedule:

- Mesna Tablets: 1 g (100 mg per mL) Multi-Dose Vials
- Mesna Injection: 1 g (100 mg per mL) Multi-Dose Vials

**Dosage and Administration**

1. Intravenous Dosing

Mesna injection may be given as a intravenous bolus schedule of single bolus intravenous injections followed by two oral administrations of mesna tablets as outlined below. The closing schedule should be repeated on each day that ifosfamide is administered. When the dosage of ifosfamide is increased or decreased, the ratio of mesna to ifosfamide should be maintained.

**Intravenous Dosing Schedule**

<table>
<thead>
<tr>
<th>Time</th>
<th>Mesna Tablets</th>
<th>Mesna Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Hours</td>
<td>240 mg</td>
<td>720 mg</td>
</tr>
<tr>
<td>2 Hours</td>
<td>240 mg</td>
<td>720 mg</td>
</tr>
<tr>
<td>6 Hours</td>
<td>240 mg</td>
<td>720 mg</td>
</tr>
</tbody>
</table>

**Monitoring for Hematuria**

Monitor patients. If a reaction occurs, discontinue mesna and provide supportive care. (5.1)

**Drug Rash with Eosinophilia and Systemic Symptoms**

Use in Patients with a History of Adverse Reactions to Thiol Compounds

**Clinical Trials Experience**

- Anaphylactic reactions: Anaphylactic reactions may include fever, nausea, vomiting, constipation, and death in neonates and premature infants. Avoid use in neonates, premature, and low-birth weight infants. (6.1)
- Laboratory test alterations: False-positive tests for urinary ketones and interference with enzymatic CPK activity may be seen. (5.4)

**Contraindications**

- Known hypersensitivity to mesna or to any of the excipients, including benzyl alcohol. (4.1)

**Warnings and Precautions**

- Hypersensitivity reactions: Anaphylactic reactions have been reported. Loss of oxygen saturation may also occur. Monitor patients. If a reaction occurs, discontinue mesna and provide supportive care. (6.1)
- Dermatologic toxicity: Skin rash with exanthem and systemic symptoms, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred. Skin rash, urticaria, and angioedema have also been seen. Monitor patients. If a reaction occurs, discontinue mesna and provide supportive care. (6.1)
- Benzyl alcohol toxicity: The preservative benzyl alcohol has been associated with various adverse reactions and death in neonates and premature infants. Avoid use in neonates, premature, and low-birth weight infants. (6.3)

**Laboratory Test Interferences**

**Adverse Reactions**

**6.1 Clinical Trials Experience**

- Anaphylactic reactions: Anaphylactic reactions may include fever, nausea, vomiting, constipation, and death in neonates and premature infants. Avoid use in neonates, premature, and low-birth weight infants. (6.1)
- Laboratory test alterations: False-positive tests for urinary ketones and interference with enzymatic CPK activity may be seen. (5.4)
- Adverse reactions: Adverse reactions to thiol compounds are at increased risk for a thiol compound and are given concurrently with ifosfamide. (6.4)
- Clinical trials experience: ClinicalTrials.gov identifies clinical studies to determine the safety and efficacy of a medicinal product. (6.1)
- Hypersensitivity reactions: Hypersensitivity reactions to mesna and to any of its excipients, including benzyl alcohol, have been reported. (6.1)

**Benzyl Alcohol Toxicity**

Avoid use in neonates, premature, and low-birth weight infants. (6.1)

**Use in Specific Populations**

**Pediatric Use**

- Use in patients with a history of adverse reactions to thiol compounds

**Drug Rash with Eosinophilia and Systemic Symptoms**

- Use in patients with a history of adverse reactions to thiol compounds

**Laboratory Test Interferences**

- Laboratory test alterations: False-positive tests for urinary ketones and interference with enzymatic CPK activity may be seen. (5.4)

**Use in Patients with a History of Adverse Reactions to Thiol Compounds**

- Use in patients with a history of adverse reactions to thiol compounds

**Clinical Trials Experience**

- Anaphylactic reactions: Anaphylactic reactions may include fever, nausea, vomiting, constipation, and death in neonates and premature infants. Avoid use in neonates, premature, and low-birth weight infants. (6.1)
- Laboratory test alterations: False-positive tests for urinary ketones and interference with enzymatic CPK activity may be seen. (5.4)
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Avoid use in neonates, premature, and low-birth weight infants. (6.1)

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Avoid use in neonates, premature, and low-birth weight infants. (6.1)

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**Drug Rash with Eosinophilia and Systemic Symptoms**

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- Clinical trials experience: ClinicalTrials.gov identifies clinical studies to determine the safety and efficacy of a medicinal product. (6.1)
- Hypersensitivity reactions: Hypersensitivity reactions to mesna and to any of its excipients, including benzyl alcohol, have been reported. (6.1)

**Benzyl Alcohol Toxicity**

Avoid use in neonates, premature, and low-birth weight infants. (6.1)
and because of the potential for adverse reactions in nursing infants from mesna, a decision should be made whether to cross into human milk and may be orally absorbed by a nursing infant. Because many drugs are excreted in human milk if clearly needed.

animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. [see Pregnancy (8.1)]. The incidence of malformations in human pregnancies has not been established for mesna. All pregnancies, regardless of area basis (1000 mg/kg in rabbits and 2000 mg/kg in rats) revealed no evidence of harm to the fetus due to mesna. The risk summary

Pregnancy Category B. [see Pregnancy (8.1)].

Use in Patients with Renal Impairment [see Dosage and Administration (2.3)]. There is no known antidote for mesna. In a clinical trial, 11 patients received intravenous mesna 10 mg/kg to 66 mg/kg per day for 3 to 5 days. Patients also received ifosfamide or cyclophosphamide. Adverse reactions included nausea, vomiting, diarrhea and fever. An increased rate of these adverse reactions has also been found in oxazaphosphorine-treated patients receiving ≥80 mg mesna per kg per day intravenously compared with patients receiving lower doses or hydroxyurea treatment only. Postmarketing, administration of 4.5 to 6.0 g of mesna resulted in hypersensitivity reactions including mild hypotension, shortness of breath, asthma, hyperventilation, rash, and flushing.

Ifosfamide and mesna were independently administered to patients receiving doses of 2.4 g/m² to 3.6 g/m² and 380 mg/m² to 540 mg/m² of ifosfamide and mesna, respectively. Adverse reactions usually occurred 24 to 48 hours after the last dose of ifosfamide or mesna. A total of 28% (range 12% to 44%) of patients developed grade 3 or 4 abnormalities in blood, including anemia, neutropenia, thrombocytopenia, and abnormalities in liver function tests. Mortality in patients with mesna was 1.2% (range 0% to 4%) and 1.2% (range 0% to 4%) for ifosfamide and mesna, respectively.

11 DESCRIPTION

Mesna is a sterile, nonpyrogenic, aqueous solution to inhibit the hemolytic cystitis induced by ifosfamide. The active ingredient, mesna, is a synthetic sulfonated compound designed as sodium-2-mercaptoethanesulfonate with a molecular formula of C₂H₅NaO₃S₂, and a molecular weight of 164.16. Its structural formula is as follows:

H₂S→CH₂S→CH₂S→NO₂

Mesna injection is a sterile, nonpyrogenic, aqueous solution of sodium-2-mercaptoethanesulfonate (mesna) in water for injection. It is a colorless to light amber, clear or slightly cloudy solution with a pH of 4.0 to 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mesna reacts chemically with the arylating substance ifosfamide metabolites, acrolein, and 4-hydroxy-ifosfamide, resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxy-ifosfamide forming a non-urotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and to other urotoxic metabolites and inhibits their effects on the bladder.

12.2 Pharmacokinetics

Absorption

Following oral administration, peak plasma concentrations were reached within 1.5 to 4 hours and 3 to 7 hours for free mesna and total mesna (mesna plus dimer and mixed disulfide), respectively. Oral bioavailability averaged 58% (range 45% to 71%) for free mesna and 80% (range 74% to 104%) for total mesna based on plasma AUC data from 8 healthy volunteers who received 1200 mg oral or intravenous doses. Food does not affect the urinary availability of orally administered mesna.

Distribution

Mesna apparent volume of distribution (Vₐ) for mesna is 0.632 ± 0.240 L/kg after intravenous administration which sagittal distribution to total body water (plasma, extracellular fluid, and intracellular water).

Metabolism

Mesna is metabolized in the liver and kidneys. Metabolism occurs primarily by conjugation with glucuronic acid, and to a lesser extent by glucosidation. The major metabolite of mesna is the dimesna disulfide.

Excretion

Following intravenous administration of a single 800 mg dose, approximately 22% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimethyl mesna, respectively. Mesna was excreted via the kidneys, and 30% of the 30% of the administered dose was excreted via the kidneys.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of mesna.

14 CLINICAL STUDIES

14.1 Intravenous Mesna

Hemorrhagic cystitis produced by ifosfamide is dose dependent (Table 4). At a dose of 1.2 g/m², ifosfamide administered daily for 5 days, 16 to 26% of the patients who received conventional chemotherapy (high fluid intake, alkalinization of the urine, and the administration of dextran) developed hemorrhagic cystitis (50 to 100 mg per cc of hematuria) [see Warnings and Precautions (5.4)]. In contrast, none of the patients who received mesna in combination with ifosfamide developed hemorrhagic cystitis (Studies 3 and 4). In two randomized studies, (Studies 5 and 6), higher doses of ifosfamide, from 2 g/m² to 4 g/m² administered for 3 to 5 days, produced hematuria in 31% to 100% of the patients. When mesna was administered together with these doses of ifosfamide, the incidence of hematuria was less than 7%.

10 DOSAGE AND ADMINISTRATION

10.1 General Use

Safety and effectiveness of mesna in pediatric patients have not been established. Mesna contains benzyl alcohol (10.4 mg benzyl alcohol per ml) which has been associated with serious adverse reactions and death in pediatric patients. The “gapping syndrome,” characterized by central nervous system depression, metabolic acidosis and gasping respiration, has been associated with benzyl alcohol dosages ≥95 mg/kg/day in neonates, premature, and low-birth weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin irritations, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Neonates, premature, and low-birth weight infants, as well as patients receiving high doses, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources [see Warnings and Precautions (5.4)] and (5.5).