MESNA
45888E/Revised: October 2014

7 DRUG INTERACTIONS

Mesna injection, for intravenous use

Initial U.S. Approval: 1988

INDICATIONS AND USAGE

Mesna injection is a cytoprotective agent indicated as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis. (1)

Limitation of Use:

Mesna injection is not indicated to reduce the risk of hematuria due to other pathological conditions such as thrombocytopenia. (1)

DOSE AND ADMINISTRATION

Mesna injection may be given on a fractionated dosing schedule of three bolus intravenous injections or a single bolus injection followed by two oral administrations of mesna tablets as outlined below. The dosing schedule should be repeated each day that ifosfamide is administered. When the dosage of ifosfamide is adjusted, the ratio of mesna injection to ifosfamide should be maintained. (2)

Intravenous Dosing Schedule:

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Ifosfamide Concentration</th>
<th>Mesna Injection Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Hours</td>
<td>1.2 g/m²</td>
<td>240 mg/m²</td>
</tr>
<tr>
<td>4 Hours</td>
<td>-</td>
<td>240 mg/m²</td>
</tr>
<tr>
<td>8 Hours</td>
<td>-</td>
<td>240 mg/m²</td>
</tr>
</tbody>
</table>

Intravenous and Oral Dosing Schedule:

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Ifosfamide Concentration</th>
<th>Mesna Injection Concentration</th>
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<tbody>
<tr>
<td>0 Hours</td>
<td>1.2 g/m²</td>
<td>240 mg/m²</td>
</tr>
<tr>
<td>2 Hours</td>
<td>-</td>
<td>480 mg/m²</td>
</tr>
<tr>
<td>6 Hours</td>
<td>-</td>
<td>480 mg/m²</td>
</tr>
</tbody>
</table>

Maintain sufficient urinary output, as required for ifosfamide treatment, and monitor urine for the presence of hematuria. (2.3)

DOSE FORMS AND STRENGTHS

- 1 gram per 10 mL (100 mg per mL) Multiple Dose Vial (3)

CONTRAINDICATIONS

- Known hypersensitivity to mesna or to any of the excipients, including benzyl alcohol. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions: Anaphylactic reactions have been reported. Less severe hypersensitivity reactions may also occur. Monitor patients. If a reaction occurs, discontinue mesna and provide supportive care. (5.1)
- Dermatologic toxicity: Skin rash with eosinophilia 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. (5.2)
- Benzyl alcohol toxicity: The preservative benzyl alcohol has been associated with serious adverse reactions and death in neonates and premature infants, as well as in infants and children with certain disorders, such as phenylketonuria. Monitor patients. If a reaction occurs, discontinue mesna and provide supportive care. (5.3)
- Laboratory test alterations: False positive tests for urinary ketones and interference with enzymatic CPK activity tests have been seen. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (>10%) when mesna is given with ifosfamide are nausea, vomiting, constipation, leukopenia, fatigue, fever, anorexia, thrombocytopenia, anemia, granulocytopenia, diarrhea, asthma, abdominal pain, headache, alopecia, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC, Vigilance & Medical Affairs at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if clearly needed. (8.1)
- Nursing mothers: Women should not breastfeed during therapy. (8.3)
- Geriatric use: Dose selection should be cautious. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: October 2014

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   2.2 Intravenous and Oral Dosing
   2.3 Monitoring for Hematuria
   2.4 Preparation for Intravenous Administration and Stability
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4 CONTRAINDICATIONS
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Mesna injection is indicated as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis.

Limitation of Use:

Mesna injection is not indicated to reduce the risk of hematuria due to other pathological conditions such as thrombocytopenia.

2 DOSAGE AND ADMINISTRATION

2.1 Intravenous Dosing

Mesna injection may be given on a fractionated dosing schedule of three bolus intravenous injections as outlined below. Mesna injection is given as intravenous bolus injections in a dosage equal to 20% of the ifosfamide dosage weight by weight (w/w) at the time of ifosfamide administration and 4 and 8 hours after each dose of ifosfamide. The total daily dose of mesna injection is 60% of the ifosfamide dose. The recommended dosing schedule is outlined in Table 1 below. Table 1: Recommended Intravenous Dosing Schedule

<table>
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The dosing 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.

2.2 Intravenous and Oral Dosing

Mesna injection may be given on a fractionated dosing schedule of a single bolus injection followed by two oral administrations of mesna tablets as outlined below. Mesna injection is given as intravenous bolus injections in a dosage equal to 20% of the ifosfamide dosage (w/w) at the time...
mesna injection may be given on a dosage schedule decided by the physician.

### Mesna Injection

- **Mesna Injection**
  - **Dosage**
  - **Dosage Forms**
  - **Stability**
  - **Storage**

### Dosage Forms and Strengths

- **Mesna Injection**
  - **Dosage**
  - **Dosage Forms**
  - **Stability**
  - **Storage**

### Dosage and Administration

- **Dosage and Administration**
  - **Dosage**
  - **Administration**
  - **Dosage and Administration**
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### Indications and Usage

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  - **Indications**
  - **Usage**

### Adverse Reactions

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### Warnings and Precautions

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6.2 Postmarketing Experience
The following adverse reactions have been reported in the postmarketing experience of patients receiving mesna in combination with ifosfamide or similar drugs, making it difficult to distinguish the adverse reactions which may be due to mesna from those caused by the concomitantly administered cytotoxic agents. Because these reactions are reported from a population of unknown size, precise estimates of frequency cannot be made.

Cardiovascular: Hypertension
Gastrointestinal: Dysgeusia
Hepatobiliary: Hepatitis
Nervous System: Convulsion
Respiratory: Hemoptysis

7 DRUG INTERACTIONS
No clinical drug interaction studies have been conducted with mesna.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category B.

Risk Summary
There are no studies of mesna in pregnant women. Reproduction studies performed in rats and rabbits at oral doses approximately 10 times the maximum recommended total daily intravenous/oral human dose on a body surface area basis (1,000 mg/kg in rabbits and 2,000 mg/kg in rats) revealed no evidence of harm to the fetus due to mesna. The incidence of malformations in human pregnancies has not been established for mesna. All pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations and 15 to 20% for pregnancy loss. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers
It is not known whether mesna or dimesa is excreted in human milk. Benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from mesna, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Safety and effectiveness of mesna in pediatric patients have not been established. Mesna injection contains benzyl alcohol (10.4 mg benzyl alcohol per mL) which has been associated with anobserved adverse reactions and death in pediatric patients. The “gassing syndrome,” characterized by central nervous system depression, metabolic acidosis and apnea with gasping respirations, has been associated with benzyl alcohol dosages >9.9 mg/kg/day in neonates, premature, and low-birth weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hemato logic abnormalities, skin breakdown, 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 dosages, 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 (5.3)].

8.5 Geriatric Use
Clinical studies of mesna did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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. The ratio of ifosfamide to mesna should remain unchanged.

8.6 Use in Patients with Renal Impairment
No clinical studies were conducted to evaluate the effect of renal impairment on the pharmacokinetics of mesna.

8.7 Use in Patients with Hepatic Impairment
No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of mesna.

10 OVERDOSAGE
There is no known antidote for mesna.

In a clinical trial, 11 patients received intravenous mesna injection 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 oxazophosphorine-treated patients receiving 280 mg mesna injection per kg per day intravenously compared with patients receiving lower doses or hydration treatment only.

Postmarketing, administration of 4.5 g to 6.9 g of mesna resulted in hypersensitivity reactions including mild hypotension, shortness of breath, asthma exacerbation, rash, and flushing.

11 DESCRIPTION
Mesna Injection is a detoxifying agent to inhibit the hemorrhagic cystitis induced by ifosfamide. The active ingredient, mesna, is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of C2H5NaO3S2 and a molecular weight of 164.18. Its structural formula is as follows:

\[
\text{HS–CH2–CH2SO3–Na+}
\]

Mesna injection is a sterile, nonpyrogenic, aqueous solution of clear and colorless appearance in glass multiple dose vials for intravenous administration. Mesna injection contains 100 mg/mL mesna, 0.25 mg/mL edetate disodium and sodium hydroxide for pH adjustment. Mesna injection multiple dose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. The solution has a pH range of 6.5 to 8.5.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Mesna reacts chemically with the urotoxic 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.

12.3 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 dimesa and mixed disufides), respectively. Oral bioavailability averaged 58% (range 45 to 71%) for free mesna and 89% (range 74 to 104%) for total mesna based on plasma radioactivity data from 8 healthy volunteers who received 1,200 mg oral or intravenous doses.

Food does not affect the urinary availability of orally administered mesna.

Distribution
Mean apparent volume of distribution (Vd) for mesna is 0.652 ± 0.242 L/kg after intravenous administration which suggests distribution to total body water (plasma, extracellular fluid, and intracellular water).

Metabolism
Analogous to the physiological cystine-cysteine system, mesna is rapidly oxidized to its major metabolite, mesna sulfoxide (dimesa). Plasma concentrations of mesna exceed those of dimesa after oral or intravenous administration.

Excretion
Following intravenous administration of a single 800 mg dose, approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesa, respectively. Mean plasma elimination half-lives of mesna and dimesa are 0.36 hours and 1.17 hours, respectively. Mesna has a plasma clearance of 1.23 L/h/kg.

13 NONCLINICAL TOXICITY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies in animals have been performed to evaluate the carcinogenic potential of mesna.
Mesna was not genotoxic in the in vitro Ames bacterial mutagenicity assay, the in vitro mammalian lymphocyte chromosomal aberration assay or the in vivo mouse micronucleus assay.

No studies on male or female fertility were conducted. No signs of male or female reproductive organ toxicity were seen in 6-month oral rat studies (≤2,000 mg/kg/day) or 28-week oral dog studies (520 mg/kg/day) at doses approximately 10-fold higher than the maximum recommended human dose on a body surface area basis.

14 CLINICAL STUDIES

14.1 Intravenous Mesna Injection

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 uroprophylaxis (high fluid intake, alkalization of the urine, and the administration of diuretics) developed hematuria (>50 RBC per hpf or macrohematuria) (Studies 1, 2, and 3). In contrast, none of the patients who received mesna injection together with this dose of ifosfamide developed hematuria (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 injection was administered together with these doses of ifosfamide, the incidence of hematuria was less than 7%.

Table 4: Percent of Mesna Injection Patients Developing Hematuria (≥50 RBC/hpf or macrohematuria)

<table>
<thead>
<tr>
<th>Study</th>
<th>Conventional Uroprophylaxis (number of patients)</th>
<th>Standard Mesna Injection Intravenous Regimen (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional Uroprophylaxis (number of patients)</td>
<td>Standard Mesna Injection Intravenous Regimen (number of patients)</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled Studies*</td>
<td>Controlled Studies†</td>
</tr>
<tr>
<td>Study 1</td>
<td>16% (7/44)</td>
<td>-</td>
</tr>
<tr>
<td>Study 2</td>
<td>26% (11/43)</td>
<td>0% (0/32)</td>
</tr>
<tr>
<td>Study 3</td>
<td>18% (7/38)</td>
<td>6% (3/46)</td>
</tr>
<tr>
<td>Study 4</td>
<td>-</td>
<td>0% (0/9)</td>
</tr>
</tbody>
</table>

*Ifosfamide dose 1.2 g/m² d x 5
†Ifosfamide dose 2 g/m² to 4 g/m² d x 3 to 5

14.2 Oral Mesna

Clinical studies comparing recommended intravenous and oral mesna dosing regimens demonstrated incidences of grade 3 to 4 hematuria of <5%. Study 7 was an open label, randomized, two-way crossover study comparing three intravenous doses with an initial intravenous dose followed by two oral doses of mesna in patients with cancer treated with ifosfamide at a dose of 1.2 g/m² to 2 g/m² for 3 to 5 days. Study 8 was a randomized, multicenter study in cancer patients receiving ifosfamide at 2 g/m² for 5 days. In both studies, development of grade 3 or 4 hematuria was the primary efficacy endpoint. The percent of patients developing hematuria in each of these studies is presented in Table 5.

Table 5: Percent of Mesna Patients Developing Grade 3 or 4 Hematuria

<table>
<thead>
<tr>
<th>Study</th>
<th>Standard Intravenous Regimen (number of patients)</th>
<th>Intravenous + Oral Regimen (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 7</td>
<td>0% (0/30)</td>
<td>3.6% (1/28)</td>
</tr>
<tr>
<td>Study 8</td>
<td>3.7% (1/27)</td>
<td>4.3% (1/23)</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING

Mesna Injection, is available as:

- Product No. 730310 63323-733-10
  - Strength: 1 gram per 10 mL (100 mg per mL)
  - Multiple Dose Vial, in packages of 10
- Product No. 730311 63323-733-11
  - Strength: 1 gram per 10 mL (100 mg per mL)
  - Multiple Dose Vial, packaged individually

This container closure is not made with natural rubber latex.

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- Advise the patient to discontinue mesna and seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction, including systemic anaphylactic reactions occur [see Warnings and Precautions (5.1)].
- Advise the patient to take mesna at the exact time and in the exact amount as prescribed. Advise the patient to contact their healthcare provider if they vomit within 2 hours of taking oral mesna, or if they miss a dose of oral mesna [see Dosage and Administration (2.2)].
- Mesna does not prevent hemorrhagic cystitis in all patients nor does it prevent or alleviate any of the other adverse reactions or toxicities associated with ifosfamide. Advise the patient to report to their healthcare provider if his/her urine has turned a pink or red color [see Dosage and Administration (2.3)].
- Advise the patient to drink 1 to 2 liters of fluid each day during mesna therapy [see Dosage and Administration (2.3)].
- Advise the patient that Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms and bullous and ulcerative skin and mucosal reactions have occurred with mesna. Advise the patient to report to their healthcare provider if signs and symptoms of these syndromes occur [see Warnings and Precautions (5.2)].