

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-811

APPROVED DRAFT LABELING

ifosfamide administration and 4 and 8 hours after each dose of ifosfamide. The total daily dose of mesna is 60% of the ifosfamide dose.

The recommended dosing schedule is outlined below:

	0 Hours	4 Hours	8 Hours
Ifosfamide	1.2 g/m ²	—	—
Mesna Injection	240 mg/m ²	240 mg/m ²	240 mg/m ²

In order to maintain adequate protection, the dosing schedule should be repeated on each day that ifosfamide is administered. When the dosage of ifosfamide is adjusted (either increased or decreased), the dose of Mesna Injection should be modified accordingly. When exposed to oxygen, mesna is oxidized to the disulfide, dimesna. The Mesna Injection multiple dose vials may be stored and used for up to 8 days.

PREPARATION OF INTRAVENOUS SOLUTIONS/STABILITY:

For IV administration the drug can be diluted by adding the Mesna Injection solution to any of the following fluids obtaining final concentrations of 20 mg mesna/mL fluid:

- 5% Dextrose Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP
- 5% Dextrose and 0.33% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 0.92% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP

For example:

One mL of Mesna Injection multiple dose vial 100 mg/mL may be added to 4 mL of any of the solutions listed above to create a final concentration of 20 mg mesna/mL fluid.

Diluted solutions are chemically and physically stable for 24 hours at 25° C (77° F).

Mesna is not compatible with cisplatin. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED:

Product No.	NDC No.	Description
730310	63323-733-10	Mesna Injection, 1 gram in a 10 mL multiple dose vial, in packages of 10.

Vial stopper does not contain natural rubber latex.

Store at controlled room temperature 15° - 30° C (59° - 86° F).

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MESNA APP 26 2001
INJECTION APP-02ED

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. Its structural formula is as follows:



C₂H₅NaO₃S₂

M.W. 164.18

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

CLINICAL PHARMACOLOGY:

Mesna Injection was developed as a prophylactic agent to prevent the hemorrhagic cystitis induced by ifosfamide. Analogous to the physiological cysteine-cystine-system, following intravenous administration, mesna is rapidly oxidized to its only metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys.

In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which 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 nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and other urotoxic metabolites.

After administration of an 800 mg dose the half-lives of mesna and dimesna in the blood are 0.36 hours and 1.17 hours respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna respectively. The majority of the dose recovered was eliminated within 4 hours. Mesna has a volume of distribution of 0.652 L/kg and a plasma clearance of 1.23 L/kg/hour. Ifosfamide has been shown to have dose dependent pharmacokinetics in humans. At doses of 2 to 4 g, its terminal elimination half-life is about 7 hours. As a result, in order to maintain adequate levels of mesna in the urinary bladder during the course of elimination of the urotoxic ifosfamide metabolites, repeated doses of Mesna Injection are required.

Based on the pharmacokinetic profiles of mesna and ifosfamide as discussed above,

mesna was given as bolus doses prior to ifosfamide and at 4 and 8 hours after ifosfamide administration. The hemorrhagic cystitis produced by ifosfamide is dose dependent. 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, alkalinization of the urine and the administration of diuretics) developed hematuria (>50 rbc/hpf or macrohematuria). In contrast, none of the patients who received mesna together with this dose of ifosfamide developed hematuria. Higher doses of ifosfamide from 2 to 4 g/m² administered for three to five 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%.

INDICATIONS AND USAGE:

Mesna Injection has been shown to be effective as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis.

CONTRAINDICATIONS:

Mesna Injection is contraindicated in patients known to be hypersensitive to mesna or other thiol compounds.

WARNINGS:

Allergic reactions to mesna were reported in patients with autoimmune disorders. The majority of the patients received high doses of mesna orally. The symptoms ranged from mild hypersensitivity to systemic anaphylactic reactions.

Mesna Injection has been developed as an agent to prevent ifosfamide induced hemorrhagic cystitis. It will not prevent or alleviate any of the other adverse reactions or toxicities associated with ifosfamide therapy.

Mesna Injection does not prevent hemorrhagic cystitis in all patients. Up to 6% of patients treated with mesna have developed hematuria (>50 rbc/hpf or WHO grade 2 and above). As a result, a morning specimen of urine should be examined for the presence of hematuria (red blood cells) each day prior to ifosfamide therapy. If hematuria develops when Mesna Injection is given with ifosfamide according to the recommended dosage schedule, depending on the severity of the hematuria, dosage reductions or discontinuation of ifosfamide therapy may be initiated.

In order to obtain adequate protection, Mesna Injection must be administered with each dose of ifosfamide as outlined in the **DOSAGE AND ADMINISTRATION** section. Mesna Injection is not effective in preventing hematuria due to other pathological conditions such as thrombocytopenia.

Because of the benzyl alcohol content, the multiple dose vial should not be used in neonates or infants and should be used with caution in older pediatric patients.

PRECAUTIONS:

Laboratory Tests

A false positive test for urinary ketones may arise in patients treated with Mesna Injection. In this test, a red-violet color develops which, with the addition of glacial acetic acid, will return to violet.

Pediatrics

Because of the benzyl alcohol content, the multiple dose vial should not be used in neonates or infants and should be used with caution in older pediatric patients.

Drug Interactions

In vitro and *in vivo* animal tumor models have shown that mesna does not have any effect on the antitumor efficacy of concomitantly-administered cytotoxic agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate the carcinogenic potential of mesna. The Ames Salmonella typhimurium test, mouse micronucleus assay and frequency of sister chromatid exchange and chromosomal aberrations in PHA-stimulated lymphocytes *in vitro* assays revealed no mutagenic activity.

Pregnancy

Pregnancy Category B

Reproduction studies in rats and rabbits with oral doses up to 1000 mg/kg have revealed no harm to the fetus due to mesna. It is not known whether Mesna Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Mesna Injection should be given to a pregnant woman only if the benefits clearly outweigh any possible risks.

Teratology studies in rats and rabbits have shown no effects.

Nursing Mothers

It is not known whether mesna or dimesna is excreted in human milk. 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.

ADVERSE REACTIONS:

Because mesna is used in combination with ifosfamide and other chemotherapeutic agents with documented toxicities, it is difficult to distinguish the adverse reactions which may be due to mesna from those caused by the concomitantly administered cytostatic agents. As a result, the adverse reaction profile of mesna was determined in three Phase 1 studies (16 subjects) utilizing intravenous and oral administration and two controlled studies in which ifosfamide and mesna were compared to ifosfamide and standard prophylaxis.

In Phase 1 studies in which IV bolus doses of 0.8 to 1.6 g/m² mesna were administered as single or three repeated doses to a total of 10 patients, a bad taste in the mouth (100%) and soft stools (70%) were reported. At intravenous and oral bolus doses of 2.4 g/m² which are approximately 10 times the recommended clinical doses (0.24 g/m²) headache (50%), fatigue (33%), nausea (33%), diarrhea (83%), limb pain (50%), hypotension (17%) and allergy (17%) have also been reported in the 6 patients who participated in this study.

In controlled clinical studies, adverse reactions which can be reasonably associated with mesna were vomiting, diarrhea and nausea.

OVERDOSAGE:

There is no known antidote for Mesna Injection.

DOSAGE AND ADMINISTRATION:

For the prophylaxis of ifosfamide induced hemorrhagic cystitis, Mesna Injection may be given on a fractionated dosing schedule of bolus intravenous injections 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 of

Final Printed Vial/Tray Label

NDC 63323-733-10 730310
MESNA
INJECTION
1 gram
FOR INTRAVENOUS USE
10 mL
Multiple Dose Vial Rx only

APR 26 2001
Each vial contains 1 gram of mesna in 10 mL water. Mesna Injection is a sterile, clear, colorless to light yellow solution containing 10% mesna in 0.9% sodium chloride injection. Contains 0.02% benzalkonium chloride as a preservative. Adjust pH to 5.5 to 8.5. Each mL contains 100 mg of mesna. Usual Dosage: See insert.
Should not be prepared without thorough knowledge of the pharmacology and toxicology as contained in accompanying literature.
Store in controlled room temperature (20° to 25°C). Do not store in excursions above 30°C. Vial stoppers do not contain natural rubber latex.

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Note: The vial label will also be used as the tray label. Therefore, "10 Vials" will be ink-jetted onto the tray during the packaging process