NDA 19884

Supplement 013

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MESNEX safely and effectively. See full prescribing information for MESNEX.

MESNEX (mesna) injection, for intravenous use
MESNEX (mesna) tablets, for oral use
Initial U.S. Approval: 1988

----------INDICATIONS AND USAGE----------
MESNEX is a cytoprotective agent indicated as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis. (1)

Limitation of Use:
MESNEX is not indicated to reduce the risk of hematuria due to other pathological conditions such as thrombocytopenia. (1)

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

Intravenous Dosing Schedule:

	0 Hours	4 Hours	8 Hours
Ifosfamide	1.2 g/m^2	--	--
MESNEX Injection	240 mg/m^2	240 mg/m^2	240 mg/m^2

Intravenous and Oral Dosing Schedule:

	0 Hours	2 Hours	6 Hours
Ifosfamide	1.2 g/m^2	--	--
MESNEX Injection	240 mg/m^2	--	--
MESNEX Tablets	--	480 mg/m^2	480 mg/m^2

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

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 1g (100 mg/mL) Multidose vials (3)
- Tablets: 400 mg with functional score (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to MESNEX 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 MESNEX 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 MESNEX 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. Avoid use in neonates, premature, and low-birth weight infants. (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 MESNEX is given with ifosfamide are nausea, vomiting, constipation, leukopenia, fatigue, fever, anorexia, thrombocytopenia, anemia, granulocytopenia, diarrhea, asthenia, abdominal pain, headache, alopecia, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare at 1-866-888-2472, 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 and FDA-approved patient labeling

Revised: 03/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitation of Use:
MESNEX 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

MESNEX may be given on a fractionated dosing schedule of three bolus intravenous injections as outlined below.

MESNEX 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 MESNEX is 60% of the ifosfamide dose. The recommended dosing schedule is outlined below in Table 1.

Table 1. Recommended Intravenous Dosing Schedule

	0 Hours	**4 Hours**	**8 Hours**
Ifosfamide	1.2 g/m^2	-	-
MESNEX Injection[1]	240 mg/m^2	240 mg/m^2	240 mg/m^2

[1]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 MESNEX to ifosfamide should be maintained.

2.2 Intravenous and Oral Dosing

MESNEX may be given on a fractionated dosing schedule of a single bolus injection followed by two oral administrations of MESNEX tablets as outlined below.

MESNEX injection is given as intravenous bolus injections in a dosage equal to 20% of the ifosfamide dosage (w/w) at the time of ifosfamide administration. MESNEX tablets are given orally in a dosage equal to 40% of the ifosfamide dose 2 and 6 hours after each dose of ifosfamide. The total daily dose of MESNEX is 100% of the ifosfamide dose. The recommended dosing schedule is outlined in Table 2.

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Table 2. Recommended Intravenous and Oral Dosing Schedule			
	0 Hours	**2 Hours**	**6 Hours**
Ifosfamide	1.2 g/m^2	-	-
MESNEX injection[1]	240 mg/m^2	-	-
MESNEX tablets	-	480 mg/m^2	480 mg/m^2

[1]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 MESNEX to ifosfamide should be maintained.

The efficacy and safety of this ratio of intravenous and oral MESNEX has not been established as being effective for daily doses of ifosfamide higher than 2 g/m^2.

Patients who vomit within two hours of taking oral MESNEX should repeat the dose or receive intravenous MESNEX.

2.3 Monitoring for Hematuria

Maintain adequate hydration and sufficient urinary output, as required for ifosfamide treatment, and monitor urine for the presence of hematuria. If severe hematuria develops when MESNEX is given according to the recommended dosage schedule, dosage reductions or discontinuation of ifosfamide therapy may be required.

2.4 Preparation for Intravenous Administration and Stability

Preparation

Determine the volume of MESNEX injection for the intended dose.

Dilute the volume of MESNEX injection for the dose in any of the following fluids to obtain a final concentration of 20 mg/mL:

- 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
- 0.9% Sodium Chloride Injection, USP
- Lactated Ringer’s Injection, USP

Stability

The MESNEX injection multidose vials may be stored and used for up to 8 days after initial puncture.

Store diluted solutions at 25°C (77°F). Use diluted solutions within 24 hours.

Do not mix MESNEX injection with epirubicin, cyclophosphamide, cisplatin, carboplatin, and nitrogen mustard.

The benzyl alcohol contained in MESNEX injection vials can reduce the stability of ifosfamide. Ifosfamide and MESNEX may be mixed in the same bag provided the final concentration of ifosfamide does not exceed 50 mg/mL. Higher concentrations of ifosfamide may not be compatible with MESNEX and may reduce the stability of ifosfamide.

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Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Any solutions which are discolored, hazy, or contain visible particulate matter should not be used.

3 DOSAGE FORMS AND STRENGTHS

- MESNEX injection: 1 g Multidose Vial, 100 mg/mL
- MESNEX tablets: 400 mg film-coated tablets with functional score

4 CONTRAINDICATIONS

MESNEX is contraindicated in patients known to be hypersensitive to MESNEX or to any of the excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

MESNEX may cause systemic hypersensitivity reactions, including anaphylaxis. These reactions may include fever, cardiovascular symptoms (hypotension, tachycardia), acute renal impairment, hypoxia, respiratory distress, urticaria, angioedema, laboratory signs of disseminated intravascular coagulation, hematological abnormalities, increased liver enzymes, nausea, vomiting, arthralgia, and myalgia. These reactions may occur with the first exposure or after several months of exposure. Monitor for signs or symptoms. Discontinue MESNEX and provide supportive care.

5.2 Dermatologic Toxicity

Drug rash with eosinophilia and systemic symptoms and bullous and ulcerative skin and mucosal reactions, consistent with Stevens-Johnson syndrome or toxic epidermal necrolysis have occurred. MESNEX may cause skin and mucosal reactions characterized by urticaria, rash, erythema, pruritus, burning sensation, angioedema, periorbital edema, flushing and stomatitis. These reactions may occur with the first exposure or after several months of exposure. Discontinue MESNEX and provide supportive care.

5.3 Benzyl Alcohol Toxicity

Benzyl alcohol, a preservative in MESNEX, has been associated with serious adverse reactions and death (including gasping syndrome) in neonates, premature, and low-birth weight infants. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Consider the combined daily metabolic load of benzyl alcohol from all sources when prescribing MESNEX (10.4 mg benzyl alcohol per mL). Neonates, premature, and low-birth weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Monitor patients for signs or symptoms of toxicity. Avoid use in neonates, premature, and low-birth weight infants *[See Use in Specific Populations (8.4)]*.

5.4 Laboratory Test Interferences

False-Positive Urine Tests for Ketone Bodies
A false positive test for urinary ketones may arise in patients treated with MESNEX when using nitroprusside sodium-based urine tests (including dipstick tests). The addition of glacial acetic acid can be used to

differentiate between a false positive result (cherry-red color that fades) and a true positive result (red-violet color that intensifies).

False-Negative Tests for Enzymatic CPK Activity
MESNEX may interfere with enzymatic creatinine phosphokinase (CPK) activity tests that use a thiol compound (e.g., N-acetylcysteine) for CPK reactiviation. This may result in a falsely low CPK level.

False-Positive Tests for Ascorbic Acid
MESNEX may cause false-positive reactions in Tillman's reagent-based urine screening tests for ascorbic acid.

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

MESNEX is a thiol compound, i.e., a sulfhydryl (SH) group-containing organic compound. Hypersensitivity reactions to MESNEX and to amifostine, another thiol compound, have been reported. It is not clear whether patients who experienced an adverse reaction to a thiol compound are at increased risk for a hypersensitivity reaction to MESNEX.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling.

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Dermatological Toxicity *[see Warnings and Precautions (5.2)]*
- Benzyl Alcohol Toxicity*[see Warnings and Precautions (5.3)]*
- Laboratory Test Interferences *[see Warnings and Precautions (5.4)]*
- Use in Patients with a History of Adverse Reactions to Thiol Compounds *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

MESNEX adverse reaction data are available from four Phase 1 studies in which single intravenous doses of 600-1200 mg MESNEX Injection without concurrent chemotherapy were administered to a total of 53 healthy volunteers and single oral doses of 600-2400 mg of MESNEX Tablets were administered to a total of 82 healthy volunteers. The most frequently reported side effects (observed in two or more healthy volunteers) for healthy volunteers receiving single doses of MESNEX Injection alone were headache, injection site reactions, flushing, dizziness, nausea, vomiting, somnolence, diarrhea, anorexia, fever, pharyngitis, hyperesthesia, influenza-like symptoms, and coughing. In two Phase 1 multiple-dose studies where healthy volunteers received MESNEX Tablets alone or intravenous MESNEX followed by repeated doses of MESNEX Tablets, flatulence and rhinitis were reported. In addition, constipation was reported by healthy volunteers who had received repeated doses of intravenous MESNEX.

Additional adverse reactions in healthy volunteers receiving MESNEX alone included injection site reactions, abdominal pain/colic, epigastric pain/burning, mucosal irritation, lightheadedness, back pain, arthralgia,

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myalgia, conjunctivitis, nasal congestion, rigors, paresthesia, photophobia, fatigue, lymphadenopathy, extremity pain, malaise, chest pain, dysuria, pleuritic pain, dry mouth, dyspnea, and hyperhidrosis. In healthy volunteers, MESNEX was commonly associated with a rapid (within 24 hours) decrease in lymphocyte count, which was generally reversible within one week of administration.

Because MESNEX is used in combination with ifosfamide or ifosfamide-containing chemotherapy regimens, it is difficult to distinguish the adverse reactions which may be due to MESNEX from those caused by the concomitantly administered cytotoxic agents.

Adverse reactions reasonably associated with MESNEX administered intravenously and orally in four controlled studies in which patients received ifosfamide or ifosfamide-containing regimens are presented in Table 3.

Table 3: Adverse Reactions in ≥5% of Patients Receiving MESNEX in combination with Ifosfamide-containing Regimens

MESNEX Regimen	Intravenous-Intravenous-Intravenous[1]	Intravenous-Oral-Oral[1]
N exposed	119 (100.0%)	119 (100%)
Incidence of AEs	101 (84.9%)	106 (89.1%)
Nausea	65 (54.6)	64 (53.8)
Vomiting	35 (29.4)	45 (37.8)
Constipation	28 (23.5)	21 (17.6)
Leukopenia	25 (21.0)	21 (17.6)
Fatigue	24 (20.2)	24 (20.2)
Fever	24 (20.2)	18 (15.1)
Anorexia	21 (17.6)	19 (16.0)
Thrombocytopenia	21 (17.6)	16 (13.4)
Anemia	20 (16.8)	21 (17.6)
Granulocytopenia	16 (13.4)	15 (12.6)
Asthenia	15 (12.6)	21 (17.6)
Abdominal Pain	14 (11.8)	18 (15.1)
Alopecia	12 (10.1)	13 (10.9)
Dyspnea	11 (9.2)	11 (9.2)
Chest Pain	10 (8.4)	11 (9.2)
Hypokalemia	10 (8.4)	11 (9.2)
Diarrhea	9 (7.6)	17 (14.3)
Dizziness	9 (7.6)	5 (4.2)
Headache	9 (7.6)	13 (10.9)
Pain	9 (7.6)	10 (8.4)
Sweating Increased	9 (7.6)	2 (1.7)
Back Pain	8 (6.7)	6 (5.0)
Hematuria	8 (6.7)	7 (5.9)
Injection Site Reaction	8 (6.7)	10 (8.4)

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Edema	8 (6.7)	9 (7.6)
Edema Peripheral	8 (6.7)	8 (6.7)
Somnolence	8 (6.7)	12 (10.1)
Anxiety	7 (5.9)	4 (3.4)
Confusion	7 (5.9)	6 (5.0)
Face Edema	6 (5.0)	5 (4.2)
Insomnia	6 (5.0)	11 (9.2)
Coughing	5 (4.2)	10 (8.4)
Dyspepsia	4 (3.4)	6 (5.0)
Hypotension	4 (3.4)	6 (5.0)
Pallor	4 (3.4)	6 (5.0)
Dehydration	3 (2.5)	7 (5.9)
Pneumonia	2 (1.7)	8 (6.7)
Tachycardia	1 (0.8)	7 (5.9)
Flushing	1 (0.8)	6 (5.0)

[1]Intravenous dosing of ifosfamide and MESNEX followed by either intravenous or oral doses of MESNEX according to the applicable dosage schedule. *[see Dosage and Administration (2)]*.

6.2 Postmarketing Experience

The following adverse reactions have been reported in the postmarketing experience of patients receiving MESNEX in combination with ifosfamide or similar drugs, making it difficult to distinguish the adverse reactions which may be due to MESNEX 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 MESNEX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

Risk Summary
There are no studies of MESNEX in pregnant women. Reproduction studies performed in rats and rabbits at oral doses approximately 10 times the maximum recommended total daily intravenous-oral-oral human dose on a body surface area basis (1000 mg/kg in rabbits and 2000 mg/kg in rats) revealed no evidence of harm to the

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fetus due to mesna. The incidence of malformations in human pregnancies has not been established for MESNEX. 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 dimesna 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 MESNEX, 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 MESNEX in pediatric patients have not been established. MESNEX contains benzyl alcohol (10.4 mg benzyl alcohol per mL) which has been associated with serious adverse reactions and death in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis and gasping respirations) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates, premature, and low-birth weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic 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 MESNEX 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 MESNEX 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 MESNEX.

8.7 Use in Patients with Hepatic Impairment

No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of MESNEX.

10 OVERDOSAGE

There is no known antidote for MESNEX.

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In a clinical trial, 11 patients received intravenous MESNEX 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 MESNEX 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 MESNEX resulted in hypersensitivity reactions including mild hypotension, shortness of breath, asthma exacerbation, rash, and flushing.

11 DESCRIPTION

MESNEX 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 $C_2H_5NaO_3S_2$ and a molecular weight of 164.18. Its structural formula is as follows:

$$HS–CH_2–CH_2SO_3–Na^+$$

MESNEX (mesna) injection is a sterile, nonpyrogenic, aqueous solution of clear and colorless appearance in clear glass multidose vials for intravenous administration. MESNEX injection contains 100 mg/mL mesna, 0.25 mg/mL edetate disodium and sodium hydroxide for pH adjustment. MESNEX Injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. The solution has a pH range of 7.5-8.5.

MESNEX (mesna) tablets are white, oblong, scored biconvex film-coated tablets with the imprint M4. They contain 400 mg mesna. The excipients are calcium phosphate, cornstarch, hydroxypropylmethylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, simethicone, and titanium dioxide.

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 dimesna and mixed disulfides), respectively. Oral bioavailability averaged 58% (range 45 to 71%) for free mesna and 89% (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 MESNEX.

Distribution

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Mean apparent volume of distribution (V_d) 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 cysteine-cystine system, mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna). Plasma concentrations of mesna exceed those of dimesna 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 dimesna, respectively. Mean plasma elimination half-lives of mesna and dimesna are 0.36 hours and 1.17 hours, respectively. Mesna has a plasma clearance of 1.23 L/h/kg.

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.

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 (≤2000 mg/kg/day) or 29-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 MESNEX

Hemorrhagic cystitis produced by ifosfamide is dose dependent (Table 4). At a dose of 1.2 g/m^2 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 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/m^2 to 4 g/m^2 administered for 3 to 5 days, produced hematuria in 31 to 100% of the patients. When MESNEX was administered together with these doses of ifosfamide, the incidence of hematuria was less than 7%.

Table 4. Percent of MESNEX Patients Developing Hematuria (≥50 RBC/hpf or macrohematuria)		
Study	**Conventional Uroprophylaxis (number of patients)**	**Standard MESNEX Intravenous Regimen (number of patients)**
Uncontrolled Studies*		

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Study 1	16% (7/44)	-
Study 2	26% (11/43)	-
Study 3	18% (7/38)	0% (0/21)
Study 4	-	0% (0/32)
Controlled Studies†		
Study 5	31% (14/46)	6% (3/46)
Study 6	100% (7/7)	0% (0/8)
*Ifosfamide dose 1.2 g/m^2 d x 5 †Ifosfamide dose 2 g/m^2 to 4 g/m^2 d x 3 to 5		

14.2 Oral MESNEX

Clinical studies comparing recommended intravenous and oral MESNEX 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 MESNEX in patients with cancer treated with ifosfamide at a dose of 1.2 g/m^2 to 2.0 g/m^2 for 3 to 5 days. Study 8 was a randomized, multicenter study in cancer patients receiving ifosfamide at 2.0 g/m^2 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 MESNEX Patients Developing Grade 3 or 4 Hematuria

	MESNEX Dosing Regimen	
Study	**Standard Intravenous Regimen (number of patients)**	**Intravenous + Oral Regimen (number of patients)**
Study 7	0% (0/30)	3.6% (1/28)
Study 8	3.7% (1/27)	4.3% (1/23)

16 HOW SUPPLIED/STORAGE AND HANDLING

MESNEX (mesna) injection 100 mg/mL

- NDC 0338-1305-01

  1 g Multidose Vial, Box of 1 vial of 10 mL
- NDC 0338-1305-03

  1 g Multidose Vial, Box of 10 vials of 10 mL

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

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MESNEX (mesna) tablets

- NDC 67108-3565-9

  400 mg scored tablets packaged in box of 10 tablets

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- Advise the patient to discontinue MESNEX 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 MESNEX 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 MESNEX, or if they miss a dose of oral MESNEX *[see Dosage and Administration (2.2)]*.
- MESNEX 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 MESNEX 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 MESNEX. Advise the patient to report to their healthcare provider if signs and symptoms of these syndromes occur *[see Warnings and Precautions (5.2)]*.

Baxter

MESNEX (mesna) injection manufactured by:

MESNEX (mesna) tablets manufactured for:

Baxter Healthcare Corporation
Deerfield, IL 60015 USA
For Product Inquiry 1800 ANA DRUG (1-800-262-3784)

Made in Germany
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Material No. TBD

Patient Information
MESNEX (MES-nex)
(mesna)
tablets

MESNEX (MES-nex)
(mesna)
injection

What is the most important information I should know about MESNEX?

MESNEX can cause serious allergic reactions and skin reactions. These side effects can happen the first time you are treated with MESNEX, or after several months of treatment with MESNEX. Stop treatment with MESNEX and call your doctor or go to the nearest hospital emergency room right away if you develop any of the symptoms listed below:

- fever
- swelling of your face, lips, mouth, or tongue
- trouble breathing or wheezing
- itching
- burning
- skin rash or hives
- skin redness or swelling
- skin blisters or peeling
- feel lightheaded or faint
- feel like your heart is racing
- nausea or vomiting
- joint or muscle aches
- mouth sores

See **"What are the possible side effects of MESNEX?"** for more information about side effects.

What is MESNEX?

MESNEX is a prescription medicine used to reduce the risk of inflammation and bleeding of the bladder (hemorrhagic cystitis) in people who receive ifosfamide (a medicine used to treat cancer).

MESNEX is not for use to reduce the risk of blood in the urine (hematuria) due to other medical conditions.

It is not known if MESNEX is safe and effective in children.

Who should not receive MESNEX?

Do not take MESNEX if you are allergic to MESNEX or any of the ingredients in MESNEX. See the end of this leaflet for a complete list of ingredients in MESNEX.

What should I tell my doctor before receiving MESNEX?

Before you receive MESNEX, tell your doctor if you:

- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if MESNEX will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if MESNEX passes into your breast milk. You and your doctor should decide if you will receive MESNEX or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive MESNEX?

Reference ID: 3472090

- MESNEX is given on the same day that you receive ifosfamide.
- MESNEX can be given by an intravenous (IV) infusion into a vein or tablets taken by mouth.
- You will receive MESNEX in one of two ways:
  1. MESNEX intravenous (IV) infusion into a vein at the time you receive ifosfamide and 4 and 8 hours after you receive ifosfamide.
  2. MESNEX intravenous (IV) infusion into a vein at the time you receive ifosfamide and MESNEX tablets taken by mouth 2 and 6 hours after you receive ifosfamide.
- Take MESNEX tablets at the exact times and the exact dose your doctor tells you to take it.
- You may need to take half of a MESNEX tablet for your complete dose. Each tablet has a groove in the middle that will make it easier to break the tablet in half.
- During treatment with MESNEX,you should drink 4 to 8 cups of liquid (1 to 2 liters) each day, whether you receive MESNEX by intravenous infusion or take MESNEX tablets by mouth.
- Tell your doctor if you:
  - vomit within 2 hours of taking MESNEX tablets by mouth
  - miss a dose of MESNEX tablets
  - have pink or red colored urine

What are the possible side effects of MESNEX?

MESNEX may cause serious side effects, including:

See **"What is the most important information I should know about MESNEX?"**

- **MESNEX that is given by intravenous infusion contains the preservative benzyl alcohol.** Benzyl alcohol has been shown to cause serious side effects and death in newborn, premature, and low-birth weight babies. MESNEX tablets do not contain benzyl alcohol.

The most common side effects of MESNEX when given with ifosfamide include:

- nausea
- vomiting
- constipation
- decreased white blood cell count
- tiredness
- fever
- decreased appetite
- decreased platelet count
- decreased red blood cell count
- diarrhea
- weakness
- stomach (abdomen) pain
- headache
- hair loss
- sleepiness

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of MESNEX. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Reference ID: 3472090

How should I store MESNEX tablets?

- Store MESNEX tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep MESNEX and all medicines out of the reach of children.

General information about the safe and effective use of MESNEX

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use MESNEX for a condition for which it was not prescribed. Do not give MESNEX to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about MESNEX that is written for health professionals.

For more information, call 1-800-262-3784.

What are the ingredients in MESNEX?

Active ingredient: mesna
Inactive ingredients:
MESNEX injection: edetate disodium, sodium hydroxide, and benzyl alcohol as a preservative.
MESNEX tablets: calcium phosphate, cornstarch, hydroxypropylmethylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, simethicone, and titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Baxter Healthcare Corporation
Deerfield, IL 60015 USA

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