PRODUCT MONOGRAPH

[Pr]UROMITEXAN

(Mesna Injection)

100 mg/mL

Uroprotector

Baxter Corporation
Mississauga, Ontario
L5N 0C2

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(Mesna Injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Oral	Solution for infusion and injection / 400 mg, 1 g ampoules	*For a complete listing see Dosage Forms, Composition and Packaging section.*
Intravenous	Solution for infusion and injection / 1 g, 5 g multi-dose vials	Benzyl alcohol *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

UROMITEXAN (mesna) is indicated for the reduction and prevention of urinary tract toxicity (hemorrhagic cystitis) of oxazaphosphorines. (see **ADVERSE REACTIONS** sections of the Procytox (cyclophosphamide) and Ifex (ifosfamide) Product Monographs)

Geriatrics:
No specific information is available.

Pediatrics (<16 years of age):
Safety and effectiveness of UROMITEXAN in pediatric patients (<16 years of age) have not been established.

CONTRAINDICATIONS

UROMITEXAN (mesna) is contraindicated in individuals with a known hypersensitivity to mesna or other thiol compounds, or to any of the excipients, including benzyl alcohol present in the multi-dose vials. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

The multi dose vials contain benzyl alcohol, which may be fatal in neonates and infants. (see **Special Populations, Pediatrics**)

General

The protective effect of UROMITEXAN (mesna) applies only to the urotoxic effects of oxazaphosphorines. Additional prophylactic or accompanying measures recommended during treatment with oxazaphosphorines are thus not affected and should not be discontinued.

UROMITEXAN is incompatible in vitro with cisplatin, carboplatin and nitrogen mustard.

The combination of an oxazaphosphorine cytostatic agent with UROMITEXAN and cisplatin, carboplatin, or nitrogen mustard in the same infusion solution is not stable and is not to be used.

Mixing UROMITEXAN and epirubicin leads to inactivation of epirubicin and should be avoided.

Benzyl alcohol contained in the UROMITEXAN injection multi-dose vials can reduce the stability of cyclophosphamide and ifosfamide.

Patients undergoing treatment with UROMITEXAN may experience syncope, lightheadedness, lethargy/drowsiness, dizziness, and blurred vision which could affect the ability to drive or use machines (see Drug-Lifestyle Interactions).

UROMITEXAN solution for injection contains approximately 59 mg of sodium per 400 mg mesna.

Carcinogenesis and Mutagenesis

See Toxicology – Mutagenicity and Carcinogenicity sections.

Genitourinary

UROMITEXAN does not prevent hemorrhagic cystitis in all patients. To identify the presence of erythrocytes in the urine, microscopic evidence of red blood cells should be obtained. Patients should be monitored accordingly.

Sufficient urinary output should be maintained, as required for oxazaphosphorine treatment.

Sensitivity/Resistance

Hypersensitivity reactions to mesna have been reported following administration of UROMITEXAN as an uroprotectant. These include:

Skin reactions characterized by symptoms such as localized or generalized urticaria or other forms of exanthema, pruritus, burning, angioedema and/or flushing.

In addition, cases of severe bullous and ulcerative skin and mucosal reactions were reported. Some reactions were considered to be consistent with Stevens-Johnson Syndrome, toxic epidermal necrolysis, or erythema exudativum multiforme.

Other reactions appeared to be consistent with a diagnosis of fixed drug eruption. Photodistribution of a rash has also been reported.

In some cases, skin reactions were accompanied by one or more other symptoms, such as

- fever,
- cardiovascular symptoms (hypotension, in some cases reported as fluid refractory, tachycardia, ECG signs consistent with perimyocarditis, hypertension; see **Post-Market Adverse Drug Reactions**)
- signs consistent with acute renal impairment,
- pulmonary symptoms (hypoxia, respiratory distress, bronchospasm, tachypnea, cough, bloody sputum; see **Post-Market Adverse Drug Reactions**)
- prolonged prothrombin time (PT) and partial thromboplastin time (PTT), laboratory signs of disseminated intravascular coagulopathy (DIC)
- hematological abnormalities (leukopenia, eosinophilia, lymphopenia, thrombocytopenia, pancytopenia; see **Post-Market Adverse Drug Reactions**)
- increased liver enzymes,
- nausea, vomiting,
- pain in the extremities, arthralgia, myalgia, malaise,
- stomatitis, and
- conjunctivitis.

Some reactions have presented as anaphylaxis.

Fever accompanied by, e.g., hypotension but no skin manifestations has also been reported.

Allergic reactions to mesna ranging from mild hypersensitivity to systemic anaphylactic reactions have been reported with the use of mesna in regimens to treat both severe systemic autoimmune disorders and malignancy. Patients with autoimmune disorders who were treated with cyclophosphamide and mesna appeared to have a higher incidence of allergic reactions.

In most cases, reactions occurred during or after a first treatment occasion or after several weeks of mesna exposure. In other cases, the initial reaction was observed only after several months of exposure.

In many cases, symptoms appeared on the day of exposure, with a tendency to shorter intervals following subsequent exposures.

In some patients, the occurrence and/or severity of reaction appeared to vary with the dose administered.

Recurrence of reactions, in some cases with increasing severity, has been reported with re-exposure. However, in some cases, a reaction did not recur with re-exposure.

Some patients with a history of a reaction have shown positive delayed-type skin test results. However, a negative delayed reaction does not exclude hypersensitivity to mesna. Positive immediate-type skin test reactions have occurred in patients regardless of previous mesna exposure or history of hypersensitivity reactions, and may be related to the concentration of the mesna solution used for testing.

Prescribers should
- be aware of the potential for such reactions and that reactions may worsen with re-exposure and may in some cases be life-threatening,
- be aware that hypersensitivity reactions to mesna were interpreted to resemble the clinical picture of sepsis and, in patients with autoimmune disorders, resemble an exacerbation of the underlying disease.

Thiol Compounds:
Mesna is a thiol compound, i.e., a sulfhydryl (SH) group-containing organic compound. Thiol compounds show some similarities in their adverse reaction profile, including a potential to elicit severe skin reactions. Examples of drugs that are thiol compounds include amifostine, penicillamine, and captopril.

It is not clear whether patients who experienced an adverse reaction to such a drug are at increased risk for any reactions, or similar reactions, to another thiol compound. However, when considering subsequent use of another thiol compound in such patients, the possibility of an increased risk should be taken into account (see **CONTRAINDICATIONS**).

Multi-dose vials:
Parenteral benzyl alcohol administration has been associated with systemic hypersensitivity reactions (see **CONTRAINDICATIONS**).

Special Populations

Pregnant Women:
There are no adequate and well-controlled studies using UROMITEXAN in pregnant women. Animal studies have not revealed any embryotoxic or mutagenic effects (see **TOXICOLOGY)**. However, in view of the fact that oxazaphosphorines are not recommended during pregnancy, this would eliminate the need for UROMITEXAN. UROMITEXAN should be given to pregnant woman only if the benefits clearly outweigh any possible risks.

Nursing Women:
It is unknown whether mesna or dimesna are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking

into account the importance of the drug to the mother.

Pediatrics (<16 years of age):
The safety and efficacy of UROMITEXAN in pediatric patients have not been established.

UROMITEXAN in multi-dose vials contains 10.4 mg benzyl alcohol per milliliter. The benzyl alcohol used in the multi-dose vials could be life-threatening or fatal in neonates or infants. Because of the risk of severe toxicities (including gasping syndrome), the multi-dose vials should not be used in neonates or infants and should be used with caution in older children.

Geriatrics (≥65 years of age)
No specific information on the use of UROMITEXAN in the elderly is available. Clinical studies of UROMITEXAN 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. However, the ratio of ifosfamide to mesna should remain unchanged.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The most frequently occurring adverse reactions (> 10%) associated with use of UROMITEXAN, per subject are: headache (36.05%), infusion site reactions (25.32%), abdominal pain/colic (22.09%), lightheadedness (16.28%), lethargy/drowsiness (12.79%), pyrexia (12.79%), rash (12.79%), diarrhea (11.63%), nausea (11.63%), flushing (10.47%), and influenza-like illness (10.47%).

The most frequently occurring adverse reactions (> 1%) associated with use of UROMITEXAN, per administration are: infusion site reactions (15.35%), headache (5.24%), abdominal pain/colic (4.39%), nausea (1.72%), diarrhea (1.53%), rash (1.72%), flushing (1.33%), lightheadedness (1.33%), lethargy/drowsiness (1.33%), and pyrexia (1.14%).

The most severe adverse reactions associated with use of UROMITEXAN are: toxic epidermal necrolysis, Stevens-Johnson syndrome, anaphylaxis, and drug rash with eosinophilia and systemic symptoms (DRESS).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The following UROMITEXAN adverse reaction data are available from pharmacokinetic studies

in healthy volunteers who received no concomitant medications.

The adverse reactions from clinical trials were identified from 6 mesna pharmacokinetic studies in healthy volunteers, who were administered UROMITEXAN without concurrent chemotherapy. In these studies, a total of 86 subjects received oral doses of UROMITEXAN. Of these 86 subjects, 79 subjects also received intravenously administered UROMITEXAN. A total of 1049 UROMITEXAN doses were administered.

Four studies administered single oral doses (tablets or solution) of 600 mg to 2400 mg; with three of these studies also administering single intravenous doses of 600 mg to 1200 mg. Two studies were multiple-dose studies that administered UROMITEXAN three times daily for 5 days. In these studies, total daily doses of UROMITEXAN tablets ranged from 1200 mg to 2400 mg, and total daily doses of intravenous UROMITEXAN infusions ranged from 334 mg to 1800 mg.

Clinical Trial Adverse Drug Reactions to UROMITEXAN

		Per subject N = 86		Per administration N = 1049	
System Organ Class (SOC)	**Adverse Reaction**	**Frequency**	**Frequency Ratio (Percentage)**	**Frequency**	**Frequency Ratio (Percentage)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**Lymphadenopathy**	Common	3/86 (3.49%)	Uncommon	3/1049 (0.29%)
CARDIAC DISORDERS	**Palpitations**	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
EYE DISORDERS	**Conjunctivitis**	Common	5/86 (5.81%)	Uncommon	5/1049 (0.48%)
	Photophobia	Common	3/86 (3.49%)	Uncommon	5/1049 (0.48%)
	Vision blurred	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
GASTROINTESTINAL DISORDERS	**Abdominal pain/colic**	Very common	19/86 (22.09%)	Common	46/1049 (4.39%)
	Nausea	Very common	10/86 (11.63%)	Common	18/1049 (1.72%)
	Diarrhea	Very common	10/86 (11.63%)	Common	16/1049 (1.53%)
	Flatulence	Common	8/86 (9.30%)	Uncommon	9/1049 (0.86%)
	Mucosal irritation[1]	Common	7/86 (8.14%)	Uncommon	7/1049 (0.67%)
	Vomiting	Common	3/86 (3.49%)	Uncommon	6/1049 (0.57%)
	Burning pain (substernal / epigastric)	Common	3/86 (3.49%)	Uncommon	4/1049 (0.38%)
	Constipation	Common	2/86 (2.33%)	Uncommon	2/1049 (0.19%)
	Gingival bleeding	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS	**Infusion site reactions**	Very common	20/79 (25.32%)	Very common	68/443 (15.35%)
	- **Infusion site pruritus**	Very common	15/79 (18.99%)	Common	35/443 (7.90%)
	- **Infusion site rash**	Very common	11/79 (13.92%)	Common	20/443 (4.51%)
	- **Infusion site pain**	Common	5/79 (6.33%)	Common	5/443 (1.13%)
	- **Infusion site erythema**	Common	3/79 (3.80%)	Uncommon	3/443 (0.68%)
	- **Infusion site urticaria**	Common	2/79 (2.53%)	Uncommon	3/443 (0.68%)
	- **Infusion site swelling**	Common	1/79 (1.27%)	Uncommon	1/443 (0.23%)
	Pyrexia	Very common	11/86 (12.79%)	Common	12/1049 (1.14%)
	Influenza-like illness[2]	Very common	9/86 (10.47%)	Unknown	Unknown

Clinical Trial Adverse Drug Reactions to UROMITEXAN

		Per subject N = 86		Per administration N = 1049	
System Organ Class (SOC)	**Adverse Reaction**	**Frequency**	**Frequency Ratio (Percentage)**	**Frequency**	**Frequency Ratio (Percentage)**
	Rigors	Common	4/86 (4.65%)	Uncommon	5/1049 (0.48%)
	Fatigue	Common	3/86 (3.49%)	Uncommon	3/1049 (0.29%)
	Chest pain	Common	2/86 (2.33%)	Uncommon	2/1049 (0.19%)
	Malaise	Common	2/86 (2.33%)	Uncommon	3/1049 (0.29%)
HEPATOBILIARY DISORDERS	**Transaminases increased**	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
METABOLISM AND NUTRITION DISORDERS	**Decreased appetite**	Common	7/86 (8.14%)	Uncommon	7/1049 (0.67%)
	Feeling of dehydration	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**Back pain**	Common	7/86 (8.14%)	Uncommon	9/1049 (0.86%)
	Arthralgia	Common	6/86 (6.98%)	Uncommon	7/1049 (0.67%)
	Myalgia	Common	6/86 (6.98%)	Uncommon	7/1049 (0.67%)
	Pain in extremity	Common	3/86 (3.49%)	Uncommon	3/1049 (0.29%)
	Pain in jaw	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
NERVOUS SYSTEM DISORDERS	**Headache**	Very common	31/86 (36.05%)	Common	55/1049 (5.24%)
	Lightheadedness	Very common	14/86 (16.28%)	Common	14/1049 (1.33%)
	Lethargy/ Drowsiness	Very common	11/86 (12.79%)	Common	14/1049 (1.33%)
	Dizziness	Common	5/86 (5.81%)	Uncommon	5/1049 (0.48%)
	Paresthesia	Common	4/86 (4.65%)	Uncommon	4/1049 (0.38%)
	Hyperesthesia	Common	2/86 (2.33%)	Uncommon	2/1049 (0.19%)
	Syncope	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
	Hypoesthesia	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
	Disturbance in attention	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
PSYCHIATRIC DISORDERS	**Insomnia**	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
	Nightmare	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
RENAL AND URINARY DISORDERS	**Dysuria**	Common	2/86 (2.33%)	Uncommon	2/1049 (0.19%)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	**Nasal congestion**	Common	5/86 (5.81%)	Uncommon	5/1049 (0.48%)
	Cough	Common	3/86 (3.49%)	Uncommon	3/1049 (0.28%)

Clinical Trial Adverse Drug Reactions to UROMITEXAN

		Per subject N = 86		Per administration N = 1049	
System Organ Class (SOC)	**Adverse Reaction**	**Frequency**	**Frequency Ratio (Percentage)**	**Frequency**	**Frequency Ratio (Percentage)**
	Pleuritic pain	Common	2/86 (2.33%)	Uncommon	3/1049 (0.29%)
	Dry mouth	Common	2/86 (2.33%)	Uncommon	2/1049 (0.19%)
	Dyspnea	Common	2/86 (2.33%)	Uncommon	2/1049 (0.19%)
	Bronchospasm	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
	Laryngeal discomfort	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
	Epistaxis	Common	1/86 (1.16%)	Uncommon	1/1049 (0.10%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**Rash**[3]	Very common	11/86 (12.79%)	Common	18/1049 (1.72%)
	Pruritus	Common	4/86 (4.65%)	Uncommon	6/1049 (0.57%)
	Hyperhidrosis	Common	2/86 (2.33%)	Uncommon	3/1049 (0.29%)
VASCULAR DISORDERS	**Flushing**	Very common	9/86 (10.47%)	Common	14/1049 (1.33%)

Legend: Adverse Drug Reaction frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)
[1]Oral, rectal
[2]The per administration frequency cannot be determined from the data reviewed.
[3]Including nonpruritic, pruritic, erythema/erythematous, eczematous, papular, and/or macular rashes.

- Time to onset

In these studies, some subjects experienced their events on first exposure to UROMITEXAN and others after the second or third exposure. In general, the complete spectrum of symptoms experienced by a subject developed over a period of several hours.

- Experience with re-exposure

Some subjects experienced no further reactions after their initial event while others experienced an exacerbation of events upon repeated dosing.

- Infusion site reactions

In some subjects experiencing local cutaneous infusion site reactions, subsequent exposure to UROMITEXAN resulted in a cutaneous event in other areas.

- Cutaneous/mucosal reactions

Cutaneous and mucosal reactions were reported to occur after both intravenous and oral UROMITEXAN. These reactions included rashes, pruritus, flushing, mucosal irritation, pleuritic pain, and conjunctivitis. Approximately one-quarter of subjects with any event experienced cutaneous/mucosal reactions in conjunction with other adverse symptoms, which included, dyspnea, fever, headache, gastrointestinal symptoms, drowsiness, malaise, myalgia, and

influenza-like symptoms.

- Gastrointestinal reactions

Gastrointestinal reactions reported in healthy subjects included nausea, vomiting, diarrhea, abdominal pain/colic, epigastric pain/burning, constipation, and flatulence and were reported to occur after intravenous and oral UROMITEXAN administration.

Abnormal Hematologic and Clinical Chemistry Findings

Hematologic

Test	Effect	Clinical Comment
Lymphocyte counts	Decreased	In pharmacokinetics studies in healthy volunteers, administration of single doses of mesna was commonly associated with a rapid (within 24 hours) and in some cases marked decrease in lymphocyte count, which was generally reversible within 1 week of administration. Data from studies with repeated dosing over several days are insufficient to characterize the time course of lymphocyte count changes under such conditions. These phenomena should be considered when interpreting laboratory results.

Clinical Chemistry

Test	Effect	Clinical Comment
Serum phosphorus levels	Increased	In pharmacokinetics studies in healthy volunteers, administration of mesna on single or multiple days was in some cases associated with moderate transient increases in serum phosphorus concentration. These phenomena should be considered when interpreting laboratory results.

Post-Market Adverse Drug Reactions

Because UROMITEXAN is used in combination with oxazaphosphorines or oxazaphosphorine-containing combination chemotherapy, it is often difficult to distinguish adverse reactions that may be due to UROMITEXAN from those caused by concomitantly administered cytotoxic agents.

The following adverse reactions have been identified from postmarketing reports of patients receiving UROMITEXAN in combination with oxazaphosphorine cytostatics and other medications.

Many of the adverse reactions listed in the following SOCs occurred as part of a syndrome suggestive of hypersensitivity reactions. (See **WARNINGS AND PRECAUTIONS**, **Sensitivity/Resistance)**

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Pancytopenia, Leukopenia, Lymphopenia, Thrombocytopenia, Eosinophilia

CARDIAC DISORDERS: Electrocardiogram abnormal (consistent with perimyocarditis), Tachycardia

EYE DISORDERS: Periorbital edema

GASTROINTESTINAL DISORDERS: Stomatitis, Bad taste

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Face edema, Edema peripheral, Asthenia, Infusion site reactions (thrombophlebitis, irritation*)

HEPATOBILIARY DISORDERS: Hepatitis, Gamma-glutamyl transferase increased, Blood alkaline phosphatase increased

IMMUNE SYSTEM DISORDERS: Anaphylaxis, Hypersensitivity

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: Occupational sensitization to other mesna formulations used for inhalation (manifested as eczema, papulovesicular rash, erythema, pruritus)

INVESTIGATIONS: Laboratory signs of disseminated intravascular coagulation, Prothrombin time prolonged, Activated partial thromboplastin time prolonged

NERVOUS SYSTEM DISORDERS: Convulsion

RENAL AND URINARY DISORDERS: Acute renal failure

RESPIRATORY, THORACIC, MEDIASTINAL DISORDERS: Respiratory distress, Hypoxia, Oxygen saturation decreased, Tachypnea, Hemoptysis

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Drug rash with eosinophilia and systemic symptoms, Ulcerations and/or bullae/blistering (mucocutaneous, mucosal, oral, vulvovaginal, anorectal), Angioedema, Fixed drug eruption, Rash (vesicular, exfoliative, maculo-papular, morbilliform), Photodistributed rash, Urticaria, Burning sensation, Erythema

VASCULAR DISORDERS: Hypotension (in some cases fluid refractory), Hypertension

*Venous irritation may be attributed to the physical properties of UROMITEXAN – (i.e., pH 6, and hypertonic solution). No venous complications were observed when the solution was given diluted with Sterile Water for Injection USP (one part mesna solution to three parts water).

DRUG INTERACTIONS

Drug-Drug Interactions
No clinical drug interaction studies have been conducted with UROMITEXAN.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Lifestyle Interactions
Patients undergoing treatment with UROMITEXAN may experience syncope, lightheadedness, lethargy/drowsiness, and blurred vision, which could affect the ability to drive or use machines. Therefore patients should refrain from driving or operating machinery until they know that UROMITEXAN does not affect their ability to drive or use machines.

Drug-Laboratory Test Interactions
UROMITEXAN (mesna) treatment may cause false positive reactions in nitroprusside sodium-based urine tests (including dipstick tests) for ketone bodies. The colour reaction for ketones observed following exposure to mesna is reddish purple rather than purple, which is less stable and fades immediately by adding glacial acetic acid.

UROMITEXAN treatment may cause false positive reactions in Tillman's reagent-based urine screening tests for ascorbic acid.

In pharmacokinetics studies in healthy volunteers, serum creatine phosphokinase (CPK) values were lower in samples taken 24 hours after mesna dosing than in pre-dosing samples. While available data are insufficient to determine the cause of this phenomenon, it might be considered to represent a significant interference with thiol (e.g., N-acetylcysteine) dependent enzymatic CPK tests.

DOSAGE AND ADMINISTRATION

Dosing Considerations
UROMITEXAN (mesna) dosing is dependent on the dose of concomitant oxazaphosphorine drug that a patient receives.

UROMITEXAN dosing schedule should be repeated each day the oxazaphosphorine drug is received.

If the oxazaphosphorine drug dose is adjusted, the mesna dose should also be modified to maintain the mesna-to-oxazaphosphorine drug ratio.

Recommended Dose and Dosage Adjustment

Intravenous Injection

UROMITEXAN is given as intravenous bolus injections, usually at a dose equal to 20% of the respective oxazaphosphorine dose (w/w) at times 0 (= administration of the cytostatic agent), 4 hours and 8 hours. In the case of IFEX (ifosfamide), the usual dose of UROMITEXAN (mesna) is 10 - 12 mg/kg i.v. at 0, 4 and 8 hours after the IFEX dose. The total daily dose of UROMITEXAN is 60% of the IFEX dose. (see **DOSAGE AND ADMINISTRATION** sections of Procytox and Ifex Product Monographs)

In the treatment of children, and particularly when administering very high doses -- such as required when conditioning patients for bone-marrow transplantations -- the UROMITEXAN doses should be given at 0, 1, 3, 6, 9 and 12 hours or dosage increased to 30% of the respective oxazaphosphorine dose.

Oral – UROMITEXAN ampoules only

10 mL and 50 mL multi-dose vials should not be administered orally.

Oral administration of UROMITEXAN -- e.g., in patients with poor veins -- is also feasible. UROMITEXAN is then given either at doses of 20% of the oxazaphosphorine dose at time 0 hours by the parenteral route, followed by oral doses of 40% of the oxazaphosphorine dose after 4 and 8 hours, taken in juice or cola, or in 3 oral doses of 40% of the oxazaphosphorine dose at time 0, 4 and 8 hours.

Administration

For intravenous infusion the drug can be diluted by adding the UROMITEXAN solution to any of the following fluids:

- 5% Dextrose Injection, USP in PVC container
- 5% Dextrose Injection with 0.45% Sodium Chloride Injection, USP in PVC container
- 0.9% Sodium Chloride Injection, USP in PVC container
- Lactated Ringer's Injection, USP in PVC container

For example: One mL of UROMITEXAN multi-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/mL.

OVERDOSAGE

Reports of inadvertent overdose and observations from a high-dose tolerability study in healthy volunteers showed that, in adults, single doses in the range of approximately 4 g to 7 g of mesna can cause symptoms such as nausea, vomiting, abdominal pain/colic, diarrhea, headache, fatigue, limb and joint pains, rash, flushing, hypotension, bradycardia, tachycardia, paresthesia, fever, and bronchospasm.

A markedly increased rate of nausea, vomiting and diarrhea has also been found in oxazaphosphorine-treated patients receiving ≥ 80 mg mesna per kg per day intravenously

compared with patients receiving lower doses or hydration treatment only.

A specific antidote for mesna is not known. Overdosage should be managed with supportive measures to sustain the patient through any period of toxicity. UROMITEXAN (mesna) has been administered at doses from 70 to 100 mg/kg without any toxic effect on hematopoiesis, hepatic and renal function or the central nervous system.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Mesna is rapidly and easily converted by autooxidation to its only metabolite disodium 2,2[1]-dithio-bis ethane sulfonate (mesna disulfide, dimesna), forming a disulphide link. Following intravenous injection, only a small portion of the administered dose is detected in the blood as a reactive thiol compound (mesna). Mesna disulphide remains in the intravascular space and is rapidly forwarded to the kidney. In the renal tubular epithelium a considerable proportion of mesna disulphide is again reduced to a free thiol compound, presumably by mediation of glutathione reductase. It is then capable of chemically reacting with acrolein or other urotoxic oxazaphosphorine metabolites in the urine, thereby developing its detoxifying activity.

The first and most important step towards detoxification is the addition of mesna to the double bond of acrolein, resulting in the formation of a stable thio ether which could be detected in the urine by chromatography. In the second step, mesna reduces the speed of degradation of the 4-hydroxy metabolite in the urine. A relatively stable, non-urotoxic condensation product from 4-hydroxy cyclophosphamide or 4-hydroxy ifosfamide and mesna is formed. By such stabilization mesna inhibits the degradation of 4-hydroxy cyclophosphamide or 4-hydroxy ifosfamide and hence the formation of acrolein. This intermediate deactivated product could also be detected by chromatographic urinalysis.

STORAGE AND STABILITY

UROMITEXAN (mesna injection) ampoules and multidose vials should be stored at 15°C to 25°C.

Stability of Solution

Solutions for infusion should be stored at 15°C to 25°C and used within 24 hours from the time of preparation.

SPECIAL HANDLING INSTRUCTIONS

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

Any solutions which are discoloured, hazy, or contain visible particulate matter should not be

used.

The UROMITEXAN multi-dose vials may be punctured up to four times and may be stored and used for up to 8 days after opening and initial puncture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

UROMITEXAN (mesna injection) 100 mg/mL is available in 4 mL and 10 mL ampoules and 10 mL and 50 mL multidose vials.

Each ampoule of UROMITEXAN contains: Mesna, Disodium Edetate, Sodium Hydroxide and Sterile Water for Injection.

Each multi-dose vial of UROMITEXAN contains: Mesna, Disodium Edetate, Sodium Hydroxide, Sterile Water for Injection, and Benzyl Alcohol (104 mg in the 10 mL vial; 520 mg in the 50 mL vial) as a preservative.

PART II: SCIENTIFIC INFORMATION

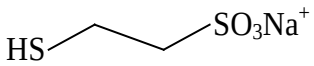
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Mesna

Chemical Name: Sodium 2-mercaptoethanesulfonate

Molecular Formula and molecular mass: $C_2H_5O_3S_2Na$, 164.18

Structural Formula: 

Physicochemical properties: White or slightly yellow crystalline powder

Solubility: Water: freely soluble; Ethanol: slightly soluble; Cyclohexane: practically insoluble

pH: 4.5 – 6.0

Melting Point: 240 ^{o}C

DETAILED PHARMACOLOGY

Mesna and dimesna are absorbed from the intestine and during absorption, dimesna undergoes reduction. In the plasma, mesna is rapidly oxidized by a metal-dependent reaction. Both mesna and dimesna pass unchanged through hepatic vasculature, are not taken up in the liver cells and are not excreted in bile. In the kidney, dimesna is subject to glomerular filtration and subsequently reabsorbed, whereupon reduction to the pharmacologically active thiol form occurs in the renal tubular epithelium, and the thiol is then re-excreted into the tubular lumen. Reduction of dimesna occurs in intestinal and renal epithelial cells by a mechanism involving the enzymes thiol transferase and glutathione reductase.

<u>Animals</u>
In guinea pigs, the elimination half-life was found to be 1.48 hours following intravenous administration of 200 mg/kg, and 3.9 hours following oral administration of 200 mg/kg. Similar rates were determined in rats and dogs.

Blood levels were quantified after oral administration in all 3 species. Serum half-life was found to be 3.5 hours in the guinea pig, 2.6 hours in the rat, and 2 hours in the dog.

Distribution of mesna in the tissues was determined in guinea pigs and rats. Following oral administration of 200 mg/kg, it was observed that mesna does not permeate all body tissues.

In the rat, placental permeability was investigated after oral administration: in the fetus, the placental barrier permits fetal blood levels of only 17.6% of the maternal blood level.

In all 3 animal species, irrespective of the route of administration, dimesna is eliminated in the urine within the first 8 hours at a rate of 38-45% of the administered mesna dose.

Humans
After intravenous administration of 60 mg/kg mesna, a half-life of 1.08 hours was established. Renal elimination starts immediately after administration and is largely completed within 8 hours after administration. In the first 4 hours, excretion occurs primarily as a free SH-compound, thereafter occurring almost exclusively in the form of disulphide.

After oral administration of 60 mg/kg, mesna appears in the blood almost entirely as its disulfide metabolite with a time-lag of 0.36 hours. Maximum serum levels occur after 1.17 hours. The elimination half-life is 1.15 hours. The rate of excretion is not different from that seen after intravenous administration.

Over 60% of the administered oral or intravenous dose (60 mg/kg) is recovered in the urine as mesna or dimesna.

TOXICOLOGY

Acute Toxicity
Mesna was found to be almost completely non-toxic. The LD_{50} values are as follows:

Species	Route of Administration	LD_{50} mg/kg
Mice	IV or IP	1800-2050
	PO	>6100
Rats	IV or IP	1225-2080
	PO	>4330

In dogs, death was observed after intravenous doses of 400 mg/kg and above, but not after oral doses of up to 2000 mg/kg.

Subacute Toxicity
The low toxicity of mesna was confirmed in tests for subacute toxicity. In a 6-week study, rats tolerated daily intravenous doses of up to 316 mg/kg without toxic symptoms. The earliest signs of toxicity were seen at doses of 1000 mg/kg. These included severe body weight loss, leucopenia and anemia.

The kidneys showed distended tubules engorged with urine which had a high protein content and

hyaline deposits in the glomerular capillaries.

Dogs tolerated 12 intravenous doses of 200 mg/kg, with vomiting and diarrhea appearing only in the first days of treatment. In a 6-week study, intravenous doses of up to 316 mg/kg were tolerated. The only toxic symptoms were vomiting and diarrhea. In the 100 mg/kg group, these symptoms subsided after about 2 weeks of administration, whereas in the 316 mg/kg group they occasionally persisted to the end of the experiment. Macroscopic and histologic examinations did not reveal any drug-related findings.

Chronic Toxicity

In a 6-month chronic toxicity test in rats (oral administration of a 40% solution), daily doses up to 2000 mg/kg were tolerated without drug-related mortality or morbidity.

In a 7-month study in dogs, mesna was administered orally at doses of 31.6, 100 and 316 mg/kg/day. The high dose was subsequently increased to 420 mg/kg/day and further increased to 560 mg/kg/day. One death occurred at 560 mg/kg/day. Other clinical signs included a dose-related incidence of semi-solid stools and sporadic emesis, and a decrease in motor activity in all dogs. There was a slight increase in alkaline phosphatase, a slight decrease in creatinine, and a slight alteration in the electrolytes in high and medium dose dogs.

Mutagenicity

No evidence of mutagenicity of mesna was found in the Ames tests on strains of *Salmonella typhimurium*.

Reproduction and Teratology

There was no evidence of interference with fetal development following oral administration to rats (doses of up to 2000 mg/kg from day 8 to day 15 of gestation) and to rabbits (doses of up to 2000 mg/kg from day 7 to day 17 of gestation).

Carcinogenicity

Mesna had no carcinogenic effects in rats.

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PART III: CONSUMER INFORMATION

[Pr]UROMITEXAN
(Mesna Injection)

This leaflet is part III of a three-part "Product Monograph" published when UROMITEXAN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about UROMITEXAN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
UROMITEXAN (mesna) is used for the reduction and prevention of bleeding in the bladder (hemorrhagic cystitis) caused by anti-cancer drugs such as cyclophosphamide and ifosfamide.

What it does:
UROMITEXAN helps to protect the lining of the bladder against damage from anti-cancer drugs. The body breaks down anti-cancer drugs to form products that can harm the bladder. UROMITEXAN works by making these breakdown products less harmful.

When it should not be used:
UROMITEXAN should not be used if:
You have a known allergy to mesna, any thiol-containing compound or to any of the nonmedicinal ingredients in particular benzyl alcohol.

What the medicinal ingredient is:
Mesna

What the nonmedicinal ingredients are:
Ampoules: Disodium Edetate, Sodium Hydroxide and Sterile Water for Injection.

Multi-dose vials: Disodium Edetate, Sodium Hydroxide, Sterile Water for Injection, and Benzyl Alcohol (104 mg in the 10 mL vial; 520 mg in the 50 mL vial) as a preservative.

What dosage forms it comes in:
UROMITEXAN (mesna injection) 100 mg/mL is available in 4 mL and 10 mL ampoules and 1 g and 5 g multi-dose vials.

WARNINGS AND PRECAUTIONS

BEFORE you use UROMITEXAN talk to your doctor or pharmacist if:

- You have any allergies to this drug or other drugs similar to UROMITEXAN, such as amifostine, penicillamine and captopril, or to any of its ingredients.
- You are scheduled to undergo urine screening tests.
- You are pregnant or planning to become pregnant.
- You are nursing an infant.
- You plan to drive or operate machinery.
- You have had previous reactions to UROMITEXAN.

UROMITEXAN does not prevent hemorrhagic cystitis in all patients. Contact your doctor or nurse immediately if you notice that your urine is pink, red, or bloody.

INTERACTIONS WITH THIS MEDICATION

There are no known drug-drug interactions with UROMITEXAN.

PROPER USE OF THIS MEDICATION

Usual dose:
Your doctor will determine what dose of UROMITEXAN is right for you and how often you should receive it.
UROMITEXAN can be taken intravenously or orally (ampoules only).

Overdose:
A specific antidote for mesna is not known.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss your scheduled treatment, contact your doctor or nurse as soon as possible to schedule your next treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Because UROMITEXAN is used in combination with other chemotherapy drugs, it is often difficult to distinguish side effects that may be caused by UROMITEXAN from those caused by other drugs.

If you notice any changes in the way you feel during or after the treatment, tell your doctor or another member of your medical team immediately.

Like all medicines, UROMITEXAN can cause side effects although not everybody gets them.
The following side effects may happen with this medicine:
Very common (affects more than 1 in 10 people):

- Headache
- Reactions at the application site
- Abdominal pain (colic)
- Feeling abnormally sleepy during the day
- Lightheadedness
- Fever
- Skin rash
- Diarrhea
- Nausea
- Flushing
- Flu-like symptoms (e.g., sore throat, fever, chills, shivering, cough, body aches)

If any of these effects persist or worsen, tell your doctor or nurse

promptly

UROMITEXAN can cause serious side effects. These include severe skin rash and skin reactions that can cause death. These problems may occur any time during treatment, but more commonly occur during or after a first treatment or after several weeks of treatment with UROMITEXAN. Sometimes the first skin reaction occurs only after several months of treatment.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect	**Talk with your doctor or pharmacist**	
	Only if severe	**In all cases**
Skin rash caused by a reaction to drugs that includes the following symptoms: - Blisters - Mouth sores - Swelling of your face - Cough - Fever		✓
Red or inflamed eyes like "pink eye" (conjunctivitis)		✓
Liver problems		✓
Chest pain, rapid heart beat		✓
Breathing difficulties		✓
Feeling unwell or like you have the flu.		✓
Tiredness		✓
Severe dizziness		✓

This is not a complete list of side effects. For any unexpected effects while taking UROMITEXAN, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 15°C to 25°C. Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

$ Report online at www.healthcanada.gc.ca/medeffect
$ Call toll-free at 1-866-234-2345
$ Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.baxter.ca
or by contacting the sponsor, Baxter Corporation, at:
1-888-719-9955.

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