Baxter

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Please read carefully!

Uromitexan 400 mg

Active substance: Mesna
Uroprotector
Composition: 4 ml injection solution contains mesna 400 mg
Excipients: sodium edetate, sodium hydroxide, water for injection
Indications: For the prevention of urothelial toxicity of oxazaphosphorines (the active components of Holoxan: ifosfamide, Endoxan: cyclophosphamide, Ixoten: trofosfamide), in particular in high-risk patients with previous radiation therapy in the area of the small pelvis, cystitis with previous Holoxan, Endoxan or Ixoten therapy or a history of urinary tract disease.
Contraindications: Hypersensitivity to the active substance or to any of the excipients (Sodium Edetate, Sodium Hydroxide, Water for Injection) .

Warnings and Precautions:

Hypersensitivity

Hypersensitivity reactions may occur following administration of mesna for uroprotection. Various cutaneous and subcutaneous reactions have been reported (see section "Side Effects"). There are also case reports of serious blistering and ulceration of the skin and mucous membranes. Some reactions were consistent with Stevens-Johnson syndrome. The skin reactions were accompanied in some cases by one or several other symptoms, including fever, cardiovascular symptoms, signs of acute renal failure, lung symptoms, hematologic abnormalities, increased levels of liver enzymes, nausea, vomiting, pain in the extremities, arthralgia, myalgia, malaise, stomatitis and conjunctivitis (see section "Side Effects"). Some reactions have presented as anaphylaxis. Fever accompanied by (for example) hypotension but no skin manifestation has also been reported. Patients with an autoimmune disease are at increased risk of allergic or anaphylactoid reactions. Uromitexan 400 mg for uroprotection should therefore be given to such patients only after careful consideration of the risks and benefits and under medical monitoring. Reactions to mesna ranging from serious to mild have been reported with the use of mesna to treat severe systemic autoimmune disorders and malignancies. In most cases, the reactions occurred during or after a first treatment occasion or several weeks after mesna exposure. In other cases, the initial reaction was not observed until several months after the exposure.Symptoms tend to appear at shorter intervals following repeated exposure. The incidence and/or severity of reaction may vary with the dose administered. Some patients experienced reactions after re-exposure, which were of increasing severity in some cases. Some patients with a history of a reaction showed 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 reactions that may worsen with re-exposure and may in some cases become life-threatening
- be aware that hypersensitivity reactions to mesna might be interpreted as resembling the clinical picture of sepsis and, in patients with autoimmune disorders, as resembling an exacerbation of the underlying disease.

Thiol compounds

Mesna is a thiol compound (contains a sulfanyl-(SH-)group). Thiol compounds show some similarities in their adverse reaction profiles and may 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 reactions to another thiol compound. In these cases, special caution is required when using thiol compounds. Mesna does not prevent hemorrhagic cystitis in all patients. Therefore, patients should be monitored accordingly. Sufficient urinary output should be maintained, as with any oxazaphosphorine treatment.

Laboratory test interactions

Mesna treatment may cause false positive reactions in nitroprusside sodium-based urine tests (including dipstick tests) for ketone bodies. Adding glacial acetic acid can help to distinguish between false-positive results (fading cherry red color) and true-positive results (reddish purple, which becomes more intense). Mesna treatment may cause false positive reactions in Tillman's reagent-based urine screening tests for ascorbic acid. For other interactions with lab tests, see the section "Pharmacokinetics".
Pediatric use: Safety and effectiveness of mesna in pediatric patients (<16 years) have not yet been established in clinical trials by Baxter, but the use of mesna in pediatric patients is described in the literature. For use in pregnancy and lactation. See section "Fertility, pregnancy, lactation".
Geriatric use: 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 oxazaphosphorines to mesna should remain unchanged. Uromitexan 400 mg contains sodium, but less than 1 mmol (23 mg) of sodium per 10 ml.

Fertility, pregnancy and lactation: As Uromitexan 400 mg is used as a uroprotectant during cytotoxic therapy with oxazaphosphorines, the risk-benefit ratio of this cytotoxic therapy applies with regard to the use of Uromitexan during pregnancy and lactation.

Pregnancy

No adequate data is available on the use of mesna during pregnancy. Animal studies have not revealed any embryotoxic or teratogenic effects of mesna (see section "Preclinical safety data")..

Breast-feeding

Breastfeeding is not allowed during treatment with Uromitexan.

Fertility

No fertility studies are available on the use of mesna.
Side-effects: The most frequently occurring adverse reactions (> 10%) associated with use of mesna are headache, infusion site reactions, abdominal pain/colic, light-headedness, lethargy/drowsiness, fever, rash, diarrhea, nausea, flushing, and flu-like illness. The most severe adverse reactions associated with use of mesna are toxic epidermal necrolysis, Stevens-Johnson syndrome, anaphylaxis, and drug rash with eosinophilia and systemic symptoms (DRESS). Because mesna is used in combination with oxazaphosphorines, it is often difficult to distinguish adverse reactions that may be due to mesna from those caused by concomitantly administered cytotoxic agents.

Adverse reactions are assessed on the basis of the following frequencies:

Very common: (≥1/10)	**Common**: (≥1/100 to <1/10)
Uncommon: (≥1/1000 to <1/100)	**Rare**: (≥1/10000 to <1/1000)
Very rare: (<1/10000)	
Not known: cannot be estimated from the available data	

The following table lists the reported adverse reactions by MedDRA system organ classes, stating the respective frequencies.

System organ class (SOC)	Adverse reaction	Frequency
Infections and infestations	Pharyngitis	Very rare
Blood and lymphatic system disorders	Lymphadenopathy	Common
	Pancytopenia Leukopenia Lymphopenia Thrombocytopenia Eosinophilia	Not known
Immune system disorders	Anaphylaxis Hypersensitivity reactions	Not known
Metabolism and nutrition disorders	Appetite decreased Feeling of dehydration	Common
Psychiatric disorders	Insomnia Nightmares	Common
Nervous system disorders	Headache Light-headedness Lethargy/drowsiness	Very common
	Dizziness Paresthesia Hyperesthesia Syncope Hypoesthesia Disturbance in attention	Common
	Convulsion	Not known
Eye disorders	Conjunctivitis Photophobia Blurred vision	Common
	Periorbital edema	Not known
Cardiac disorders	Palpitations	Common
	Electrocardiogram abnormalities Tachycardia	Not known
Vascular disorders	Flushing	Very common
	Hypotension Hypertension	Not known
Respiratory, thoracic and mediastinal disorders	Nasal congestion Cough Pleuritic pain Xerostomia Bronchospasm Dyspnea Laryngeal discomfort Epistaxis	Common
	Difficulty breathing Hypoxia Reduced oxygen saturation Tachypnea Hemoptysis	Not known
Gastrointestinal disorders	Abdominal pain/colic Nausea Diarrhea	Very common
	Mucosal irritation[1] Flatulence Burning pain (substernal/epigastric) Constipation Gingival bleeding	Common
	Stomatitis Dysgeusia	Not known
Hepatobiliary disorders	Transaminases increased	Common
	Hepatitis Gamma glutamyl transferase levels increased Blood alkaline phosphatase levels increased	Not known
Skin and subcutaneous tissue disorders	Rash[2]	Very common
	Pruritus Hyperhidrosis	Common
	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Drug rash[3] Ulceration and/or bullae/blistering[4] Angioedema Rash Photosensitivity Urticaria Burning sensation Erythema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia Back pain Myalgia Pain in the extremities Jaw pain	Common
Renal and urinary disorders	Dysuria	Common
	Acute renal failure	Not known
General disorders and administration site conditions	At the infusion site: pruritus, rash Fever Flu-like illness	Very common
	At the infusion site: Pain, erythema, urticaria, swelling Rigors Fatigue Chest pain Malaise	Common
	Facial edema, Peripheral edema Asthenia At the infusion site: thrombophlebitis, skin irritation	Not known
Investigations	Lab signs of disseminated intravascular coagulation Prothrombin time prolonged Activated partial thromboplastin time prolonged	Not known

[1] Oral, rectal
[2] Including erythema with or without pruritus and erythematous, eczematous, papular and/or macular rashes.
[3] with eosinophilia and systemic symptoms
[4] mucocutaneous, mucosal, oral, vulvovaginal, anorectal

Onset of symptoms and re-exposure

Adverse reactions may occur after the first exposure to mesna. In some cases, symptoms are not observed until after the second or third exposure. In general, the complete spectrum of symptoms developed over a period of several hours. Following re-exposure, some patients experienced no further reactions while others experienced definite reactions.

Infusion site reactions

In some patients experiencing local cutaneous infusion site reactions after administration of the drug, subsequent exposure resulted in cutaneous reactions at other locations.

Cutaneous/mucosal reactions

Cutaneous and mucosal reactions have been reported to occur after both intravenous and oral administration of mesna. Approximately one-quarter of subjects with any adverse event experienced cutaneous/mucosal reactions in conjunction with other adverse symptoms, including dyspnea, fever, headache, gastrointestinal symptoms, drowsiness, malaise, myalgia and flu-like symptoms.

	Date:	Date:
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Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

Overdose: Reports of inadvertent overdose and observations from a high-dose tolerability study in healthy subjects showed that, in adults, single doses in the range of approximately 4 g to 7 g of mesna can cause symptoms such as, but not limited to: nausea, vomiting, abdominal pain/colic, diarrhea, headache, fatigue, limb and joint pains, rash, flushing, hypotension, bradycardia, tachycardia, paresthesia, fever and bronchospasm. Compared with patients receiving lower mesna doses or hydration treatment only, a markedly increased rate of nausea, vomiting and diarrhea has been found in oxazaphosphorine-treated patients receiving ≥ 80 mg mesna per kg per day. A specific antidote for mesna is not known. It should be ensured that adequate emergency medication is available for individuals with autoimmune diseases.

Interactions with other drugs: No interaction studies have been performed.

Incompatibilities: Mesna is incompatible in vitro with carboplatin, cisplatin and nitrogen mustard. However, concomitant administration is possible if separate injection sites are used. These medications do not interact within the body.

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

Dosage instructions and mode of use: Unless otherwise prescribed, Uromitexan 400 mg is usually administered by i.v. injection in adults at a dose of 20 % of the respective oxazaphosphorine dose, at times 0 (administration of the oxazaphosphorine), 4 hours and 8 hours.

Example of administration of Uromitexan 400 mg with oxazaphosphorine injection:

Hour (Time)	0 (8.00 a.m.)	4 (12.00 noon)	8 (4 p.m.)
Oxazaphosphorine dose	40 mg/kg body weight	–	–
Uromitexan dose	8 mg/kg body weight	8 mg/kg body weight	8 mg/kg body weight

If ifosfamide (Holoxan) is given by continuous infusions, it is advisable to add Uromitexan 400 mg after a bolus injection (20 %) at time 0 (start of infusion, hour "0") at dosage of up to 100 % of the respective dose of continuous infusion ifosfamide. The uroprotectant effect should be maintained for another 6 to 12 hours after completion of the ifosfamide infusion with up to 50% of the respective ifosfamide dose..

Example of administration of Uromitexan 400 mg with a 24-hour infusion of ifosfamide:

Hours	0	24 30 36
Ifosfamide infusion	5 g/m² body surface area (≈ 125 mg/kg body weight)	
Uromitexan 400 mg bolus	1 g/m² body surface area (≈ 25 mg/kg body weight)	
Uromitexan 400 mg infusion	Up to 5 g/m² body surface area (≈ 125 mg/kg body weight) Addition to Ifosfamide infusion	Up to 2.5 g/m² body surface area (≈ 62.5 mg/kg body weight)

The dose depends on

- Whether ifosfamide or cyclophosphamide is being administered as tablets or by injection
- Whether the patient has a urinary tract infection
- Whether the patient ever had signs of bladder damage from ifosfamide, cyclophosphamide or trofosfamide
- Whether the patient has had radiation therapy near the bladder.

Method of administration

Intravenous use. Check the medicinal product for visible particles and discoloration prior to use. Do not use solutions that are discolored or hazy or contain visible particles. The duration of use of Uromitexan 400 mg depends on the duration of Oxazaphosphorine treatment.

Children: Children generally urinate more frequently than adults, so it may be necessary to shorten the interval between doses (e.g., 3 hours) and/or increase the number of individual doses (e.g., up to 6 doses).

Elderly: There is no special information regarding use in elderly patients. In clinical trials involving patients over 65 years of age, no adverse reactions specific to this age group were observed.

Pharmacodynamic: Pharmacotherapeutic group: detoxifying agents for antineoplastic treatment, antidote for oxazaphosphorines.

ATC code: V03AF01.

Mesna's uroprotectant mechanism of action is based on stabilization of the urotoxic hydroxy metabolites of oxazaphosphorines and on the formation of non-toxic additive compounds with acrolein. These reactions enable regional detoxification in the kidneys and efferent urinary tract.

Pharmacokinetics: Mesna administered as a free thiol compound is rapidly converted in the serum to the mesna disulfide metabolite, a considerable proportion of which is reduced back to the free thiol compound following glomerular filtration. Excretion is almost exclusively via the kidneys. Renal elimination starts immediately after administration. In the first 4 hours after a single dose, excretion occurs primarily as a free SH compound, thereafter occurring almost exclusively in the form of disulfide. Renal elimination is largely completed within approximately 8 hours after administration. The relevant compartment with regards to protection of the bladder is the urine, in which 30% of an intravenous dose is bioavailable in the form of free SH mesna.

In-vivo effect on lymphocyte counts: In pharmacokinetic 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 one week after administration. Data from studies with repeated dosing over several days are insufficient to characterize the time course of lymphocyte count changes.

In-vivo effect on serum phosphate levels: 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 phosphate concentration. In addition, serum creatinine phosphokinase (CPK) values were lower in samples taken 24 hours after mesna dosing than in pre-dosing samples. This might be due to significant interference with thiol (e.g., N-acetylcysteine) dependent enzymatic CPK tests.

Preclinical safety data: Mesna is a pharmacologically and physiologically largely inert and non-toxic thiol compound. It is eliminated very rapidly via the kidneys and does not permeate body tissues. The detoxifying effect is limited to the kidneys and urinary tract. The systemic side effects and antineoplastic efficacy of oxazaphosphorines are not affected. No evidence of mutagenic, carcinogenic or teratogenic properties of mesna has been found in animal studies.

Store drugs out of children´s reach !

Name and permanent address of the manufacturer

Baxter Oncology GmbH · Kantstrasse 2 · D-33790 Halle/Westfalen, Germany

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Presentation: 15 ampoules of 4 ml

Uromitexan is available on prescription only.