Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Uromitexan® 400mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 100 mg of mesna.

Excipients with known effect: Sodium edetate, sodium hydroxide

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear, colorless solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of urinary passage toxicity of oxazaphosphorines (the active components of Holoxan: Ifosfamide , Endoxan: Cyclophosphamide, Ixoten: Trofosamide), in particular in high-risk patients with previous radiation therapy in the area of the lesser pelvis, cystitis with previous Holoxan, Endoxan or Ixoten , urinary passage diseases in anamnesis.

4.2 Posology and method of administration

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 oxazaphosphorine), 4 hours and 8 hours.

Example of administration of **Uromitexan 400 mg** concurrently with oxazaphosphorine injection:

Hours (Time)	0 (08:00 p.m.)	4 (12:00 p.m.)	8 (4:00 p.m.)
Oxazaphosphorine Dose	40 mg/kg body weight	–	–
Uromitexan 400mg Dose	8 mg/kg body weight	8 mg/kg body weight	8 mg/kg body weight

Therapeutic experience with children has shown that in individual cases it is advisable to administer **Uromitexan 400 mg** more frequently (e. g. up to six times) and at shorter intervals (e. g. of 3 hours).

If ifosfamide (Holoxan®) is given by continuous infusion it is advisable to add **Uromitexan 400 mg** after a bolus injection (20 %) at time 0 (start of infusion, hour,"0") at dosages 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 using up to 50 % of the respective ifosfamide dose.

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

Hours	0	24 30 36
Ifosfamide infusion	5 g/m^2 body surface area (≈ 125 mg/kg body weight)	
Uromitexan 400 mg Bolus	1 g/m^2 body surface area (≈ 25 mg/kg body weight)	
Uromitexan 400 mg Infusion	up to 5 g/m^2 body surface area (≈ 125 mg/kg body weight) Addition to ifosfamide infusion	up to 2.5 g/m^2 Body surface area (≈ 62.5 mg/kg body weight)

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
Hypersensitivity reactions may occur following administration of mesna for uroprotection. Various cutaneous and subcutaneous reactions have been reported (see section 4.8).

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 4.8). Some reactions have presented as anaphylaxis. Fever accompanied by (for example) hypotension but no skin manifestations 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 pharmacokinetic data in section 5.2.

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 4.6.

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) sodium per 10 ml.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. See section 6.2

4.6 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 400 mg** 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 5.3).

Breast-feeding
Breastfeeding is not allowed during treatment with **Uromitexan 400 mg**.

Fertility
No fertility studies are available on the use of mesna.

4.7 Effects on ability to drive and use machines

Patients undergoing treatment with mesna may experience side effects that would affect the ability to drive or use machines (including syncope, light-headedness, lethargy/drowsiness, dizziness and blurred vision).
Uromitexan 400 mg has major influence on the ability to drive and use machines.
It should be determined in each individual case whether the patient is fit to drive a vehicle or use machines.

4.8 Undesirable 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**:* (≥1/1,000 to < 1/100)	***Rare:*** (≥1/10,000 to < 1/1,000)
Very rare: (<1/10.000)	
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	 Not known

	Thrombocytopenia Eosinophilia	
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	Not known

	levels increased Blood alkaline phosphatase levels increased	
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.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: detoxifying agents for antineoplastic treatment, antidote for oxazaphosphorines
ATC Code: V03AF01

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

5.2 Pharmacokinetic properties

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 regard to protection of the bladder is the urine, in which about 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 creatine 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.

5.3 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 detoxifiying effect is limited to the kidneys and urinary tract. The systemic side effects and antineoplastic efficacy of the oxazaphosphorines are not affected. No evidence of mutagenic, carcinogenic or teratogenic properties of mesna has been found in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium edetate, sodium hydroxide, water for injections

6.2 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.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30˚C

After reconstitution :

From a microbial point of view: use immediately

From a chemical point of view: 24 hours stored at 25 °C

Compatible with:

- 0.9% Sodium Chloride Solution in glass-bottles
- 5.0% Glucose Solution in glass-bottles
- Ringer Lactate Solution in glass-bottles
- 0.9% Sodium Chloride Solution in PVC-bags
- Ringer Lactate Solution in PVC-bags
- 5.0% Dextrose Solution in PVC-bags
- 5.0% Dextrose + 0.45% Sodium Chloride Solution in PVC-bags
- Ringer Lactate Solution in PE-bottles
- 5.0% Dextrose + 0.45% Sodium Chloride Solution in PE-bottles

Discard any unused remaining solution

6.5 Nature and contents of container

Ampoules of 4 mL:

1 ampoule

15 ampoules

Hospital pack with 50 ampoules

6.6 Instructions for use and handling

No special requirements.

7. MANUFACTURER

Baxter Oncology GmbH, Halle Westfalen, Germany

8. LICENSE HOLDER

Megapharm Ltd, HATIDHAR ST. 15, RA'ANANA, 4366517, ISRAEL

9. MARKETING AUTHORISATION NUMBER

153-48-34007

Revised in September 2023 according to MOHs guidelines.

URO SPC 092023 P.1