Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Uromitexan® 400mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains mesna 100 mg.
Excipients: Sodium edetate, sodium hydroxide
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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), four hours and eight 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 BW	–	–
Uromitexan 400mg Dose	8 mg/kg BW	8 mg/kg BW	8 mg/kg BW

Therapeutic experience with children has shown that in individual cases it is advisable to administer Uromitexan® 400mg 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® 400mg after a bolus injection (20%) at time 0 (commencement of infusion, hour „0“) at dosages of up to 100% of the respective dose of continuous infusion ifosfamide. Moreover, the uroprotective effect should be maintained for another 6 to 12 hours upon completion of the ifosfamide infusion using up to 50% of the respective ifosfamide dose.

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

Hours	0	24 30 36
Ifosfamide infusion	5 g/m² body surface area (≈ 125 mg/kg BW)	
Uromitexan 400 mg Bolus	1 g/m² body surface area (≈ 25 mg/kg BW)	
Uromitexan 400 mg Infusion	up to 5 g/m² body surface area (≈ 125 mg/kg BW) Addition to ifosfamide infusion	up to 2.5 g/m² Body surface area (≈ 62.5 mg/kg BW)

Duration of administration
The duration of administration of Uromitexan® 400 mg depends on the duration of oxazaphosphorine therapy.

4.3 Contraindications

Known hypersensitivity to mesna, other thiol compounds, or any of the excipients.

4.4 Special warnings and precautions for use

Autoimmune diseases are associated with an increased risk of allergic and/or anaphylactoid reactions (see Section 4.8). For that reason, protection of the urinary tract using Uromitexan® 400 mg in such patients requires careful risk/benefit assessment and the supervision of a physician.

For use during pregnancy and lactation as well as other precautionary and accompanying measures see Section 4.6.

Uromitexan® 400 mg does contain sodium, but less than 1 mmol (23 mg) sodium per 10 ml.

4.5 Interaction with other medicinal products and other forms of interaction

Treatment with Uromitexan® 400 mg may cause false-positive reactions in tests for ketone bodies in the urine. However, the colour reaction is reddish purple rather than purple, less stable and fades immediately by adding glacial acetic acid.
See Section 6.2.

4.6 Fertility, pregnancy and lactation

Since Uromitexan® 400 mg is used as Uroprotektor® concurrently with cytostatic treatment with oxazaphosphorines, the criteria of these cytostatic therapies concerning use during pregnancy and lactation apply. Animal testing did not yield any evidence of embryotoxic or teratogenic effects of Uromitexan® 400 mg.

4.7 Effects on ability to drive and use machines

Even if used as directed, Uromitexan◊ 400 mg is known to cause adverse reactions such as nausea, vomiting or circulatory reactions which can alter the capacity for reactions to an extent that impairs e. g. the ability to drive and use machines. As Uromitexan◊ 400 mg is given in combination with oxazaphosphorines, their effects on the capacity for reactions must be observed in addition.

4.8 Undesirable effects

Assessment of side effects is based on the following frequency specifications:

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: Not known (cannot be estimated from the available data)	

Anaphylactoid and other hyperergic reactions following administration of mesna have been commonly reported, e. g. in some cases associated with a drop in the platelet number. Patients with autoimmune diseases have a 3.5-fold higher risk than patients with tumour diseases (without autoimmune diseases).

Skin and mucosal reactions such as urticaria, pruritus, exanthema which may develop into blisters, enanthema, Lyell syndrome, Stevens-Johnson syndrome, local tissue swelling, conjunctivitis as well as unspecific general symptoms such as fever, chills, facial rash, cough, pharyngitis, exhaustion, fatigue, headache, back pain, arthralgia, nausea and vomiting, flatulence, diarrhoea, constipation, colic (e. g. hypogastric pain), anorexia and influenza-like symptoms have been observed. Circulatory reactions such as drop in blood pressure and tachycardia (pulse rate > 100/min), tachypnoea, increase in blood pressure, ST elevation and myalgia as well as a transient elevation in various liver function tests (such as e. g. transaminases) have been observed. Local oedema and venous irritation at the site of injection have been uncommon.

In a tolerance test involving intravenous and oral administration of high doses of mesna nausea, vomiting, diarrhoea, headache, limb and joint pain, drop in blood pressure and tachycardia, skin reactions, exhaustion, lack of strength, depression, irritability and exanthema occurred if doses of 60 mg/kg body weight and higher were given all at once. During treatment the undesirable effects mentioned above cannot always be clearly distinguished from those caused by the oxazaphosphorines (Holoxan®, Endoxan®, Ixoten®) or other concomitant medications used.

SOC	Common	Uncommon	Rare	Very rare
Infections and infestations				Pharyngitis
Immune system disorders	Hypersensitivity reactions, hyperergic reactions		Anaphylactoid reactions, allergic reactions	
Metabolism and nutrition disorders				Anorexia
Psychiatric disorders				Irritability, depression
Nervous system disorders				Headache
Eye disorders			Conjunctivitis	
Cardiac disorders				Tachycardia
Vascular disorders			Drop in blood pressure, increase in blood pressure, facial rash, circulatory reactions	
Respiratory, thoracic and mediastinal disorders				Tachypnoea, cough
Gastrointestinal disorders	Nausea, vomiting		Diarrhoea	Flatulence, constipation, colic, hypogastric pain
Skin and subcutaneous tissue disorders	Itching, exanthema, reactions of the mucous membranes	Urticaria		Stevens-Johnson syndrome, Lyell syndrome
Musculoskeletal, connective tissue and bone disorders		Local tissue swelling	Back pain	Arthalgia, myalgia, limb pain, joint pain
General disorders and administration site conditions	Fever	Local oedema Venous irritation at the injection site Chills	Exhaustion, lack of strength, mucous membrane reactions, lassitude, fatigue	Influenza-like symptoms
Investigations			Increase in various hepatic laboratory parameters	Drop in platelet count, heart rate > 100/min, ST elevation
Injury, poisoning and procedural complications				Toxic reactions

4.9 Overdose

No specific antidote for mesna is known. Concerning the anaphylactoid reactions described in Sections 4.4 and 4.8 the provision of emergency medication should be considered in patients with autoimmune disorders if necessary.

Overdosage may result in the reactions described in Section 4.8 concerning tolerance testing.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agent used in antineoplastic treatment, antidote for oxazaphosphorines
ATC Code: V03AF01

On the one hand, the mechanism of action of the Uroprotektor® Uromitexan® 400 mg is based on the stabilisation of the urotoxic hydroxy oxazaphosphorine metabolites and on the other hand on the formation of nontoxic additive compounds with acrolein. These reactions allow for regional detoxification in the kidneys and the efferent urinary tract.

5.2 Pharmacokinetic properties

In the serum the mesna applied as a free thiol compound is rapidly converted to the metabolite mesna disulfide a considerable proportion of which is reduced back to the free thiol compound following glomerular filtration. It is almost exclusively eliminated via the kidneys. Renal elimination begins immediately after application. During the first four hours following single dose application it is mainly excreted as a free SH compound, and afterwards almost exclusively in the form of a disulfide. Renal elimination is largely completed after approx. 8 hours.
In view of urinary bladder protection urine is the relevant compartment, where approx. 30 % is bioavailable as free SH mesna following intravenous application.

5.3 Preclinical safety data

Mesna is a pharmacologically and physiologically largely inert and nontoxic thiol compound which is eliminated very rapidly via the kidneys and does not pass into the tissues. The detoxifiying effect is limited to the kidneys and the urinary tract. The systemic side effects and the antitumoral efficacy of the oxazaphosphorines are not affected. Animal studies have not revealed any mutagenic, cancerogenic or teratogenic effects of mesna.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium edetate, sodium hydroxide, water for injections

6.2 Incompatibilities

In vitro mesna is incompatible with carboplatin, cisplatin and nitrogen mustard. However, concomitant administration is possible if performed via separate injection sites. These medications do not interact within the body.

6.3 Shelf life

Uromitexan® 400 mg, solution for injection has a shelf life of five years.
Discard any unused remaining solution.

6.3 Shelf life
Uromitexan ® 400 mg injection solution can be stored for 5 years.
Dispose of residual amounts after that.

6.4 Special precautions for storage
Store below 30˚C
After reconstitution - store at 25˚C up to 24 hours

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
Residual amount of Uromitexan ® 400 mg can be added to the household waste.

7. MANUFACTURER

Baxter Oncology GmbH, Halle Westfalen, Germany

8. LICENSE HOLDER

Megapharm Ltd, P.O.B 519, Hod Hasharon 4510501

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