Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Uromitexan Tablets 600mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 600 mg Mesna.
Excipients: Contains 88.905mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
White, oblong, biconvex tablet, with divisional notch to allow breaking for ease of swallowing, marked with M6.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the prevention of urothelial toxicity including haemorrhagic cystitis, microhaematuria and macrohaematuria in patients treated with ifosfamide and cyclophosphamide, in doses considered to be urotoxic.

4.2 Posology and method of administration

Sufficient mesna must be given to adequately protect the patient from the urotoxic effects of the oxazaphosphorine.

The duration of mesna treatment should equal that of the oxazaphosphorine treatment plus the time taken for the urinary concentration of oxazaphosphorine metabolites to fall to non-toxic levels. This usually occurs within 8-12 hours after the end of oxazaphosphorine treatment but may vary depending on the scheduling of oxazaphosphorine. When calculating the dose of mesna the quantity should be rounded down to the nearest whole tablet. Urinary output should be maintained at 100 ml/hr (as required for oxazaphosphorine treatment) and the urine monitored for haematuria and proteinuria throughout the treatment period.

Compared with intravenous administration, overall availability of mesna in urine after oral administration is approximately 50%; and the onset of urinary excretion is delayed by up to 2 hours and is more prolonged than following intravenous dosing.

For intermittent oxazaphosphorine therapy

Oral administration of 40% of the dosage of the oxazaphosphorine on a weight for weight basis rounded down to the nearest whole tablet. The oral dose of Uromitexan should be taken 2 hours before and at 2 hours and 6 hours after oxazaphosphorine dosing.

If the Uromitexan is to be administered intravenously in the first instance, the oral administration at -2 hours should be replaced by the i.v. at 0 hours.

Where ifosfamide is used as a 24 hour infusion

Oral mesna should be taken as the combined infusion of ifosfamide and mesna finishes. Then at 2 hours and 6 hours after the time at the finish of the infusion. All doses are 40% (w/w) of the ifosfamide dose rounded down to the nearest whole tablet.

Where ifosfamide is used as a long-term continuous infusion

Oral mesna should be taken as the combined infusion of ifosfamide and mesna finishes, then at 2 hours and 6 hours after the time at the finish of the infusion. All oral mesna doses should be 40% (w/w) of the final 24 hour ifosfamide dose rounded down to the nearest whole tablet.

Children

Safety and effectiveness of Mesna in paediatric patients (<16 years of age) have not been established in clinical studies performed by Baxter. However, the use of mesna in paediatric patients is referenced in the medical literature, see section 4.4.

In children it may be necessary to shorten the interval between doses and/or to increase the number of individual doses. This regime protects children who generally have increased micturition.

Elderly

No specific information is available. Clinical trials have included patients over 65 and no adverse reactions specific to this age group have been reported.

High risk patients

Patients who have damaged urothelium from previous treatment with oxazaphosphorines or pelvic irradiation, or who are not adequately protected by Uromitexan at the standard dose, e.g. patients with history of urinary tract disease:

the dose of 40% of oxazaphosphorine dose should be given at intervals shorter than 4 hours and/or the number of doses increased.

4.3 Contraindications

Known hypersensitivity to mesna or any of the excipients.

4.4 Special warnings and precautions for use

WARNINGS

Hypersensitivity

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

Various skin and subcutaneous tissue symptoms (see Section 4.8)

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 (see Section 4.8),

§ signs consistent with acute renal impairment,

§ pulmonary symptoms (see Section 4.8),

§ laboratory signs of disseminated intravascular coagulopathy (DIC)

§ haematological abnormalities (see Section 4.8),

§ 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.
Severe as well as minor reactions were reported with the use of mesna in regimens to treat both severe systemic autoimmune disorders and malignancy.

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.

<u>Thiol Compounds:</u>

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.

PRECAUTIONS

Mesna does not prevent haemorrhagic cystitis in all patients. Patients should be monitored accordingly.

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

Lactose Content

Mesna tablets contain lactose. This should be taken into account when using the tablets in patients with lactose intolerance, glucose-galactose malabsorption, or galactose intolerance.

Lab test interferences

Mesna treatment may cause false positive reactions in nitroprusside sodium-based urine tests (including dipstick tests) for ketone bodies. The addition of glacial acetic acid can be used to differentiate between a false positive result (cherry-red colour that fades) and a true positive result (red-violet colour that intensifies).

Mesna 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.

See also Section 4.8 for information on laboratory test abnormalities observed in pharmacokinetic studies.

Paediatric use

Safety and effectiveness of Mesna in paediatric patients (<16 years of age) have not been established in clinical studies performed by Baxter. However, the use of mesna in paediatric patients is referenced in the medical literature.

4.5 Interaction with other medicinal products and other forms of interactions

The systemic effects of oxazaphosphorines are not affected by Uromitexan. In clinical trials it was shown that overdoses of Uromitexan did not diminish the acute toxicity, subacute toxicity, leucocytic activity, and immunosuppressive efficacy of oxazaphosphorines. Animal studies with ifosfamide and cyclophosphamide in a variety of tumours, have also demonstrated that Uromitexan does not interfere with their antineoplastic activity.

Uromitexan also does not affect the antineoplastic efficacy of other cytostatics (e.g. adriamycin, BCNU, methotrexate, vincristine), nor the therapeutic effect of other drugs such as digitalis glycosides.

Food does not influence the absorption and urinary elimination of mesna.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of mesna in pregnant or lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing mesna.

Pregnancy and lactation are contraindications for cytostatic treatment, and consequently Uromitexan is not likely to be used under these circumstances. Should an individual patient be undergoing oxazaphosphorine therapy during pregnancy then Uromitexan should be administered to this patient. Animal studies have shown no evidence of embryotoxic or teratogenic effects of Uromitexan.

4.7 Effects on ability to drive and use machines

Patients undergoing treatment with mesna may experience undesirable effects (including, e.g., syncope, light-headedness, lethargy/drowsiness, dizziness, and blurred vision) which could affect the ability to drive or use machines. The decision to drive or operate machinery should be made on an individual basis.

4.8 Undesirable effects

The most frequently occurring adverse reactions (> 10%) associated with use of mesna: headache, infusion site reactions, abdominal pain/colic, lightheadedness, lethargy/drowsiness, pyrexia, rash, diarrhoea, nausea, flushing, and influenza-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 or oxazaphosphorine-containing combination chemotherapy, it is often difficult to distinguish adverse reactions that may be due to mesna from those caused by concomitantly administered cytotoxic agents.
ADR 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), Unknown (adverse reactions reported in the post-marketing experience)

System Organ Class (SOC)	Adverse Reaction	Frequency
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy	Common
	Pancytopenia	Unknown
	Leukopenia	Unknown
	Lymphopenia	Unknown
	Thrombocytopenia	Unknown
	Eosinophilia	Unknown
IMMUNE SYSTEM DISORDERS	Anaphylaxis	Unknown
	Hypersensitivity	Unknown
METABOLISM AND NUTRITION DISORDERS	Decreased appetite	Common
	Feeling of dehydration	Common
PSYCHIATRIC DISORDERS	Insomnia	Common
	Nightmare	Common
NERVOUS SYSTEM DISORDERS	Headache	Very common
	Light-headedness	Very common
	Lethargy/Drowsiness	Very common
	Dizziness	Common
	Paresthesia	Common
	Hyperesthesia	Common
	Syncope	Common
	Hypoesthesia	Common
	Disturbance in attention	Common
	Convulsion	Unknown

System Organ Class (SOC)	Adverse Reaction	Frequency
EYE DISORDERS	Conjunctivitis	Common
	Photophobia	Common
	Vision blurred	Common
	Periorbital oedema	Unknown
CARDIAC DISORDERS	Palpitations	Common
	Electrocardiogram abnormal	Unknown
	Tachycardia	Unknown
VASCULAR DISORDERS	Flushing	Very common
	Hypotension	Unknown
	Hypertension	Unknown
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Nasal congestion	Common
	Cough	Common
	Pleuritic pain	Common
	Dry mouth	Common
	Bronchospasm	Common
	Dyspnea	Common
	Laryngeal discomfort	Common
	Epistaxis	Common
	Respiratory distress	Unknown
	Hypoxia	Unknown
	Oxygen saturation decreased	Unknown
	Tachypnea	Unknown
	Hemoptysis	Unknown
GASTROINTESTINAL DISORDERS	Abdominal pain/colic	Very common
	Nausea	Very common
	Diarrhoea	Very common
	Mucosal irritation[1]	Common
	Flatulence	Common
	Vomiting	Common
	Burning pain (substernal / epigastric)	Common
	Constipation	Common
	Gingival bleeding	Common
	Stomatitis	Unknown
	Bad taste	Unknown
HEPATOBILIARY DISORDERS	Transaminases increased	Common
	Hepatitis	Unknown
	Gamma-glutamyl transferase increased	Unknown
	Blood alkaline phosphatase increased	Unknown

System Organ Class (SOC)	Adverse Reaction	Frequency
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash[2] Pruritus Hyperhidrosis Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Drug rash [3] Ulcerations and/or bullae/blistering [4] Angioedema Fixed drug eruption Photodistributed rash Urticaria (localised or generalised) Burning sensation Erythema	Very common Common Common Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia Back pain Myalgia Pain in extremity Pain in jaw	Common Common Common Common Common
RENAL AND URINARY DISORDERS	Dysuria Acute renal failure	Common Unknown

System Organ Class (SOC)	Adverse Reaction	Frequency
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS	Infusion site reactions - Infusion site pruritus - Infusion site rash - Infusion site pain - Infusion site erythema - Infusion site urticaria - Infusion site swelling Pyrexia Influenza-like illness Rigors Fatigue Chest pain Malaise Face edema Edema peripheral Asthenia Infusion site reactions[5]	Very common Very common Very common Common Common Common Common Very common Very common Common Common Common Common Unknown Unknown Unknown Unknown
INVESTIGATIONS	Laboratory signs of disseminated intravascular coagulation Prothrombin time prolonged Activated partial thromboplastin time prolonged	Unknown Unknown Unknown

1 Oral, rectal

2 Including nonpruritic, pruritic, erythema/erythematous, eczematous, papular, and/or macular rashes.

3 with eosinophilia and systemic symptoms

4 mucocutaneous, mucosal, oral, vulvovaginal, anorectal

5 thrombophlebitis, irritation

- Time to onset and experience with re-exposure

Some subjects experienced their events on first exposure to mesna 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.
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 mesna resulted in a cutaneous event in other areas.

- Cutaneous/mucosal reactions

Cutaneous and mucosal reactions were reported to occur after both intravenous and oral mesna. 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 mesna administration.

- In-vivo effect on lymphocyte counts

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.

- In-vivo effect on serum phosphorus 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 phosphorus concentration.
These phenomena should be considered when interpreting laboratory results.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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 4g to 7g of mesna can cause symptoms such as nausea, vomiting, abdominal pain/colic, diarrhoea, headache, fatigue, limb and joint pains, rash, flushing, hypotension, bradycardia, tachycardia, paresthesia, fever, and bronchospasm.

A markedly increased rate of nausea, vomiting and diarrhoea 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 to mesna is not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: detoxifying agent for antineoplastic treatment.

ATC code: V03AF01

Uromitexan (mesna) is an antidote, and offers the possibility of reliably preventing urotoxic side-effects associated with aggressive cancer chemotherapy using oxazaphosphorine cytostatics. Extensive and wide-ranging pharmacological and toxicological investigations have shown that Uromitexan has no intrinsic pharmacodynamics and low toxicity. The pharmacological and toxicological inertness of Uromitexan administered systemically and its excellent detoxifying effect in the efferent urinary tract and bladder, are due to the nature of its pharmacokinetics.

5.2 Pharmacokinetic properties

Uromitexan is easily and rapidly transformed by auto-oxidation into its only metabolite mesna-disulphide (dimesna). Dimesna remains in the intravascular compartment and is quickly transported to the kidneys. In the epithelium of renal

tubuli, dimesna is reduced to the free thiol compound, which is then able to react chemically in the urine with toxic oxazaphosphorine metabolites.

Following oral administration, absorption occurs in the small intestine. Mean peak concentrations of free thiols in the urine occur between 2-4 hours after dosing. Approximately 25 ± 10% of the given dose appears as free mesna in the urine in the first 4 hours.

5.3 Preclinical safety data

Nothing relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate,
Microcrystalline cellulose,
Calcium hydrogen phosphate dihydrate,
Maize starch,
Povidone K25,
Magnesium stearate

Film-coating (Pharma coat):
Hypromellose,
Macrogol 6000,
Titanium dioxide (E171),
Simeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Folding box containing blister packs consisting of: aluminium 20 µm (top layer), polyamide 25 µm, aluminium 45 µm, PVC 60 µm (bottom layer).

One blister strip contains 10 tablets.
Pack sizes: 10 tablets, 20 tablets, 50 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2299/024/003

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Renewal of Authorisation: 30 April 2006

10 DATE OF REVISION OF THE TEXT

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