

Data Sheet

UROMITEXAN

Mesna 400mg and 600mg Tablets

Description

UROMITEXAN is a detoxifying agent used to reduce and prevent the urothelial toxicity (haemorrhagic cystitis) induced by oxazaphosphorine alkylating agents, such as cyclophosphamide and ifosfamide. The active ingredient, mesna, is a synthetic sulphhydryl compound designated as sodium 2-mercapto-ethane sulphonate with a molecular formula of $C_2H_5NaO_3S_2$ and a molecular weight of 164.18. Its structural formula is as follows:



UROMITEXAN[®] tablets are white, oblong, biconvex film-coated tablets, scored on one side and marked "M 4" or "M 6", containing 400mg or 600mg (respectively) of mesna as the active ingredient.

Pharmacology

UROMITEXAN was developed as a prophylactic agent to prevent the urothelial toxicity (haemorrhagic cystitis) induced by oxazaphosphorine alkylating agents viz. ifosfamide or cyclophosphamide.

Analogous to the physiological cysteine-cystine system, mesna is rapidly and easily converted by autoxidation to its only metabolite, disodium 2,2'-dithio-bisethane sulphonate (mesna disulphide, dimesna) forming a disulphide link. Following intravenous injection, only a small portion of the administered dose is detected in the blood as a reduced thiol compound (mesna). Mesna disulphide remains in the intravascular space and is rapidly delivered to the kidney. In the renal tubular epithelium a considerable proportion of mesna disulphide is again reduced to a free thiol compound, presumably mediated by glutathione reductase. Acrolein or other urotoxic oxazaphosphorine metabolites are detoxified by chemical reaction with the free thiol compound ie mesna.

The first and most important step towards detoxification is the reaction of mesna with the double bond of acrolein, resulting in the formation of a stable thioether which can 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. As a result of this chemical interaction, mesna inhibits the degradation of 4-hydroxy cyclophosphamide or 4-hydroxy ifosfamide and hence the formation of acrolein. The presence of this intermediate chemical species can be detected by chromatographic urinalysis.

Pharmacokinetics

Two bioavailability studies have been undertaken comparing mesna tablets with mesna injection. In one study, the urinary recovery of mesna 24 hours after 2 x 600mg tablets was 48% of that after 1200mg mesna given intravenously. In the second study, the corrected urinary recovery of mesna 24 hours after 2 x 600mg tablets was 80% of that after 600mg mesna given intravenously. The reason for the higher recovery of mesna in this study is not clear.

Dosing regimes are based on the observation that the urinary excretion of mesna after tablet administration begins two hours later than after intravenous administration, and on the assumption that the bioavailability of the tablets is 50%, based on the two studies summarised above. Hence, the recommended dosing (see Dosage and Administration) is that, when oral mesna is administered, tablets should be taken two hours before oxazaphosphorine therapy and then at 2 and 6 hours. If an initial intravenous dose of mesna is given with cytotoxic therapy, tablets should be taken 2 and 6 hours later. The dose of oral mesna should be double that of intravenous mesna (ie 40% of the oxazaphosphorine dose).

Clinical Trials

Evidence of the efficacy of oral mesna is based on studies with the drinking ampoule which was administered either following an initial dose of intravenous mesna or as the only form of mesna therapy. In 18 studies involving 320 patients and 700 courses of treatment, macroscopic haematuria was observed in 1.6% of courses. This may be compared with results from two other studies in which patients were hydrated instead of receiving mesna therapy. In these studies, the incidence of macroscopic haematuria after 65 courses of treatment was 45%.

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.

Contraindications

UROMITEXAN is contraindicated in individuals with a known hypersensitivity to the drug and other thiols.

Precautions

Warnings

The protective effect of mesna applies only to the urothelial toxic effect of oxazaphosphorines (viz. ifosfamide or cyclophosphamide) not to their renal and other toxic effects. Additional prophylactic or accompanying measures recommended during treatment with oxazaphosphorines are thus not affected and should not be discontinued.

Laboratory Tests

A false positive test for urinary ketones may arise in patients treated with UROMITEXAN. In this test, a red-violet colour develops which, with the addition of glacial acetic acid, will return to violet.

Mesna may cause false positive or false negative reactions in the dipstick test for erythrocytes in urine. To exactly determine erythrocytes in the urine, urinary microscopy is recommended.

Carcinogenesis, Mutagenesis and Impairment of Fertility

No long term animal studies have been performed to evaluate the carcinogenic potential of mesna.

Use in Pregnancy

(Category B1)

Teratology studies with oral doses of mesna to rabbits at up to 1000mg/kg/day and to rats at up to 2000mg/kg/day have revealed no harm to the foetus. Animal studies of potential toxicity in a fertility and general reproductive screen and in a peri-/post-natal screen have not been carried out. It is not known whether UROMITEXAN can cause foetal harm when administered to a pregnant woman or affect reproductive capacity. UROMITEXAN should be given to a pregnant woman only if the benefits clearly outweigh any possible risks.

Use in Lactation

It is not known 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

breast-fed 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.

Drug Interactions

In vitro and in vivo animal tumour models have shown that mesna does not have any effect on the anti-tumour efficacy of concomitantly administered cytotoxic agents.

Oral mesna should be replaced by i.v. mesna in patients experiencing vomiting.

Severe allergic symptoms, such as systemic anaphylactic reactions, have occurred with mesna, especially in patients suffering from autoimmune diseases.

Adverse Reactions

Because UROMITEXAN is used in combination with oxazaphosphorine alkylating agents and other chemotherapeutic agents with documented toxicities, it is difficult to distinguish the adverse reactions which may be due to UROMITEXAN from those caused by the concomitantly administered cytostatic agents. Consequently, the side effect profile of mesna has been assessed from studies in which oral mesna was given alone.

In an early dose-ranging study, six patients were given an oral solution of mesna at doses of 60-70mg/kg. Diarrhoea (83%), headache (67%), fatigue (50%), nausea (33%), limb pain (50%), cardiovascular collapse (17%) and allergy (17%) were reported.

In four pharmacokinetic studies involving 72 subjects given mesna tablets (0.6 to 2.4g) on up to 10 occasions, the most common adverse events were diarrhoea (6%), headache (12%), nausea (5%), vomiting (2%) and fatigue (1%).

Post-marketing data do not indicate any other significant adverse events, but rare events ($\geq 1/10,000$ and $< 1/1,000$) may not have been identified due to the number of patients treated.

The occurrence of hypersensitivity reactions (hyperergic reactions) following UROMITEXAN (see Contraindications) has been reported more frequently in patients with autoimmune disorders than in tumour patients. Skin and mucosal reactions have been observed (rash, urticaria, exanthema, enanthema), increase of transaminase activity and non-specific common symptoms such as fever, fatigue, exhaustion and nausea. Circulatory effects, including hypotension and tachycardia, have also been reported as part of this hypersensitivity reaction/syndrome.

Dosage and Administration

Sufficient mesna must be given to protect the patient adequately 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 100mL/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 mesna, 40% (w/w) of the oxazaphosphorine dose, should be given 2 hours prior to the oxazaphosphorine dose, and repeated at 2 and at 6 hours after oxazaphosphorine administration. Alternatively, an initial intravenous dose of mesna (20% (w/w) of the oxazaphosphorine dose) can be given with the cytotoxic dose and additional oral mesna, 40% (w/w) of the oxazaphosphorine, given at 2 and 6 hours.

eg.

	-2 hrs	0 hrs	2 hrs	6 hrs
Oxazaphosphorine	-	1 g iv	-	
UROMITEXAN (oral only)	400mg po	-	400 mg po	400 mg po
UROMITEXAN (oral and iv)	-	200 mg iv	400 mg po	400 mg po

Following 24 hour infusion of ifosfamide or cyclophosphamide and mesna

The first oral mesna dose of 40% (w/w) of the cumulated dose of ifosfamide or cyclophosphamide is given as the infusion is stopped, and the same dose is repeated after 2 and 6 hours.

Higher doses of mesna can be given if urothelial toxicity occurs.

Elderly

No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

Children

Due to increased micturition, children may require shorter intervals between doses and/or an increased number of individual doses.

High Risk Patients

Those who have had previous irradiation of the small pelvis, occurrence of cystitis during previous cyclophosphamide or ifosfamide therapy or a history of urinary tract lesions may require shorter intervals between doses and/or an increased number of doses.

Overdosage

No specific antidote for mesna is known. Overdosage should be managed with supportive measures to sustain the patient through any period of toxicity. Mesna has been administered at doses from 70 to 100mg/kg without any toxic effect on haematopoiesis, hepatic or renal function or the CNS.

Presentation

UROMITEXAN (mesna) 400mg (film coated) Tablets in pack sizes of 10, 20 & 50

UROMITEXAN (mesna) 600mg (film coated) Tablets in pack sizes of 10, 20 & 50

Storage Conditions

UROMITEXAN Tablets have a shelf life of 3 years when stored below 30°C.

Medicine Classification

Prescription Medicine

Name and Address

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland

Date of Preparation

1 October 2002

UROMITEXAN is a trademark of Baxter Healthcare S.A.