

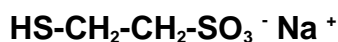
Data Sheet

UROMITEXAN

Mesna 200mg, 400mg & 1g Injection

Description

UROMITEXAN is a detoxifying agent used to 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 is a sterile preservative-free aqueous solution of clear and colourless appearance in clear glass ampoules for intravenous administration. UROMITEXAN contains 100 mg/mL mesna, edetate disodium, and sodium hydroxide for pH adjustment. The solution has a pH range of 6.5 - 8.5.

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, following intravenous administration, 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 i.v. 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 i.e. 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.

Indications

For the prophylaxis of haematuria and haemorrhagic cystitis in patients treated with cyclophosphamide or ifosfamide in doses considered to be urotoxic.

UROMITEXAN is also indicated in at risk patients even though these patients may be receiving relatively low doses of oxazaphosphorines. At risk patients include those that have experienced previous irradiation of the small pelvis, cystitis with earlier oxazaphosphorine therapy, and/or a case history of urinary tract disease.

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 antitumour efficacy of concomitantly administered cytotoxic agents.

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.

As a result, the adverse reaction profile of UROMITEXAN was determined in three Phase 1 studies (16 subjects) utilising intravenous and oral administration and two controlled studies in which ifosfamide and UROMITEXAN were compared to ifosfamide and standard prophylaxis.

In Phase 1 studies in which i.v. bolus doses of 0.8 - 1.6 g/m² UROMITEXAN were administered as a single or three repeated doses to a total of 10 subjects, a bad taste in the mouth (100%) and soft stools (70%) were reported. At intravenous and oral bolus

doses of 2.4 g/m², headache (50%), fatigue (33%), nausea (33%), diarrhoea (83%), limb pain (50%), hypotension (17%) and allergy (17%) were reported in the 6 subjects who participated in this study.

In controlled clinical studies, adverse reactions which can be reasonably associated with UROMITEXAN were vomiting, diarrhoea and nausea.

Venous irritation may occur in rare instances. This reaction may be attributed to the physical properties of mesna (i.e. pH 6, and hypertonic solution). No venous complications were observed when the solution was given diluted with Sterile Water for Injection BP (1 part mesna solution to 3 parts water).

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

Where oxazaphosphorines are used as an i.v. bolus, UROMITEXAN should be administered by intravenous injection, usually at doses 20% of the respective oxazaphosphorine dose, at times 0 (= administration of the cytostatic agent), 4 hours, and 8 hours.

In the treatment of children and particularly when administering very high doses - such as required when conditioning patients for bone-marrow transplantations - the UROMITEXAN doses should be increased or time intervals reduced, and additional administration of UROMITEXAN is advisable.

Where ifosfamide is used as a 24 hour infusion:-

UROMITEXAN is given as an i.v. bolus at a total dose of 60% of the ifosfamide dose, in 7 divided doses every 4 hours from 0 - 24 hours, then 3 further i.v. boluses of the same dose at 28, 32 and 36 hours.

It can be used as an infusion, with an initial bolus of 20% of the dose of ifosfamide at 0 hours, and a continuous infusion of 60-100% of the dose of ifosfamide throughout the 24 hours, with a further 3 i.v. boluses of 20% at 28, 32 and 36 hours.

There is evidence that the dose necessary for urothelial protection in children is 40% of the dose of the oxazaphosphorine given at 0, 3, 6 and 9 hours.

It has been shown at some centres that UROMITEXAN is effective when taken orally. The dose is 40% of the dose of the oxazaphosphorine at 0, 3, 6 and 9 hours. It should be taken immediately the ampoule is opened in a soft drink (e.g orange juice).

UROMITEXAN can be given in the same "giving set" as the oxazaphosphorine.

If necessary the dose of UROMITEXAN given as a bolus, can be increased from 30% given 3 times at 4 hourly intervals, to 40% given 4 times at 3 hourly intervals. This dose is recommended in patients who may have damaged urothelium from previous treatment with oxazaphosphorines or pelvic irradiation, or who are not adequately protected by UROMITEXAN given at the standard dose.

Urinary output should be kept above 100 mL/hour. A diuretic may be used if necessary and the urine should be monitored for haematuria.

Preparation

For i.v. administration the drug can be diluted by adding the contents of a UROMITEXAN ampoule to any of the following fluids obtaining final concentrations of 1.5 to 3mg mesna/mL fluid:

- Glucose Injection 5%
- Sodium Chloride Injection 0.9%
- Sodium Chloride and Glucose Injection, with concentrations ranging from 0 - 0.9% Sodium Chloride, and 0 - 5% Glucose
- Lactated Ringer's Injection

Solutions of mesna when diluted in the solutions nominated above may be prepared and, if necessary, stored for short periods under refrigeration. However, the diluted solutions do not contain an antimicrobial preservative, and in order to reduce microbial hazards it is recommended that dilution should be effected as soon as practicable prior to use, and infusion commenced as soon as practicable thereafter.

Infusion should be started within 6 to 8 hours of preparation of the admixture and completed within 24 hours, with any residue discarded.

Diluted solutions should be inspected visually before use. Any solutions which are discoloured, hazy or contain visible particulate matter should not be used.

Compatibility and Stability

In vitro mesna is incompatible with cisplatin. The combination of an oxazaphosphorine cytostatic agent with mesna and cisplatin in the same infusion solution is not stable and is not to be used.

Holoxan (ifosfamide, 3mg/mL) may be admixed with diluted mesna solutions 1.5 to 3.0 mg/mL (0.15 to 0.3%). Admixtures of Holoxan 3.0 mg/mL and UROMITEXAN 1.5 to 3.0

mg/mL stored in PVC plastic bags and refrigerated have been shown to be chemically and physically stable for 24 hours when diluted in the following sterile solutions:

- Sodium Chloride Injection 0.9%
- Compound Sodium Lactate Injection
- Glucose Injection 5%
- Glucose 2.5% + Sodium Chloride 0.45% Injection

However, because of the risk of microbial contamination it is recommended that admixtures be administered within 6 to 8 hours of preparation.

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 100 mg/kg without any toxic effect on haematopoiesis, hepatic or renal function or the CNS.

Presentation

UROMITEXAN (mesna) Solution for Injection 100mg/mL

200 mg Single Dose Ampoule. Box of 15 ampoules of 2mL
(colour-ring coding turquoise/yellow)

400 mg Single Dose Ampoule. Box of 15 ampoules of 4 mL
(colour-ring coding blue/green)

1 g Single Dose Ampoule. Box of 15 ampoules of 10 mL
(colour-ring coding blue/green)

Storage Conditions

UROMITEXAN has a shelf life of 5 years when stored below 25°C (unopened vials).

Medicine Classification

Prescription Medicine

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