MESNA Stada® 400 mg/4ml Concentrated Solution for Injection

Name of the medicinal products

MESNA Stada 400mg/4ml Concentrated Solution for injection

Description and composition

1 vial [ampoule] MESNA Stada 400 mg with 4 ml solution for injection contains: mesna 400 mg (100 mg/ml)

Excipient: 1 ml solution for injection contains 14.3 mg sodium.

Excipients: Sodium edetate (Ph. Eur.), sodium hydroxide, water for injections.

Pharmaceutical form
Solution for injection
Clear, colourless solution, free from particles.

Clinical particulars
Therapeutic indications

Prevention of urinary tract toxicity of oxazaphosphorines (e.g.ifosfamide, cyclophosphamide or trofosfamide).

In the case of a tumour therapy with ifosfamide MESNA Stada must always be given. In the case of a tumour therapy with cyclophosphamide or trofosfamide, MESNA Stada must always be given when dosages above 10 mg/kg are used and in patients at risk. Risks are in particular: previous radiation therapy in the area of the true pelvis, cystitis following previous therapy with ifosfamide, cyclophosphamide or trofosfamide and a history of uropathy.

Posology and method of administration

IV: Unless prescribed otherwise, MESNA Stada is normally administered intravenously to adults at a dose of 20% of the oxazaphosphorine dose at time zero (the time of administration of the oxazaphosphorine), and then at 4 and 8 hours.

Example of MESNA Stada administration with oxazaphosphorine injection:			
Hour (Time)	0 (8 hrs)	4 (12 hrs)	8 (16 hrs)
Oxazaphosphorine dose	40mg/kg body weight	-	-
MESNA Stada dose	8mg/kg body weight	8mg/kg body weight	8mg/kg body weight

Clinical experience with children has shown that it is beneficial in individual cases to give MESNA Stada at shorter intervals (eg, every 3 hrs, total MESNA Stada dose = 60% of oxazaphosphorine dose). With very high-dose oxazaphosphorine cytostatic therapy (eg, before bone marrow transplantation), the total MESNA Stada dose can be increased to between 120% and 160% of the oxazaphosphorine dose. It is recommended that after administration of 20% MESNA Stada (related to the total dose of oxazaphosphorine) at time 0, the remaining calculated dose should be given continuously IV over a period of 24 hrs with a perfusor. Alternatively, an intermittent bolus injection is possible: For adults 3 x 40% (at times 0, 4, 8 hrs) or 4 x 40% (at times 0, 3, 6, 9 hrs), respectively. For children due to more frequent micturition, the bolus injections should always be given in 3-hr intervals (eg, 20% at times 0, 1, 3, 6, 9, 12 hrs). Instead of a bolus injection, short infusions of 15-min duration are possible. With a continuous infusion of ifosfamide (Holoxan), it has been shown to be of benefit to give MESNA Stada at time zero following the initial 20% bolus injection (start of infusion, time 0), followed by infusion to up to 100% of the ifosfamide dose, and to continue uroprotection for a further 6 to 12 hours after termination of the ifosfamide infusion.

Example of the Administration of MESNA Stada with Ifosfamide infusion			
Time (hrs)	**0-24**	**30**	**36**
Ifosfamide infusion	5 g/m^2 body surface (equal 125 mg/kg body weight)	-	-
MESNA Stada bolus dose	*1 g/m^2 body surface (equal 125 mg/kg body weight)	-	-
MESNA Stada infusion	Up to 5 g/m^2 body surface (equal 125 mg/kg body weight)	Up to 2.5 g/m^2 body surface (equal 62.5 mg/kg body weight)	
*Start of the infusion.			

Contraindications

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

As mesna is only indicated in combination with oxazaphosphorines, the contraindications which apply to cyclophosphamide, ifosfamide and trofosfamide should also be observed.

Special warnings and precautions for use

The protective effect of MESNA Stada applies only to the urinary tract. Other precautions and concomitant measures recommended for the use of oxazaphosphorines (ifosfamide, cyclo-phosphamide, trofosfamide) are not affected and should be continued.

A false-positive detection of urinary ketones may arise during the treatment with MESNA Stada. The colour is red-violet rather than violet, it is less stable and it will fade immediately on the addition of glacial acetic acid.

This medicinal product contains less than 1 mmol sodium (23 mg) per 1ml solution for injection.

The occurrence of hypersensitivity reactions (hyperegic reactions) following MESNA Stada therapy has been reported more frequently in patients with autoimmune disorders than in tumour patients. Skin and mucosal reactions have been observed (rash, urticarial, exanthema, enanthema), a rise in liver transaminases and non-specific common symptoms like fever, exhaustion, nausea and vomiting. Isolated circulatory reactions with hypotension and tachycardia have been observed as well. Protection of the urinary tract with MESNA Stada should therefore only be undertaken in such patients following careful risk-benefit analysis and under medical supervision.

Interactions with other medicinal products and other forms of interactions

In vitro, Mesna is incompatible with Carboplatin, Cisplatin and Nitrogen mustard.

Pregnancy and lactation

As MESNA Stada is only used in combination with oxazaphosphorines (ifosfamide, cyclophosphamide or trofosfamide) for uroprotection in cytostatic therapy, criteria of such cytostatic therapy apply for use in pregnancy and lactation. Animal experiments have shown no evidence of embryotoxic or teratogenic effects of MESNA Stada.

Effects on ability to drive and use machines

Administration of MESNA Stada may result in an impairment caused by nausea and vomiting, also due to the concurrent tumour therapy.

Undesirable effects

Isolated cases of partially organ-related hypersensitivity reactions (hyperergic reactions) eg, skin and mucosal reactions of varying extent and severity (itching, redness, vesiculation), local tissue swelling (urticarial oedema), rare cases of drop in blood pressure and increased pulse rate >100/min (tachycardia) due to severe acute hypersensitivity reactions (anaphylactoid reactions), and also a transient rise in certain liver function tests (transaminases) have been reported. There have been rare cases of venous irritation at the injection site. In a tolerability study using high IV and oral doses of mesna, single doses of ≥60 mg/kg body weight were associated with nausea, vomiting, diarrhea, headache, joint pain, drop in blood pressure, tachycardia, skin reactions, exhaustion and weakness. During treatment, the previously mentioned side effects cannot always be clearly differentiated from those caused by oxazaphosphorines (Holoxan, Endoxan), or other concomitant medication.

Overdose

MESNA Stada® 400 mg/4ml Concentrated Solution for Injection

A specific antidote to mesna is not known.

In connection with the anaphylactoid reactions in patients with autoimmune disease described in the section of contraindication and undesirable effect, suitable emergency medicine should be available.

Overdose may lead to the reactions described in section on undesirable effects (single doses exceeding 60 mg/kg BW).

Pharmacological properties

Pharmacodynamic properties

Substance or indication group
Sodium 2-mercaptoethanesulphonate
Antidote to oxazaphosphorines

The mode of action of the uroprotector mesna is based on the stabilisation of the urotoxic hydroxy metabolites of oxazaphosphorines on the one hand and on the other hand on formation of non-toxic compounds with acrolein. A regional detoxification in the kidneys and the lower urinary tract is achieved due to this reaction.

Pharmacokinetic properties

Following administration, the mesna monomer (free thiol compound) is rapidly metabolised to mesna disulphide (dimesna) in serum, which is again reduced in considerable amounts to the free thiol compound following glomerular filtration.

Mesna is almost exclusively eliminated via the kidneys and hardly via the bile. Following administration, renal elimination begins immediately and is largely completed after 8 hours. Within the first 4 hours after administration, mesna is mainly eliminated as free SH compound and then almost exclusively in form of the disulphide (dimesna).

Bioavailability
With regard to protection of the urinary bladder, the relevant compartment is the urine, where approx. 30% is bioavailable as free SH mesna after intravenous administration.

Preclinical safety data

Mesna is a pharmacologically and physiologically almost inert and non-toxic thiol compound which is excreted rapidly via the kidneys and does not penetrate tissues. In animal experiments, mesna showed no mutagenic, carcinogenic or teratogenic properties.

Pharmaceutical particulars

Incompatibilities

In vitro, mesna is incompatible with carboplatin, cisplatin and nitrogen mustard.

Shelf life

The shelf life of MESNA Stada is 3 years.

Chemical and physical in-use stability after dilution with 5% glucose solution and a solution containing ifosfamide has been demonstrated for 4 days at 2°C to 8°C and after dilution with 0,9% sodium chloride solution and a solution containing ifosfamide for 4 days at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Do not store above 30°C.

Single use vial – discard appropriately any contents remaining after first use.

Nature and contents of container

Vials [ampoules]

Packs with 1 x 1, 10 x 1 or 15 x 1 vial MESNA Stada 400 mg

Not all presentation will be available locally

Manufactured by:

Haupt Pharma Wolfratshausen GmbH
Pfaffenrieder Strasse 5
82515 Wolfratshausen, Germany

Date of revision of the text:

May 2022

[SINMES400170522]