SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

MESNA-cell® 100 mg/ml

Active substance: mesna

2. Qualitative and quantitative composition

1 ampoule MESNA-cell® with 4 ml solution for injection contains 400 mg mesna.

1 vial MESNA-cell® with 10 ml solution for injection contains 1,000 mg mesna.

1 vial MESNA-cell® with 50 ml solution for injection contains 5,000 mg mesna.

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

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection

Clear, colourless solution, free from particles

4. Clinical particulars

4.1 Therapeutic indications

Prevention of urinary passage toxicity of oxazaphosphorines (the active components of Ifosfamide, Cyclophosphamide, Trofosamide), in particular in high-risk patients with previous radiation therapy in the area of the lesser pelvis, cystitis with previous Ifosfamide, Cyclophosphamide or Trofosamide, urinary passage diseases in anamnesis.

4.2 Posology and method of administration

Unless otherwise prescribed, MESNA-cell® is usually administered in adults intravenously at time 0 (time of oxazaphosphorine administration), after 4 hours and after 8 hours, with each dose being 20% of the oxazaphosphorine dose.

Example of MESNA-cell® administration in oxazaphosphorine injection:

Hours (Time)	0 (8 a.m.)	4 (12 a.m.)	8 (4 p.m.)
Oxazaphosphorine dose	40 mg/kg BW	--	--
MESNA dose	8 mg/kg BW	8 mg/kg BW	8 mg/kg BW

Therapeutic experience in children has shown that a more frequent (e.g six times) administration at shorter intervals (e.g 3 hours) is useful.

In the case of continuous infusions of ifosfamide, it has proven effective to administer a mesna bolus injection (20% of the ifosfamide dose) at time 0 (start of infusion) and to add MESNA-cell® to the continous infusion at a dose of up to 100% of the ifosfamide dose. To maintain the uroprotection after the end of the ifosfamide infusion, a mesna dose equivalent to up to 50% of the ifosfamide dose should be given for further 6 - 12 hours.

Example of MESNA-cell® administration with a 24-hour ifosfamide infusion:

Hours	0 h	24 h 30 h 36 h
Ifosfamide dose	5 g/m^2 BSA (approx. 125 mg/kg BW)	
Mesna bolus dose	1 g/m^2 BSA (approx. 25 mg/kg BW)	
Mesna addition to ifosfamide infusion	up to 5 g/m^2 BSA (approx. 125 mg/kg BW)	
Mesna after end of the 24h-ifosfamide infusion		up to 2.5 g/m^2 BSA (approx. 62.5 mg/kg BW)

Duration of treatment
The duration of treatment with MESNA-cell® is defined by the duration of the oxazaphosphorine therapy.

4.3 Contraindications

- Hypersensitivity to the active substance, other thiol compounds or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In the presence of autoimmune disease, there is an increased risk to develop allergic or anaphylactoid reactions (see also Undesirable Effects). Therefore, protection of the urinary tract with MESNA-cell® should only be carried out in these patients after a careful risk-benefit assessment and under medical supervision.

Please refer to section 4.6 for use in pregnancy and lactation and other precautions and concomitant measures.

Excipients
MESNA-cell® contains 14.3 mg sodium per 1 ml solution for injection, equivalent to 0.72% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This should be considered in patients on a sodium-controlled (low sodium/low salt) diet.

4.5 Interactions with other medicinal products and other forms of interactions

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

4.6 Fertility, pregnancy and lactation

Animal experiments have shown no evidence of embryotoxic or teratogenic effects of mesna.

As MESNA-cell® 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.

4.7 Effects on ability to drive and use machines

Known adverse effects such as nausea, vomiting or circulatory reactions of MESNA-cell® may, even when used as directed, change the ability to react to such an extent that the ability to actively participate in road traffic or to use machines is impaired. As MESNA-cell® is administered in combination with oxazaphosphorines, additional its effects on the ability to react must also be taken into account.

4.8 Undesirable effects

In this section frequencies of undesirable effects are defined as follows: 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 (cannot be estimated from the available data).

Commonly the occurrence of anaphylactoid and other hyperergic reactions have been reported, e.g. in some cases in connection with the reduction of the thrombocyte count, were reported after the use of mesna. This risk is approx. 3.5 times higher in patients with autoimmune disease than in patients with tumour disease (without autoimmune disease).

Skin and mucous membrane reactions, such as urticaria, itching, exanthema up to the formation of blisters, enanthema, Lyell's syndrome, Stevens-Johnson syndrome, local tissue swellings, conjunctivitis as well as unspecific general symptoms such as fever, chills, face redness, cough, pharyngitis, fatigue, tiredness, headache, back pain, arthralgia, nausea and vomiting, flatulence, diarrhoea, constipation, colics (e.g. abdominal pain), anorexia, influenza-like symptoms occurred. Circulatory reactions such as a drop in blood pressure and tachycardia (pulse rate >100/min), tachypnoea, hypertension, ST-segment elevation and myalgia and also a transient increase of values of different liver function tests (such as e.g transaminases) were observed. Uncommonly, local oedema and venous irritation at the injection site occurred.

In a tolerability study with high intravenous or oral doses of mesna, nausea, vomiting, diarrhoea, headache, limb and joint pain, drop in blood pressure and tachycardia, skin reactions, exhaustion, weakness, depression, irritability and exanthema occurred, when a single dose of 60 mg/kg body weight was administered. During treatment, the undesirable effects mentioned above cannot always be distinguished from those of the oxazaphosphorines or other concomitant medication.

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, hypertension, face redness, circulatory reactions	

SOC	Common	Uncommon	Rare	Very rare
Respiratory, thoracic and mediastinal disorders				Tachypnoea, cough
Gastrointestinal disorders	Nausea, vomiting		Diarrhoea	Flatulence, constipation, colics, abdominal pain
Skin and subcutaneous tissue disorders	Itching, exanthema, enanthematous skin reactions	Urticaria		Stevens-Johnson syndrome, Lyell's syndrome
Musculoskeletal and connective tissue disorders		Local tissue swelling	Back pain	Arthralgia, Myalgia, limb pain, joint pain
General disorders and administration site conditions	Fever	Local oedema, venous irritation at the injection site, chills	Exhaustion, weakness, mucous skin reactions, fatigue, tiredness	Influenza-like symptoms
Investigations			Increase of the values of different liver function tests	Reduction of the thrombocyte count, pulse rate > 100/min, ST-segment elevation
Injury, poisoning and procedural complications				Toxic reactions

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose
Treatment of intoxication
A specific antidote to mesna is not known.

Symptoms of intoxication
In connection with the anaphylactoid reactions in patients with autoimmune disease described in the sections 4.3 and 4.8, suitable emergency medicine should be available.

Overdose may lead to the reactions described in section 4.8 (single doses exceeding 60 mg/kg BW).

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Detoxification agent for the treatment with cytostatic agents, antidote to oxazaphosphorines.
ATC code: V03AF01

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.

5.2 Pharmacokinetic properties
Following administration, the free thiol compound mesna is rapidly metabolised to mesna metabolite mesna disulphide 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. Renal elimination begins immediately after application. During the first 4 hours after single application the elimination is performed mainly as free SH compound, afterwards almost exclusively in form of disulphide. After about 8 hours the renal elimination is largely completed.

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.

5.3 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. The detoxifying effect is limited to the kidneys and the urinary tract, the systemic side effects and the antitumour efficacy of oxazaphosphorines are not influenced. In animal experiments, mesna showed no mutagenic, carcinogenic or teratogenic properties.

6. Pharmaceutical particulars

6.1 List of excipients
Disodium 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 this is carried out via separate accesses. These medicines do not affect each other in the body.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

Mesna-Cell can be diluted with 5% glucose solution or 0.9% sodium chloride solution.
From a microbiological point of view, the ready-to-use preparation should be used immediately. If the ready-to-use preparation is 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 under controlled and validated aseptic conditions.

6.4 Special precautions for storage
MESNA-cell® 100 mg/ml: 400 mg
Store below 30°C.

MESNA-cell® 100 mg/ml: 1,000 mg
MESNA-cell® 100 mg/ml: 5,000 mg
Store below 25°C.

6.5 Nature and contents of container
MESNA-cell® 100 mg/ml: 400 mg
10 ampoules

MESNA-cell® 100 mg/ml: 1,000 mg
1 or 5 vials

MESNA-cell® 100 mg/ml: 5,000 mg
1 vial

6.6 Instructions for use and handling

MESNA-cell® is for single use only. Discard appropriately any contents remaining after first use.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. Manufacturer

STADAPHARM GmbH
Stadastraße 2-18, 61118 Bad Vilbel
Germany

8. Registration holder

MBI Pharma Ltd.
P.O.B 5061, Kadima
Israel

9. Registration number

154-04-34131

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