SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Mesna 100 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution for injection/infusion contains 100 mg mesna.

Each 2 ml ampoule contains 200 mg mesna.
Each 4 ml ampoule contains 400 mg mesna.

Excipient(s) with known effect:
Each ml of solution contains 0.610 mmol/ml of sodium.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Solution for injection/infusion.

The solution is a clear colourless, sterile solution for injection, free from visible particle

Osmolarity: 1000 mOsmol/L to 1500 mOsmol/L.

pH between 6.50 and 7.30

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the prevention of urothelial toxicity including haemorrhagic cystitis, microhaematuria and macrohaematuria in patients treated with oxazaphosphorine (e.g. ifosfamide, cyclophosphamide and trofosfamid), in doses considered to be urotoxic, especially in patients considered to be at risk due to prior pelvic irradiation, cystitis from prior oxazaphosphorine treatment or anamnestic urinary tract diseases.
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 nontoxic levels. This usually occurs within 8-12 hours after the end of oxazaphosphorine treatment but may vary depending on the scheduling of oxazaphosphorine. 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.

Where oxazaphosphorine is used as an iv bolus: Mesna is given by intravenous injection over 15-30 minutes at 20% of the simultaneously administered oxazaphosphorine on a weight for weight basis (w/w). The same dose of mesna is repeated after 4 and 8 hours. The total dose of mesna is 60% (w/w) of the oxazaphosphorine dose. This is repeated on each occasion that the cytotoxic agents are used.

Example dosages schedule:

<table>
<thead>
<tr>
<th></th>
<th>0 HRS</th>
<th>4 HRS</th>
<th>8 HRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxazaphosphorine</td>
<td>40 mg/kg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mesna 100 mg/ml solution for injection/infusion</td>
<td>8 mg/kg</td>
<td>8 mg/kg</td>
<td>8 mg/kg</td>
</tr>
</tbody>
</table>

If necessary the dose of mesna can be increased to 40% of the oxazaphosphorine dose given four times at three hourly intervals (0, 3, 6 and 9 hours). (Total dose = 160% (w/w) of the oxazaphosphorine dose). This larger dose is recommended in children, in patients whose urothelium may be damaged from previous treatment with oxazaphosphorine or pelvic irradiation, or in patients who are not adequately protected by the standard dose of mesna.

Example dosage schedule:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>3 HRS</th>
<th>6</th>
<th>9 HRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxazaphosphorine</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mesna 100 mg/ml solution for injection/infusion</td>
<td>16 mg/kg</td>
<td>16 mg/kg</td>
<td>16 mg/kg</td>
<td>16 mg/kg</td>
</tr>
</tbody>
</table>

Where oxazaphosphorine is used as a 24-hour infusion: Mesna can be used as a concurrent infusion. An initial 20% (w/w) of the total oxazaphosphorine dose is given as an i.v. bolus, then an infusion of 100% (w/w) of the oxazaphosphorine over 24 hours, followed by a further 12-hour infusion of up to 50% (w/w) of the oxazaphosphorine dose. Total mesna dose = <170% of the oxazaphosphorine dose.

Example dosage schedule:

<table>
<thead>
<tr>
<th></th>
<th>0 hrs</th>
<th>0-24 hrs</th>
<th>24 hrs</th>
<th>28 hrs</th>
<th>32 hrs</th>
<th>36 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxazaphosphorine</td>
<td>-</td>
<td>5 g/m² infusion</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Mesna 100 mg/ml solution for injection | 1 g/m² i.v. | 5 g/m² infusion | 3 g/m² infusion |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g/m² i.v.</td>
<td>1 g/m² i.v.</td>
<td>1 g/m² i.v.</td>
</tr>
</tbody>
</table>

Where oxazaphosphorine is used as a long-term infusion:
An initial 20% (w/w) of the first 24 hour oxazaphosphorine dose is given as an i.v. bolus as the oxazaphosphorine infusion starts. Then each 24 hour infusion of oxazaphosphorine is given with a concurrent 24 hour infusion (100% w/w) of mesna. A 12 hour infusion of mesna (60% w/w) of the final 24 hour dose of oxazaphosphorine should be commenced as the oxazaphosphorine mesna infusion finishes.

Example dosage schedule:

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 hrs</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
</tr>
<tr>
<td>Oxazaphosphorine</td>
<td>-</td>
<td>2 g/m² infusion</td>
<td>2 g/m² infusion</td>
</tr>
<tr>
<td>Mesna 100 mg/ml solution for injection</td>
<td>0.4 g/m² iv</td>
<td>2 g/m² infusion</td>
<td>2 g/m² infusion</td>
</tr>
</tbody>
</table>

The final 12-hour infusion of mesna, after long-term or 24 hour infusion of oxazaphosphorine, may be replaced by boluses at 28, 32 and 36 hours, each of 20% (w/w) of the oxazaphosphorine dose, or by oral mesna. Mesna can be mixed in the same infusion bag as the oxazaphosphorine.

Paediatric population:
Children generally urinate more frequently than adults and therefore it may be necessary to shorten the interval between doses and/or to increase the number of individual doses. The dose of mesna can be increased to 40% of the oxazaphosphorine dose given four times at three hourly intervals (0, 3, 6 and 9 hours) (Total dose = 160% w/w of the oxazaphosphorine dose).

Older people:
No specific information is available. Clinical trials have included patients over 65 and no adverse reactions specific to this age group have been reported.
4.3 **Contraindications**
Known hypersensitivity to the active substance, any thiol-containing compounds or to any of the excipients listed in section 6.1.

4.4 **Special warnings and precautions for use**
In patients with autoimmune disease an increased incidence of pseudo allergic reactions compared to cancer patients has been reported. Reactions of the skin and mucous membranes (pruritus, rash, urticaria, exanthema, enanthema), transient increases in transaminases as well as non-specific general symptoms such as fever, fatigue, nausea and vomiting were observed. In rare cases, circulatory reactions such as hypotension and tachycardia occurred. Thus the prevention of urotoxicity with mesna should only be undertaken after medical guidance and careful consideration of risks and benefits.

Treatment with mesna may cause false positive reactions in dipstick tests for ketone bodies, (e.g. Rothera's test, NMultistix reagent strip) and false positive or false negative reactions in the dipstick tests for erythrocytes in the urine. The colour reaction for ketones is reddish purple rather than purple, it is less stable, and fades immediately on the addition of glacial acetic acid. To exactly determine the presence of erythrocytes in the urine, urinary microscopy is recommended.

Mesna Injection contains 0.610 mmol/ml sodium (1.22 mmol sodium per 2 ampoule and 2.44 mmol per 4ml ampoule).

This should be taken into consideration by patients on a controlled sodium diet.”

4.5 **Interaction with other medicinal products and other forms of interaction**
The systemic effects of oxazaphosphorines are not affected by mesna. In clinical trials it was shown that overdoses of mesna did not diminish the acute toxicity, subacute toxicity, leucocytic activity, and immunosuppressive efficacy of oxazaphosphorines. Animal studies with oxazaphosphorine and cyclophosphamide on a variety of tumours have also demonstrated that mesna does not interfere with their antineoplastic activity.

Mesna 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 glucosides.

4.6 **Fertility, pregnancy and lactation**

**Pregnancy**
Pregnancy and lactation are contraindications for cytostatic treatment, and consequently Mesna 100 mg/ml solution for injection/infusion is not likely to be used under these circumstances.

Should an individual patient be undergoing oxazaphosphorine therapy during pregnancy then Mesna 100 mg/ml solution for injection/infusion should be administered to this patient.

**Breast-feeding**

Mothers should not breast-feed whilst being treated with these drugs.

**Fertility**

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

### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Known adverse reactions of mesna like nausea, vomiting or circulatory reactions can impair the ability to drive and use machines also at recommended doses.

### 4.8 Undesirable effects

Hypersensitization reactions have been reported more frequently by immune-compromised patients than by those with cancer. Cases of venous irritation at site of injection have been reported. During treatment it is difficult to clearly assess adverse reactions to Uromitexan from those related to other drugs administered at the same time.

Clinical studies on subjects of age beyond 65 have not shown age-specific adverse reactions.

Frequency categories are as follows:

- **Very common**: ($\geq$1/10),
- **Common**: ($1/100$ to $<1/10$),
- **Uncommon**: ($1/1000$ to $<1/100$),
- **Rare**: ($1/10000$ to $<1/1000$),
- **Very rare**: ($<1/10000$ including isolated reporting).

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Common ($\geq1/100$ and $&lt;1/10$)</th>
<th>Uncommon ($1/1000$ and $&lt;1/100$)</th>
<th>Rare ($1/10000$ and $&lt;1/1000$)</th>
<th>Very rare ($&lt;1/10000$ including isolated reporting)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Immune system</td>
<td>Hypersensitivity</td>
<td>Anaphylactoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorders</td>
<td>Reactions, Hyperergic Reactions</td>
<td>Reactions, Allergic Reactions</td>
<td>Disorders</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>---------------------------------</td>
<td>------------------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>Irritability, Depression</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Conjunctivitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension, Hypertension, Flushing, Cardiovascular Reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Tachypnea, Cough</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, Vomiting</td>
<td>Diarrhea</td>
<td>Flatulence, Constipation, Colic, Abdominal Pain</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Itching, Rashes, Skin Reactions, Enanthem</td>
<td>Urticaria</td>
<td>Steven-Johnson Syndrome, Lyell Syndrome</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Ocal Tissue Swelling</td>
<td>Back Pain</td>
<td>Arthralgia, Myalgia, Joint Pain, Articular Pain</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fever, Local Edema, Vein Irritation at Injection Site, Chills</td>
<td>Fatigue, Asthenia, Mucocutaneous Reactions, Influenza-like Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Increase in the Values of Various Liver Function Tests</td>
<td>Decrease in Platelet Count, Pulse Rate &gt;100/min, ST Elevation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and</td>
<td></td>
<td></td>
<td>Toxic Reactions</td>
<td></td>
</tr>
</tbody>
</table>
**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. You can also report any side effects directly
United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

### 4.9 Overdose
Healthy volunteers given single bolus doses of 70 mg/kg mesna showed no evidence of major toxic side-effects.
A specific antidote to mesna is not known.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group:* detoxifying agent for antineoplastic treatment

*ATC Code:* VO3AF01.

Mesna is an antidote preventing urotoxic side effects associated with cancer chemotherapy based on oxazaphosphorine. Pharmacological studies have shown that mesna has no intrinsic pharmacodynamics activity. The mechanism of action is based on the stabilisation of the urotoxic hydroxyl metabolites of the oxazaphosphorines and on the formation of atoxic addition products with acrolein. By this, a regional detoxification of kidneys and the urinary tract is achieved.

#### 5.2 Pharmacokinetic properties

**Absorption**

Mesna, a free thiol, is easily and rapidly transformed by auto-oxidation into its only metabolite mesna-disulphide (dimesna).

**Distribution**

Dimesna remains in the intravascular compartment and is quickly transported to the kidneys. In the epithelium of renal tubuli, dimesna is again reduced to the free thiol compound, which is then able to react chemically in the urine with toxic oxazaphosphorine metabolites.
Elimination

Elimination (being almost exclusively renal) starts immediately after administration. Excretion is as the free thiol (mesna) in the first 4 hours after a single dose, and almost exclusively as the disulphide (dimesna) thereafter. Renal elimination is almost complete after approximately 8 hours.

Approximately 30% of an intravenous dose is bioavailable as free thiol (mesna) in the urine.

5.3 Preclinical safety data

Animal studies have shown no evidence of mutagenic, carcinogenic or teratogenic effects of mesna.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Sodium hydroxide
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

30 months.

After opening: The product must be used immediately.

For single use. Any unused solution must be discarded.

Mesna Injection is chemically compatible with Compound Sodium Lactate injection, 0.9 % saline and with 5.0 % dextrose containing diluents for 24 hours.

For microbiological point of view, product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of
6.4 Special precautions for storage
Do not store above 30°C. Keep the container in the outer carton to protect from light.

6.5 Nature and contents of container
The solution is a clear colourless, sterile solution for injection, free from visible particle
2 ml and 4 ml type I clear glass ampoules in packs of 5 or 10 or 25.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Mesna Injection is chemically compatible with Compound Sodium Lactate injection, 0.9 % saline and with 5.0 % dextrose containing diluents for 24 hours.

7 MARKETING AUTHORISATION HOLDER
Claris Lifesciences UK Limited
Crewe Hall, Crewe, Cheshire CW16UL

8 MARKETING AUTHORISATION NUMBER(S)
PL 20568/0044

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY
25/09/2014

10 DATE OF REVISION OF THE TEXT
25/09/2014