PRODUCT MONOGRAPH

MESNA for Injection
100 mg / mL
Uroprotector

Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON M9W 0C8

Date of Preparation:
March 30, 2015

Control No.: 182981
PRODUCT MONOGRAPH

MESNA for Injection

100 mg / mL

Uroprotector

ACTION

Mesna is rapidly and easily converted by auto-oxidation to its only metabolite disodium 2,2'-dithio-bis ethane sulfonate (mesna disulfide, dimesna), forming a disulphide link. Following intravenous injection, only a small portion of the administered dose is detected in the blood as a reactive thiol compound (mesna). Mesna disulphide remains in the intravascular space and is rapidly forwarded to the kidney. In the renal tubular epithelium, a considerable proportion of mesna disulphide is again reduced to a free thiol compound, presumably by mediation of glutathione reductase. It is then capable of chemically reacting with acrolein or other urotoxic oxazaphosphorine metabolites in the urine, thereby developing its detoxifying activity.

The first and most important step towards detoxification is the addition of mesna to the double bond of acrolein, resulting in the formation of a stable thio ether which could 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. By such stabilization, mesna inhibits the degradation of 4-hydroxy cyclophosphamide or 4-hydroxy ifosfamide and hence the formation of acrolein. This intermediate deactivated product could also be detected by chromatographic urinalysis.

INDICATIONS

Mesna is indicated for the reduction and prevention of urinary tract toxicity (hemorrhagic cystitis) of oxazaphosphorines. (See ADVERSE REACTIONS sections of the CYTOXAN and Ifosfamide for Injection, USP Product Monographs.)

CONTRAINDICATIONS

Mesna is contraindicated in individuals with a known hypersensitivity to it.

WARNINGS

The protective effect of mesna applies only to the urotoxic effects of oxazaphosphorines. Additional prophylactic or accompanying measures recommended during treatment with oxazaphosphorines are thus not affected and should not be discontinued.
**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.

**PRECAUTIONS**

Mesna treatment may cause false positive reactions in tests for ketone bodies in the urine. The colour reaction is reddish purple rather than purple. The reddish purple colour is less stable, and fades immediately by adding glacial acetic acid.

**Use in Children**

Mesna has been administered to patients as young as 13 years of age. Due to the presence of benzyl alcohol, the product should not be used in neonates or infants.

**Use in Pregnancy**

Although the use of mesna in pregnant women has not been established, animal studies have not revealed any embryotoxic or mutagenic effects. However, in view of the fact that oxazaphosphorines are not recommended during pregnancy, this would eliminate the need for mesna.

**ADVERSE REACTIONS**

At recommended doses, side effects are not usually observed.

The following adverse reactions have been reported in a phase I trial in healthy volunteers:

1) diarrhea;
2) abdominal pain;
3) headache;
4) pain in limbs and joints;
5) transient drop in blood pressure;
6) increase in pulse rate.

These reactions occurred at doses of 60 mg / kg or more, given as a single bolus.

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, USP (one part mesna solution to three parts water).
SYMPTOMS AND TREATMENT OF 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 hematopoiesis, hepatic and renal function or the central nervous system.

DOSAGE AND ADMINISTRATION

Mesna should be administered by intravenous injection, usually at 20% of the respective oxazaphosphorine dose, at times 0 (= administration of the cytostatic agent), 4 and 8 hours. In the case of Ifosfamide for Injection, USP, the usual dose of Mesna is 10-12 mg / kg intravenous at 0, 4 and 8 hours after the Ifosfamide for Injection, USP dose. (See DOSAGE AND ADMINISTRATION sections of the CYTOXAN and Ifosfamide for Injection, USP Product Monographs.)

In the treatment of children, and particularly when administering very high doses, such as required when conditioning patients for bone-marrow transplantations, the Mesna doses should be given at 0, 1, 3, 6, 9 and 12 hours or dosage increased to 30% of the respective oxazaphosphorine dose.

Oral administration of mesna, e.g., in patients with poor veins, is also feasible. Mesna is then given either at doses of 20% of the oxazaphosphorine dose at time 0 hour by the parenteral route, followed by oral doses of 40% of the oxazaphosphorine dose after 4 and 8 hours, taken in juice or cola, or in 3 oral doses of 40% of the oxazaphosphorine dose at times 0, 4 and 8 hours.
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Mesna
Chemical Name: Sodium 2-mercaptopethanesulfonate

Structural Formula: \( \text{HS-CH}_2\text{-CH}_2\text{-SO}_3^- \text{Na}^+ \)

Molecular Formula: \( \text{C}_2\text{H}_5\text{O}_3\text{S}_2\text{Na} \)

Molecular Weight: 164.18

Description:
Mesna is a white to slightly cream-coloured crystalline or microcrystalline powder with a characteristic odour. It is freely soluble in water, sparingly soluble in methanol and practically insoluble in the usual organic solvents.

Composition:

Each mL of Mesna for Injection contains: 100 mg Mesna, 10.4 mg Benzyl Alcohol, Edetate Disodium, Water for Injection, and Sodium Hydroxide for pH adjustment.

STABILITY AND STORAGE RECOMMENDATIONS

Store the vials between 15 °C - 30 °C. Vials must be discarded 28 days after initial puncture.

Solutions for Intravenous Infusion

- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP

Solutions for infusion should be made up at a concentration of 1 mg/mL or greater.

Stability of Solution

Storage: Solutions for infusion should be used within 24 hours, if stored below 25 °C, or 48 hours if stored refrigerated (2 °C - 8 °C), from the time of preparation.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration. The unused portion should be discarded.
AVAILABILITY OF DOSAGE FORMS

Mesna for Injection is available as 100 mg / mL in 10 mL multiple-dose vials as follows:

C730310 10 mL vials in packages of 10 vials.

PHARMACOLOGY

Mesna and dimesna are absorbed from the intestine and during absorption, dimesna undergoes reduction. In the plasma, Mesna is rapidly oxidized by a metal-dependent reaction. Both Mesna and dimesna pass unchanged through hepatic vasculature, are not taken up in the liver cells and are not excreted in bile. In the kidney, dimesna is subject to glomerular filtration and subsequently reabsorbed, whereupon reduction to the pharmacologically active thiol form occurs in the renal tubular epithelium, and the thiol is then re-excreted into the tubular lumen. Reduction of dimesna occurs in intestinal and renal epithelial cells by a mechanism involving the enzymes thiol transferase and glutathione reductase.

In guinea pigs, the elimination half-life was found to be 1.48 hours following intravenous administration of 200 mg / kg, and 3.9 hours following oral administration of 200 mg / kg. Similar rates were determined in rats and dogs.

Blood levels were quantified after oral administration in all 3 species. Serum half-life was found to be 3.5 hours in the guinea pig, 2.6 hours in the rat, and 2 hours in the dog.

Distribution of Mesna in the tissues was determined in guinea pigs and rats. Following oral administration of 200 mg / kg, it was observed that Mesna does not permeate all body tissues.

In the rat, placental permeability was investigated after oral administration; in the fetus, the placental barrier permits fetal blood levels of only 17.6% of the maternal blood level.

In all 3 animal species, irrespective of the route of administration, dimesna is eliminated in the urine within the first 8 hours at a rate of 38-45% of the administered Mesna dose.

Humans

After intravenous administration of 60 mg / kg Mesna, a half-life of 1.08 hours was established. Renal elimination starts immediately after administration and is largely completed within 8 hours after administration. In the first 4 hours, excretion occurs primarily as a free SH-compound, thereafter occurring almost exclusively in the form of disulphide.

After oral administration of 60 mg / kg, Mesna appears in the blood almost entirely as its disulfide metabolite with a time-lag of 0.36 hour. Maximum serum levels occur after 1.17 hours. The elimination half-life is 1.15 hours. The rate of excretion is not different from that seen after intravenous administration.
Over 60% of the administered oral or intravenous dose (60 mg / kg) is recovered in the urine as mesna or dimesna.

**TOXICOLOGY**

**Acute Toxicity**

Mesna was found to be almost completely non-toxic. The LD$_{50}$ values are as follows:

<table>
<thead>
<tr>
<th>Species</th>
<th>Route of Administration</th>
<th>LD$_{50}$ (mg / kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>intravenous or intraperitoneal oral</td>
<td>1 800-2 050 &gt; 6 100</td>
</tr>
<tr>
<td>Rats</td>
<td>intravenous or intraperitoneal oral</td>
<td>1 225-2 080 &gt; 4 330</td>
</tr>
</tbody>
</table>

In dogs, death was observed after intravenous doses of 400 mg / kg and above, but not after oral doses of up to 2 000 mg / kg.

**Subacute Toxicity**

The low toxicity of Mesna was confirmed in tests for subacute toxicity. In a 6-week study, rats tolerated daily intravenous doses of up to 316 mg / kg without toxic symptoms. The earliest signs of toxicity were seen at doses of 1 000 mg / kg. These included severe body weight loss, leucopenia and anemia.

The kidneys showed distended tubules engorged with urine which had a high protein content and hyaline deposits in the glomerular capillaries.

Dogs tolerated 12 intravenous doses of 200 mg / kg, with vomiting and diarrhea appearing only in the first days of treatment. In a 6-week study, intravenous doses of up to 316 mg / kg were tolerated. The only toxic symptoms were vomiting and diarrhea. In the 100 mg / kg group, these symptoms subsided after about 2 weeks of administration, whereas in the 316 mg / kg group they occasionally persisted to the end of the experiment. Macroscopic and histologic examination did not reveal any drug-related findings.

**Chronic Toxicity**

In a 6-month chronic toxicity test in rats (oral administration of a 40% solution), daily doses up to 2 000 mg / kg were tolerated without drug-related mortality or morbidity.

In a 7-month study in dogs, mesna was administered orally at doses of 31.6, 100 and 316 mg / kg / day. The high dose was subsequently increased to 420 mg / kg / day and further increased to 560 mg / kg / day. One death occurred at 560 mg / kg / day. Other clinical signs included a dose-related incidence of semi-solid stools and sporadic emesis, and a decrease in
motor activity in all dogs. There was a slight increase in alkaline phosphatase, a slight decrease in creatinine, and a slight alteration in the electrolytes in high- and medium-dose dogs.

**Mutagenicity**

No evidence of mutagenicity of Mesna was found in the Ames tests on strains of *Salmonella typhimurium*.

**Reproduction and Teratology**

There was no evidence of interference with fetal development following oral administration to rats (doses of up to 2000 mg / kg from day 8 to day 15 of gestation) and to rabbits (doses of up to 2000 mg / kg from day 7 to day 17 of gestation).

**Carcinogenicity**

Mesna had no carcinogenic effects in rats.
BIBLIOGRAPHY

Clinical


**Preclinical**


