UROMES Injection

Mesna 100 mg/mL

COMPOSITION
Each ampule (1 mL) contains
Mesna ..... 100 mg

DESCRIPTION
Clear, colorless solution in colorless ampules

PHARMACODYNAMICS
Mesna chemically interacts with urotoxic metabolites of oxazaphosphorine derivatives (e.g., ifosfamide, cyclosphamide) to prevent or decrease the incidence and severity of bladder toxicity (e.g., hemorrhagic cystitis, hematuria) induced by these drugs. In urine, mesna reacts chemically with the urotoxic metabolites of ifosfamide or cyclophosphamide(e.g., binding with double-bonds of acrolein) and with their precursors (e.g., binding with 4-hydroxyifosfamide to form 4-sulfoethylthiocyclophosphamide) resulting in detoxification of these metabolites. In addition, mesna enhances urinary excretion of cysteine, which also can react chemically with acrolein, and this effect may contribute to the uroprotective activity of mesna.
Although mesna can undergo alkylation and presumably could reduce the cytotoxic effectiveness of oxazaphosphorine derivatives by interfering with their mechanism of action, mesna and dimesna (the principal form circulating in plasma) are hydrophilic and do not enter most cells, including tumor cells.
Evidence from in vitro and in vivo tumor models and clinical studies in humans indicate that mesna does not deactivate active oxazaphosphorine metabolites in tumor cells nor interfere with the antineoplastic activity of oxazaphosphorine agents. There is some evidence from studies in rats that mesna may decrease the incidence of secondary bladder tumors associated with cyclophosphamide therapy.
Although some sulfhydryl-containing compounds are free radical scavengers and have been shown to be radioprotective, results from in vitro test systems and clinical experience indicate that mesna may safety be used in regimens that include total body irradiation.
Whether mesna affects bone marrow engraftment has not been conclusively determined. In one study, a higher incidence of graft failure was reported when mesna was used concurrently with cyclophosphamide in a limited number of patients receiving an allogenic bone marrow transplant for aplastic anemia; however, there was no clinically important difference in the incidence or severity of graft-versus-host disease (GVHD) in these patients and graft failure has not been reported in other studies.
Like acetylcysteine, mesna reduces the viscosity of pulmonary secretions. The mucolytic effect of the drug depends on the free sulfhydryl group, which reduces the disulfide linkages of mucoproteins.

PHARMACOKINETICS
Efficacy of mesna as an uroprotective agent has been attributed to its distinctive pharmacokinetic profile.
Mesna is oxidized to the chemically stable and pharmacologically inert disulfide metabolite, dimesna (mesna disulfide), in systemic circulation. Subsequently dimesna is partially reduced to the active drug, mesna, in the kidney. In urine, mesna reacts chemically with urotoxic metabolites of oxazaphosphorine derivatives resulting in their detoxification.

Absorption
Following IV or oral administration, mesna is rapidly and almost completely oxidized in systemic circulation to dimesna (mesna disulfide). In a limited number of healthy adults who received a single 800 mg IV dose of mesna, peak plasma concentrations of mesna and dimesna averaged 18.2 and 59.7 ㎍/mL, respectively. Following oral administrations of mesna and dimesna were achieved within 4 and 3 hours and averaged 3.3 and 7.3 ㎍/mL, respectively. Following oral administration, bioavailability of mesna/dimesna based on urinary excretion is approximately 76% compared with IV administration.

Distribution
Because mesna and dimesna are hydrophilic, they remain principally in the intravascular compartment and appreciable distribution outside the compartment does not occur. The volume of distribution for mesna has been reported to be approximately 0.65 L/kg in healthy adults. The drug does not cross the blood-brain barrier.
Studies in rats indicate that approximately 10% of circulating mesna/dimesna is bound to plasma proteins.

Elimination
Plasma concentrations of mesna reportedly decline in a linear manner following IV administration. In healthy adults who received a single 800-mg IV dose of mesna, the terminal plasma elimination half-lives of mesna and dimesna averaged 0.36 and 1.17 hours, respectively.

Mesna and dimesna are eliminated principally in urine, and most of a dose of mesna is eliminated in urine within 4 hours. Because mesna and dimesna are highly water soluble and poorly distibuted outside the vascular compartment, they are rapidly cleared from the plasma by the kidney. In the glomerular filtration, reabsorption in the proximal tubule, and secretion into the tubule lumen, about 30% of filtered dimesna is reduced to mesna by the glutathione system.

In healthy adults who received a single 800-mg IV dose of mesna, approximately 31 and 28% of the dose were excreted in urine within 4 hours as mesna and dimesna, respectively; approximately 32 and 33% were excreted within 24 hours as mesna and dimesna, respectively. Follwing IV administration of a single 800 mg mesna dose, peak urine concentrations are achieved within 4 hours and average 1.57 and 1.4 mg/mL for mesna and dimesna, respectively. In contrast, peak urine concentrations are achieved within 8 hours following oral administration of a single 800-mg dose. A urine mesna concentration of 0.1 mg/mL has been proposed as the minimum effective uroprotective concentration.

Mesna and dimesna do not undergo hepatic metabolism

INDICATION
Prevention of urothelial toxicity due to oxazaphosphorines (Cyclophosphamide, Ifosfamide). UROMES should always be given in tumour therapy with Ifosfamide. Where cyclophophamide or Ifosfamide are being used for tumour therapy, UROMES should always be given with bolus doses (over 10mg/kg) of the cytotoxic agent and in all patients at special risk. The principle risk factors are : previous pelvic radiotherapy, cystitis with previous Cyclophosphamide, Ifosfamide therapy or a history of disorders of the urinary tract.

RECOMMENDED DOSE
Unless otherwise prescribed, Uromes 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 Uromes administration with oxazaphosphorine injection:

Hours (Time)	0 (8h)	4 (12h)	8 (16h)
Oxazaphosphorine dose	40 mg/kg BW	-	-
Uromes dose	8 mg/kg BW	8 mg/kg BW	8 mg/kg BW

With continuous infusion of ifosfamide , it has been shown to be of benefit to give Uromes 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 Uromes administration with a 24 hour ifosfamide infusion:

Hours (Time)	0	24	30	36
Ifosfamide dose	5 g/m^2 body surface (= 125 mg/kg BW)			
Uromes bolus dose	1 g/m^2 body surface (= 25 mg/kg BW)			
Uromes infusion	Up to 5g/m^2 body surface (= 125 mg/kg BW) Addition to Ifosfamide infusion	Up to 2.5g/m^2 body surface (= 62.5 mg/kg BW)		

CONTRAINDICATION
UROMES is contraindicated in patients known to be hypersensitive to mesna or other thiol compounds.

WARNING AND PRECAUTIONS
The occurrence of hypersensitivity reactions (hyperergic reactions) following Uromes therapy 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), 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 Uromes should therefore only be undertaken in such patients following careful resk-benefit analysis and under medical supervision.
As Uromes is used as a uroprotector in the context of cytostatic treatment with oxazaphosphorines, its use during pregnancy and lactation is governed by the criteria for this type of cytostatic therapy. Animal studies have shown no evidence of embryotoxic or teratogenic effects of Uromes.
The protective action of Uromes applies only to the urinary tract. All other recommended precautions are unaffected by its use and recommendations relating to them remain in force.

INTERACTIONS WITH OTHER MEDICAMENTS
Mesna is incompatible in vitro with cisplatin, carboplatin and nitrogen mustard.

PREGNANCY AND LACTATION
Pregnancy: Pregnancy "Category B". Reproduction studies in rats and rabbits with oral doses up to 1000 mg/kg have revealed no harm to the fetus due to mesna. It is not known whether UROMES can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. UROMES should be given to a pregnantwoman only if the benefits clearly outweigh any possible risks.
Teratology studies in rats and rabbits have shown no effects.

Nursing Mothers: It is not known whether mesna or dimesna is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from mesna, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

SIDE EFFECTS
Isolated cases of partially organ-related hypersensitivity reactions (hyperergic reactions),e.g.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 above 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 intravenous and oral doses of mesna, single doses of 60 mg/kg body weight and above were associated with nausea, vomiting, diarrhoea, headache, pain in the limbs, drop in blood pressure, tachycardia, skin reactions, exhaustion and weakness. During treatment, the above side-effects cannot always be clearly differentlated from those caused by oxazaphosphorines (Cyclophosphamide, Ifosfamide), or other concomitant medication.

SYMPTOMS AND TREATMENT OF OVERDOSE
No specific antidote for mesna is known. Overdosage should be managed with supportive measures to sustain the patient through any period of toxicity

STORAGE CONDITION
Preserve in hermetic containers. Store at room temperature not exceeding 30℃.

PACK SIZE
400mg/4mL. 10 Ampules/box

Product Registration Holder:
FIRST PHARMACEUTICAL SDN. BHD.
20, Jalan SS 19/5, 47500 Subang Jaya, Selangor

Manufacturer:
KOREA UNITED PHARM INC
25-23, Nojanggongdan-gil, Jeondong-myeon, Sejong-si, Korea

Revision: January 2018