ifomes

Mesna 400 mg Injection

COMPOSITION

Ifomes Injection: Each 4 ml contains Mesna BP 400 mg.

DESCRIPTION

Mesna is a drug used to reduce the undesired side effects of certain chemotherapy drugs. It is referred to as a "chemoprotectant."

CLINICAL PHARMACOLOGY

Mechanism of Action

Mesna was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by Ifosfamide. Analogous to the physiological cysteine-cystine system, Mesna is rapidly oxidized to its major metabolite, Mesna disulfide (diMesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys. In the kidney, the Mesna disulfide is reduced to the free thiol compound, Mesna, which reacts chemically with the urotoxic Ifosfamide metabolites (acrolein and 4-hydroxy-Ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of Mesna to 4-hydroxy-Ifosfamide forming a nonurotoxic 4-sulfoethylthiolfosfamide. Mesna also binds to the double bonds of acrolein and to other urotoxic metabolites. In multiple human xenograft or rodent tumor model studies of limited scope, using IV or IP routes of administration, Mesna in combination with Ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy.

Pharmacokinetics

At doses of 2-4 g/m^2, the terminal elimination half-life of Ifosfamide is about 4-8 hours. As a result, in order to maintain adequate levels of Mesna in the urinary bladder during the course of elimination of the urotoxic Ifosfamide metabolites, repeated doses of Mesna are required.

The urinary bioavailability of oral Mesna ranged from 45-79% of intravenously administered Mesna. Food does not affect the urinary availability of orally administered Mesna. Approximately 18-26% of the combined intravenous and oral Mesna dose appears as free Mesna in the urine. When compared to intravenously administered Mesna, the intravenous plus oral dosing regimen increases systemic exposures (150%) and provides more sustained excretion of Mesna in the urine over a 24-hour period.

Approximately 5% of the Mesna dose is excreted during the 12-24 hour interval, as compared to negligible amounts in patients given the IV regimen. The fraction of the administered dose of Mesna excreted in the urine is independent of dose. Protein binding of Mesna is in a moderate range (69-75%).

INDICATIONS

- Prevention of ifosfamide-induced hemorrhagic cystitis (syndrome of bleeding and irritation of the bladder).
- Prevention of high-dose cyclophosphamide-induced hemorrhagic cystitis.

DOSAGE AND ADMINISTRATION

For the prophylaxis of Ifosfamide induced hemorrhagic cystitis, Mesna may be given on a fractionated dosing schedule of three bolus intravenous injections or a single bolus injection followed by IV administration of Mesna as outlined below.

Intravenous Schedule

Mesna is given as intravenous bolus injections in a dosage equal to 20% of the Ifosfamide dosage (w/w) at the time of Ifosfamide administration and 4 and 8 hours after each dose of Ifosfamide. The total daily dose of Mesna is 60% of the Ifosfamide dose.

The recommended dosing schedule is outlined below:

	0 Hours	4 Hours	8 Hours
Ifosfamide	1.2 g/m^2	-	-
Mesna	240 mg/m^2	240 mg/m^2	240 mg/m^2

Intravenous Dosing

Mesna Injection is given as intravenous bolus injections in a dosage equal to 20% of the Ifosfamide dosage (w/w) at the time of Ifosfamide administration. The recommended dosing schedule is outlined below:

	0 Hours	2 Hours	6 Hours
Ifosfamide	1.2 g/m^2	-	-
Mesna	240 mg/m^2	240 mg/m^2	240 mg/m^2

Preparation of Intravenous Solutions/Stability

For IV administration the drug can be diluted by adding the Mesna Injection solution to any of the following fluids obtaining final concentrations of 20 mg Mesna/mL: 5% Dextrose Injection, 5% Dextrose and 0.2% Sodium Chloride Injection, 5% Dextrose and 0.33% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, 0.92% Sodium Chloride Injection, Lactated Ringer's Injection.

For example:

One mL of Mesna Injection multidose vial 100 mg/mL may be added to 4 mL of any of the solutions listed above to create a final concentration of 20 mg Mesna/mL. Diluted solutions are chemically and physically stable for 24 hours at 25˚C (77˚ F). Mesna is not compatible with cisplatin or carboplatin. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Special Populations

Gender Effect

An analysis was conducted in four male and four female volunteers; no differences in plasma pharmacokinetics were detected.

Pediatrics and Geriatrics

Pharmacokinetic data of Mesna in pediatric and geriatric patients are not available.

Hepatic and Renal Insufficiency

No clinical studies were conducted to evaluate the effect of hepatic impairment or renal impairment on the pharmacokinetics of Mesnea.

Drug-Drug Interaction

No clinical drug interaction studies have been conducted with Mesnea.

CONTRAINDICATIONS

Mesna is contraindicated in patients known to be hypersensitive to Mesna or other thiol compounds.

WARNINGS

Allergic reactions to Mesna ranging from mild hypersensitivity to systemic anaphylactic reactions have been reported.

Patients with autoimmune disorders who were treated with cyclophosphamide and Mesna appeared to have a higher incidence of allergic reactions. The majority of these patients received Mesna orally.

Mesna has been developed as an agent to reduce the risk of Ifosfamide induced hemorrhagic cystitis. It will not prevent or alleviate any of the other adverse reactions or toxicities associated with Ifosfamide therapy.

Mesna does not prevent hemorrhagic cystitis in all patients. Up to 6% of patients treated with Mesna have developed hematuria (>50 RBC/hpf or WHO grade 2 and above). As a result, a morning specimen of urine should be examined for the presence of hematuria (microscopic evidence of red blood cells) each day prior to Ifosfamide therapy. If hematuria develops when Mesna is given with Ifosfamide according to the recommended dosage schedule, depending on the severity of the hematuria, dosage reductions or discontinuation of Ifosfamide therapy may be initiated. In order to reduce the risk of hematuria, Mesna must be administered with each dose of Ifosfamide as outlined in the DOSAGE AND ADMINISTRATION section. Mesna is not effective in reducing the risk of hematuria due to other pathological conditions such as thrombocytopenia. Because of the benzyl alcohol content, the multidose vial should not be used in neonates or infants and should be used with caution in older pediatric patients.

PRECAUTIONS

Laboratory Tests

A false positive test for urinary ketones may arise in patients treated with Mesna. In this test, a red-violet color develops which, with the addition of glacial acetic acid, will return to violet.

Drug Interactions

No clinical drug studies have been conducted.

Pregnancy

Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at oral doses of 1000 mg/kg in rabbits and 2000 mg/kg in rats (approximately 10 times the maximum recommended total daily IV-oral-oral human dose on a body surface area basis) and have revealed no evidence of harm to the fetus due to Mesna. There are however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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.

Pediatric Use

Safety and effectiveness of Mesna in pediatric patients have not been established.

Geriatric Use

Clinical studies of Mesna did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. However, the ratio of Ifosfamide to Mesna should remain unchanged.

ADVERSE REACTIONS

Mesna adverse reaction data are available from four phase I studies in which single IV bolus doses of 600-1200 mg Mesna Injection without concurrent chemotherapy were administered to a total of 53 subjects and single oral doses of 600-2400 mg of Mesna Tablets were administered to a total of 82 subjects. The most frequently reported side effects (observed in two or more patients) for patients receiving single doses of Mesna IV were headache, injection site reactions, flushing, dizziness, nausea, vomiting, somnolence, diarrhea, anorexia, fever, pharyngitis, hyperaesthesia, influenza-like symptoms, and coughing. Among patients who received a single 1200-mg dose as an oral solution, rigors, back pain, rash, conjunctivitis, and arthralgia were also reported. In two phase I multiple-dose studies where patients received Mesna Tablets alone or IV Mesna followed by repeated doses of Mesna Tablets, flatulence and rhinitis were reported. In addition, constipation was reported by patients who had received repeated doses of IV Mesna.

Postmarketing Surveillance

Allergic reactions, decreased platelet counts associated with allergic reactions, hypertension, hypotension, increased heart rate, increased liver enzymes, injection site reactions (including pain and erythema), limb pain, malaise, myalgia, ST-segment elevation, tachycardia, and tachypnea have been reported as part of postmarketing surveillance.

OVERDOSAGE

There is no known antidote for Mesna. Oral doses of 6.1 and 4.3 g/kg were lethal to mice and rats, respectively. These doses are approximately 15 and 22 times the maximum recommended human dose on a body surface area basis. Death was preceded by diarrhea, tremor, convulsions, dyspnea, and cyanosis.

PHARMACEUTICAL INFORMATION

Storage condition

Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Ifomes Injection: Each commercial pack contains 2 ampoules of Mesna BP 400 mg injection in Alu-PVC blister.

Manufactured By
BEACON Pharmaceuticals Limited
Mymensingh, Bangladesh

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