adverse reactions or toxicities associated with the 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 (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 obtain adequate protection, **Mesna** must be administered with each dose of ifosfamide as per instruction given in the DOSAGE AND ADMINISTRATION. **Mesna** is not effective in preventing hematuria due to other pathological conditions such as thrombocytopenia.

Pediatric : Multiple dosage should not be used in neonates or infants and should be used with caution in older pediatric patients as **Mesna** contains Benzyl Alcohol.

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.

Carcinogenesis, mutagenesis and Impairment of fertility: No long term animal studies have been performed to evaluate the carcinogenic potential of **Mesna**. The Ames salmonella typhimurium test, mouse micronucleus assay and frequency of sister chromatid exchange and chromosomal aberrations in PHA-stimulated lymphocytes in vitro assays revealed no mutagenic activity.

Pregnancy and Lactation : 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 **Mesna** can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. **Mesna** should be given to a pregnant woman only if the benefits clearly outweigh any possible risks.

Nursing Mothers : It is not know whether mesna or dimesna is excreted in human milk. However a decision to discontinue nursing or to discontinue the drug, must be taken taking into account the importance of the drug to the mother.

DOSAGE AND ADMINISTRATION

For the prophylaxis of ifosfamide induced hemorrhagic cystitis, **Mesna** may be given on a fractionated dosing schedule of bolus intravenous injections as outlined below. **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

In order to maintain adequate protection, this dosing schedule should be repeated on each day that ifosfamide is administered. When the dosage of ifosfamide is adjusted (either increased or decreased), the dose of **Mesna** should be modified accordingly. When exposed to oxygen, **Mesna** is oxidized to the disulfide dimesna. The multiple dose of **Mesna** may be stored and used for up to 8 days.

PREPARATION OF INTRAVENOUS SOLUTIONS :

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 fluid. 5% Dextrose injection I.P., 5% Dextrose and 0.2% Sodium Chloride Injection I.P.,5% Dextrose and 0.33% Sodium Chloride Injection I.P.,5% Dextrose and 0.45% Sodium Chloride injection I.P.,0.92% Sodium Chloride Injection, I.P., Lactated Ringer's injection, I.P.

OVERDOSAGE

There is no known antidote for **Mesna**.

DIRECTIONS

Store below 30°C.Protect from light. To be sold on prescription only. Keep out of the reach of children.

PRESENTATION

IFOMID - M 500mg is available as 1 Vial in a mono carton along with package insert.

IFOMID - M 1g is available as 1 Vial in a mono carton along with package insert.

IFOMID - M 2g is available as 1 Vial in a mono carton along with package insert.

IFOMID - M 4gis available as 1 Vial in a mono carton along with package insert.

Marketed by:

Revive healthcare

503, 5th Floor, Eden Heights, 6 Main Gulberg, Jail Road, Lahore - Pakistan 54600.

Manufactured by:
United Biotech (P) Limited
Bagbania, Baddi-Nalagarh Road, Distt. Solan (HP) - 174 101 - India

آیفومیڈ-ایم ۱گرام انجیکشن

(آئیفوسفامائیڈ)

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دوا کو دھوپ اور نمی سے محفوظ رکھیں۔
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
بچوں کی پہنچ سے دور رکھیں۔

EBa01403

Rx Ifosfamide for Injection

IFOMID-M 500mg/1g/2g/4g

PHARMACEUTICALS WORLDWIDE — UNITED BIOTECH — The Emergence of a New Standard

WARNINGS

IFOMID-M should be administered only under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Urotoxic side effects, especially hemorrhagic cystitis, as well as CNS toxicities such as confusion and coma have been associated with ifosfamide therapy. The cessation of ifosfamide therapy may be required if the symptoms are noticed. Severe myelosuppression has also been reported.

COMPOSITION

IFOMID-M 500mg
Each vial contains:
Ifosfamide (B.P. Specs.) 500mg

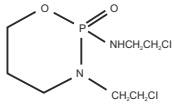
IFOMID-M 1g
Each vial contains:
Ifosfamide (B.P. Specs.) 1.0g

IFOMID-M 2g
Each vial contains:
Ifosfamide (B.P. Specs.) 2.0g

IFOMID - M 4g
Each vial contains :
Ifosfamide (B.P. Specs.) 4.0g

DESCRIPTION

Ifosfamide is a chemotherapeutic agent chemically related to the nitrogen mustards and a synthetic analog of cyclophosphamide. Ifosfamide is 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide. The molecular formula is : $C_7H_{15}Cl_2N_2O_2P$ and its molecular weight is 261.1. Its structural formula is :



Ifosfamide isa white crystalline powder that is freely soluble in water.

CLINICAL PHARMACOLOGY

Ifosfamide exhibits dose-dependent pharmacokinetics in humans. At single doses of 3.8-5.0g/m^2, the plasma concentrations decay biphasically and the mean terminal elimination half-life is about 15 hours. At doses of 1.6-2.4 g/m^2/day, the plasma decay is mono exponential and the terminal elimination half-life is about 7 hours. Ifosfamide is extensively metabolized in humans and the metabolic pathways appear to be saturated at high doses. After administration of doses of 5 g/m^2 of ^{14}C labeled Ifosfamide 70% to 86% of the dosed radioactivity was recovered in the urine with about 61% of the dose excreted as parent compound. At doses of 1.6-2.4 g/m^2 only 12% to 18% of the dose was excreted in the urine as unchanged drug within 72 hours. Two different dechloroethylated derivatives of ifosfamide, 4-carboxyifosfamide, thiodiacetic acid and cysteine conjugates of chloroacetic acid have been identified as the major urinary metabolites of ifosfamide in humans and only small amounts of 4-hydroxyifosfamide and acrolein are present. Small quantities (nmol/ml) of ifosfamide mustard and 4-hydroxyifosfamide and detectable in human plasma. Metabolism of ifosfamide is required for the generation of the biologically active species and while metabolism is extensive, it is also quite variable among patients. A study of 50 fully evaluable patients with germ cell testicular cancer 47 out of 50 were treated with ifosfamide in combination with cisplatin and either vinblastine or etoposide after failing at least two prior chemotherapy regimens consisting of cisplatin / vinblastine / bleomycin, (PVB, cisplatin / vinblastine / actinomycinD / bleomycin / cyclophasphamide, (VAB6), or the combination of cisplatin and etoposide. While remaining 3 patient were selected for cisplatin sensitivity because they had previously responded to a cisplatin-containing regimen and had not progressed while on the cisplatin-containing regimen or within 3 weeks of stopping it. Patients served as there own control based on the premise that long term complete responses could not be achieved by retreatment with a regimen of which they had previously responded and subsequently relapsed.Ten of the 50 fully evaluable patients were still alive 2 to 5 years after treatment. Four of the 10 long term survivors were rendered free of cancer by surgical resection after treatment with the ifosfamide regimen; median survival for the entire group of 50 fully evaluable patients was 53 weeks.

INDICATIONS

Ifosfamide Injection is used in combination with certain other approved antineoplastic agents, is indicated for third line chemotherapy of germ cell testicular cancer. It should ordinarily be used in combination with a prophylactic agent such as Mesna for hemorrhagic cystitis.

DOSAGE AND ADMINISTRATION

IFOMID-M should be administered intravenously at a dose of 1.2 g/m^2 per day for 5 consecutive days. Treatment is repeated every 3 weeks or after recovery from hematologic toxicity (Platelets ≥ 100,000/µL, WBC ≥ 4,000/µL). In order to prevent bladder toxicity, IFOMID- M should be given with extensive hydration consisting of at least 2 liters of oral or intravenous fluid per day. Mesna should also be used to prevent hemorrhagic cystitis. IFOMID-M should be administered as a slow intravenous infusion lasting a minimum of 30 minutes. IFOMID-M although administered to a small number of patients with compromised hepatic and/or renal function, studies to establish optimal dose schedules in such patients have not been conducted.

Preparation for Intravenous Administration : Injections are prepared for parenteral use by adding *Sterile Water for Injection, IP* or *Sterile Bacteriostatic Water for Injection, USP* (benzyl alcohol or parabens preserved), to the vial and shaking to dissolve. Use the quantity of diluent shown below to constitute the product :

Dosage Strength	Quantity of Diluent	Final Concentration
500 mg	10 ml	50 mg/ml
1 g	20 ml	50 mg/ml
2 g	40 ml	50 mg/ml
4 g	80 ml	50 mg/ml

Solutions of ifosfamide may be diluted further to achieve concentrations of 0.6 to 20 mg/mL in the following fluids: 5% Dextrose injection I.P., 5% Dextrose and 0.2% Sodium Chloride Injection I.P.,,5% Dextrose and 0.33% Sodium Chloride Injection, I.P.,,5% Dextrose and 0.45% Sodium Chloride injection, I.P.,,0.9% Sodium Chloride Injection, I.P., Lactated Ringer's injection, I.P. and Sterile water for injection I.P. Constituted and further diluted solutions of IFOMID M should be refrigerated and used within 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Note : Ifosfamide Injection should only be administered by IV route as a slow intravenous infusion lasting for a minimum of 30 minutes. Extensive hydration using at least 2 liters of oral or IV fluid/day and/or a protector like mesna should be given with ifosfamide infusion to prevent hemorrhagic cystitis.

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered.

Skin reactions associated with accidental exposure to ifosfamide may occur. The use of gloves is recommended. If ifosfamide solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water.

CONTRAINDICATIONS

Continuous use of ifosfamide is contraindicated in patients with severely depressed bone marrow function. Ifosfamide is also contraindicated in patients who have demonstrated a previous hypersensitivity to it.

SIDE EFFECTS

In patients where Ifosfamide is used as a single agent, the dose-limiting toxicities are myelosuppression and urotoxicity. Dose fractionation, vigorous hydration, and a protector such as mesna can significantly reduce the incidence of hematuria, especially gross hematuria, associated with hemorrhagic cystitis. At a dose of 1.2 g/m^2 daily for 5 consecutive days, leukopenia, when it occurs, is usually mild to moderate. Other significant side effects include alopecia, nausea, vomiting, and central nervous system toxicities.

Hematologic Toxicity : Myelosuppression was dose related and dose limiting. It consisted mainly of leukopenia and, to a lesser extent, thrombocytopenia. A WBC count < 3000/µL is expected in 50% of the patients treated with ifosfamide single agent at doses of 1.2 g/m^2 per day for 5 consecutive days. At this dose level, thrombocytopenia (platelets < 100,000/µL) occurred in about 20% of the patients. At higher dosages, leukopenia was almost universal, and at total dosages of 10-12 g/m^2 /cycle, one half of the patients had a WBC count below 1000/µL and 8% of patients had platelet counts less than 50,000/µL. Myelosuppression was usually reversible and treatment can be given every 3 to 4 weeks. When ifosfamide is used in combination with other myelosuppressive agents, adjustments in dosing may be necessary. Patients who experience severe myelosuppression are potentially at increased risk for infection.Anemia has been reported as part of postmarketing surveillance.

Digestive System : Nausea and vomiting occurred in 58% of the patients who received IFOSFAMIDE. They were usually controlled by standard antiemetic therapy. Other gastrointestinal side effects include anorexia, diarrhea, and in some cases, constipation.

Urinary System : Urotoxicity consisted of hemorrhagic cystitis, dysuria, urinary frequency and other symptoms of bladder irritation. Hematuria occurred in 6% to 92% of patients treated with IFOSFAMIDE. The incidence and severity of hematuria can be significantly reduced by using vigorous hydration, a fractionated dose schedule and a protector such as mesna. At daily doses of 1.2 g/m^2 for 5 consecutive days without a protector, microscopic hematuria is expected in about one half of the patients and gross hematuria in about 8% of patients.

Renal toxicity occurred in 6% of the patients treated with ifosfamide as a single agent. Clinical signs, such as elevation in BUN or serum creatinine or decrease in creatinine clearance, were usually transient. They were most likely to be related to tubular damage. One episode of renal tubular acidosis which progressed into chronic renal failure was reported. Proteinuria and acidosis also occurred in rare instances. Metabolic acidosis was reported in 31% of patients in one study when IFOSFAMIDE was administered at doses of 2.0 to 2.5 g/m^2 /day for 4 days. Renal tubular acidosis, Fanconi syndrome, renal rickets and acute renal failure have been reported. Close clinical monitoring of serum and urine chemistries including phosphorus, potassium, alkaline phosphatase and other appropriate laboratory studies is recommended. Appropriate replacement therapy should be administered as indicated.

Central Nervous System : CNS side effects were observed in 12% of patients treated with IFOSFAMIDE. Those most commonly seen were somnolence, confusion, depressive psychosis, and hallucinations. Other less frequent symptoms include dizziness, disorientation, and cranial nerve dysfunction. Seizures and coma with death were occasionally reported. The incidence of CNS toxicity may be higher in patients with altered renal function.

Other : Alopecia occurred in approximately 83% of the patients treated with IFOSFAMIDE as a single agent. In combination, this incidence may be as high as 100%, depending on the other agents included in the chemotherapy regimen.

Increases in liver enzymes and/or bilirubin were noted in 3% of the patients. Other less frequent side effects included phlebitis, pulmonary symptoms, fever of unknown origin, allergic reactions, stomatitis, cardiotoxicity, and polyneuropathy.

DRUG INTERACTIONS

The physician should be alert for possible combined drug actions, desirable or undesirable, involving ifosfamide even though ifosfamide has been used successfully concurrently with other drugs, including other cytotoxic drugs.

WARNINGS & PRECAUTIONS

General

Ifosfamide should be given cautiously to patients with impaired renal function as well as to those with compromised bone marrow reserve, as indicated by : leucopenia, granulocytopenia extensive bone marrow metastases, prior radiation therapy, or prior therapy with other cytotoxic agents.

Urinary System

It is recommended that a urinalysis should be obtained prior to each dose of ifosfamide. If microscopic hematuria (greater than 10 RBCs per high power field) is present, then subsequent administration should be withheld until complete resolution. Further administration of ifosfamide should be given with vigorous oral or parenteral hydration.

Hematopoietic System

Close hematologic monitoring is recommended. White blood cell (WBC) count, platelet count and hemoglobin should be obtained prior to each administration and at appropriate intervals. Unless clinically essential, ifosfamide should not be given to patients with a WBC count below 2000/µL and/or platelet count below 50,000/µL.

Central Nervous System

Neurologic manifestations consisting of somnolence, confusion, hallucinations and in some instances, coma, have been reported following ifosfamide therapy. The occurrence of these symptoms requires discontinuing ifosfamide therapy. Supportive therapy should be maintained until their complete resolution.

Laboratory Test

During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression. Urine should also be examined regularly for red cells, which may precede hemorrhagic cystitis.

Carcinogensis, Mutagenesis, Impairment of Fertility

Ifosfamide has been shown to be carcinogenic in rats.The mutagenic potential of ifosfamide has been documented in bacterial systems in vitro and mammalian cells in vivo. In vivo, ifosfamide has induced mutagenic effects in mice and Drosophila melanogaster germ cells, and has induced a significant increase in dominant lethal mutations in male mice as well as recessive sex-linked lethal mutations in Drosophila. Embryo lethal effects were observed in rats following the administration of 54 mg/m^2 doses of ifosfamide from the 6th through the 15th day of gestation and embryotoxic effects were apparent after dams received 18 mg/m^2 doses over the same dosing period. The number of anomalies was also significantly increased over the control group.

Pediatric Use : Safety and effectiveness in pediatric patients have not been established.

PREGNANCY AND LACTATION

Pregnancy : Category D : Administration of ifosfamide in pregnant women may lead to fetal damage. Patients should be apprised of these possible hazards, if the drug is to be administered during pregnancy or if the patients become pregnant during treatment.

Ifosfamide has shown to be excreted in breast milk. Ifosfamide has shown tumorogenic activity and can cause serious adverse effect, either the drug or nursing should be discontinued taking into consideration risk/benefit ratio.

OVERDOSE

No specific antidote for ifosfamide overdose is known. Symptoms of overdose include myelosuppression, nausea, vomiting, diarrhea, and alopecia, which are direct extension of the drug's pharmacological effects requiring general supportive measures (hydration) to sustain the patient through any period of toxicity that might occur.

STORAGE

Store at 20°C to 25°C, excursion permitted between 15°C & 30°C.

Sodium 2- Sulphanylethanesulphonate (Mesna) Injection 2ml/4ml

COMPOSITION

Each ml contains:

Sodium 2-Sulphanylethanesulphonate BP	100mg
Water for Injections IP	q.s.

DESCRIPTION

Mesna is a synthetic sulfhydryl compound designated as Sodium 2-Sulphanylethanesulphonate BP with a molecular formula of $C_2H_5NaO_3S_2$ and a molecular weight of 164. 18. Its structural formula is as follows:

$$HS\text{-}CH_2\text{-}CH_2SO_3Na^+$$

It is a sterile, non pyrogenic, aqueous solution of clear and colorless appearance for intravenous administration.

CLINICAL PHARMACOLOGY

Mesna was developed as a prophylactic agent to prevent the hemorrhagic cystitis induced by ifosfamide. It is analogous to the physiological cysteine cystine system, following intravenous administration. **Mesna** is rapidly oxidized to its only 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.

Ifosfamide has been shown to have dose dependent pharmacokinetics in humans. At doses of 2-4g/m^2, its terminal elimination half-life 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. After administration of an 800 mg dose the half-lives of **Mesna** and dimesna in the blood are 0.36 hours and 1.17 hours respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as **Mesna** and dimesna respectively. The majority of the dose recovered was eliminated within 4 hours. **Mesna** has a volume of distribution of 0.652 L/kg and a plasma clearance of 1.23 L/kg/hour.

INDICATIONS AND USAGE

Mesna is effective as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis.

CONTRAINDICATIONS

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

ADVERSE REACTIONS

As **Mesna** is used in combination with ifosfamide and other chemotherapeutic agents with documented toxicities, it is difficult to distinguish the adverse reactions caused by **Mesna** .As a result, the adverse reaction profile of **Mesna** was determined in three phase I studies (16 subjects) utilizing intravenous and oral administration and two controlled studies in which ifosfamide and mesna were compared to ifosfamide and standard prophylaxis. In phase I studies in which IV bolus doses of 0.8-1.6 g/m2 **Mesna** were administered as single or three repeated doses to a total of 10 patients, a bad taste in the mouth (100%) and soft stools (70%) were reported. At intravenous and oral bolus doses of 2.4g/m^2 which are approximately 10 times the recommended clinical doses (0.24 g/m^2) headache (50%), fatigue (33%), nausea (33%), diarrhea (83%) limb pain (50%), hypotension (17%) and allergy (17%), have also been reported in the 6 patients who participated in this study. In controlled clinical studies, adverse reactions which can be associated with **mesna** were vomiting, diarrhea and nausea.

DRUG INTERACTIONS

In vitro and in vivo animal tumor models have shown that **Mesna** does not have any effect on the antitumor efficacy of concomitantly administered cytotoxic agents.

PRECAUTIONS & WARNINGS

Allergic reactions to **Mesna** were reported in patients with autoimmune disorders. The majority of the patients received high doses of **Mesna** orally. The symptoms ranged from mild hypersensitivity to systemic anaphylactic reactions. **Mesna** though used to prevent ifosfamide induced hemorrhagic cystitis will not prevent or alleviate any of the other