Summary of Product Characteristics

FOSFA-2gm

1. *Name of the medicinal product:*

***a) Product Name: IFOSFAMIDE FOR INJECTION USP b) Strength*:** 2gm

***c) Pharmaceutical Dosage Form*:** Powder for Concentrate for solution for infusion.

2. *Qualitative and quantitative composition*

Each vial contains

Sterile Ifosfamide USP 2g

3. Pharmaceutical form: Powder for Concentrate for solution for infusion.

4. Clinical particulars

***A.* Therapeutic indications**

B. Ifosfamide is a cytotoxic drug for the treatment of malignant disease. As a single agent it has successfully produced objective remissions in a wide range of malignant conditions. Ifosfamide is also frequently used in combination with other cytotoxic drugs, radiotherapy and surgery.

C. Posology and method of administration

Ifosfamide should be administered intravenously at a dose of 1.2 g/m^2 per day for 5 consecutive days. Treatment should be repeated every 3 weeks or after recovery from hematologic toxicity (Platelets ≥ 100,000/il, WBC ≥ 4,000/il). In order to prevent bladder toxicity, Ifosfamide should be given with extensive hydration consisting of at least 2 liters of oral or intravenous fluid per day. A protector, such as mesna, should also be used to prevent hemorrhagic cystitis.

Ifosfamide should be administered as a slow intravenous infusion lasting a minimum of 30 minutes. When administered in combination with mesna, the usual dose of mesna is 20 % of the Ifosfamide dose, given just before and at 4 & 8 hours after Ifosfamide infusion (the total mesna dose is 60 % of Ifosfamide). When mesna is to be used with continuous Ifosfamide infusion, mesna may be administered as a bolus dose equal to 20 % of the Ifosfamide dose followed by a continous dose of mesna equal to 40 % of the Ifosfamide dose, continuing for 12- 24 hours after the completion of Ifosfamide infusion. Studies to establish

optimal dose schedules of Ifosfamide in patients with compromised hepatic and/or renal function have not been conducted.

Administration

Injections are prepared for parenteral use by adding Sterile Water for Injection USP or Sterile Bacteriostatic Water for Injection USP (benzyl alcohol or paraben preservative) to the vial and shaking to dissolve.

If dissolution does not take place immediately, allow to stand for few minutes and shake again. It is advisable to use the preparation immediately after reconstitution. Use the quantity of diluent shown below to constitute the product:

Dosage of Strength	Quantity of diluent	Final Concentration
1g	25ml	40mg/ml
2g	50ml	40mg/ml
3g	75ml	40mg/ml

Solutions of may be diluted further to achieve concentrations of 0.6 to 20 mg/ml in either 5 % Dextrose Injection USP, 0.9 % Sodium Chloride Injection USP, Lactated Ringer's Injection USP and Sterile Water for Injection USP. For intravenous infusions lasting approximately 30 minutes, dilution with 250 ml Ringer's solution or 5 % dextrose solution or 0.9 % sodium chloride solution is appropriate; however for intravenous infusions lasting from 1-2 hours, dilution with 500 ml Ringer's solution or 5 % dextrose solution or 0.9 % sodium chloride solution has been found to be appropriate. The use of large volume parenteral glass bottles for infusion is also acceptable. Reconstituted or constituted and further diluted solutions of Ifosfamide should be refrigerated and used within 24 hours. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

D. Contraindications

Ifosfamide should only be administered when there are facilities for regular monitoring of clinical, biochemical and haematological parameters before, during and after administration and under the direction of a specialist oncology service.

Absolute Contraindications:

Ifosfamide is contra-indicated in patients with known hypersensitivity to ifosfamide,

bone marrow aplasia, myelosuppression, urinary tract obstruction, **Relative Contraindications:**

It is contraindicated in acute infections including urinary tract infection, or with acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy.
Ifosfamide is contra-indicated in patients with renal impairment (serum creatinine greater than 120 mcmol/l or 1.5 mg/100 ml) or hepatic impairment (bilirubin greater than 17 mcmol/l or 1 mg/100 ml), or serum transaminases or alkaline phosphatase more than 2.5 times the upper limit of normal.

Contraindication during Pregnancy and Lactation Pregnancy
It is contraindicated in pregnant women.
The administration of ifosfamide during organogenesis has been shown to have a fetotoxic effect in mice, rats, and rabbits and therefore may cause fetal damage when administered to pregnant women.
There are only very limited data available on the use of ifosfamide during pregnancy in humans. Fetal growth retardation and neonatal anaemia have been reported following exposure to ifosfamide containing chemotherapy regimens during pregnancy. Multiple congenital deviations have been reported after use during the first trimester of pregnancy.
Animal data generated with cyclophosphamide, another oxazaphosphorine cytotoxic agent suggest that an increased risk of failed pregnancy and malformations may persist after discontinuation of the agent as long as oocytes/follicles exist that were exposed to the agent during any of their maturation phases.
In addition, exposure to cyclophosphamide has been reported to cause miscarriage, malformations (following exposure during the first trimester), and neonatal effects, including leukopenia, pancytopenia, severe bone marrow hypoplasia, and gastroenteritis.
Based on the results of animal studies, human case reports and the substance's mechanism of action, the use of Ifosfamide during pregnancy, particularly in the first trimester, is advised against.
In every individual case, the benefits of the treatment will have to be weighed against possible risks for the foetus.
If ifosfamide is used during pregnancy, or if the patient becomes pregnant while taking this drug or after treatment, the patient should be apprised of the potential hazard to a fetus.
Lactation
It is contraindicated in lactating women.

Ifosfamide is passed into the breast milk and may cause neutropenia, thrombocytopenia, low haemoglobin concentrations and diarrhoea in children. Women must not breastfeed during treatment with ifosfamide.

E. Special warnings and precautions for use

In individual patients, risk factors for ifosfamide toxicities and their sequelae described here and in other sections may constitute contraindications. In such situations, individual assessment of risk and expected benefits is necessary.

Adverse reactions, depending on their severity, may require dosage modification or discontinuation of treatment

Warnings Myelosuppression, Immunosuppression, Infections

Treatment with ifosfamide may cause myelosuppression and significant suppression of immune responses, which can lead to severe infections. Fatal outcome of ifosfamide-associated myelosuppression has been reported.

Ifosfamide-induced myelosuppression can cause leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding events), and anaemia.

Administration of ifosfamide is normally followed by a reduction in the leukocyte count. The nadir of the leukocyte count tends to be reached approximately during the second week after administration. Subsequently, the leukocyte count rises again.

Severe myelosuppression and immunosuppression must be expected particularly in patients pre-treated with and/or receiving concomitant chemotherapy/haematotoxic agents, immunosuppressants and/or radiation therapy.

Where indicated, use of haematopoiesis-stimulating agents (colony stimulating factors and erythropoiesis-stimulating agents) may be considered to reduce the risk of myelosuppressive complications and/or help facilitate the delivery of the intended dosing. For information on a potential interaction with G-CSF and GM-CSF

(granulocyte colonystimulating factor, granulocyte macrophage colony-stimulating factor). The risk of myelosuppression is dosedependent and is increased with administration of a single high dose compared to fractionated administration.

The risk of myelosuppression is increased in patients with reduced renal function. Severe immunosuppression has led to serious, sometimes fatal, infections. Infections reported with ifosfamide include

pneumonias, as well as other bacterial, fungal, viral, and parasitic infections. Sepsis and septic shock also have been reported.
Latent infections can be reactivated. In patients treated with ifosfamide, reactivation has been reported for various viral infections.
Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician.
Close hematologic monitoring is recommended. White blood cell count, platelet count, and haemoglobin levels should be obtained prior to each administration and at appropriate intervals after administration.

Central Nervous System Toxicity, Neurotoxicity
Administration of ifosfamide can cause CNS toxicity and other neurotoxic effects, including confusional state, somnolence, coma, hallucinations, blurred vision, psychotic behavior, extrapyramidal symptoms, urinary incontinence, and seizures. Ifosfamide neurotoxicity may become manifest within a few hours to a few days after first administration and in most cases resolves within 48 to 72 hours of ifosfamide discontinuation. Symptoms may persist for longer periods of time. Occasionally, recovery has been incomplete. Fatal outcome of CNS toxicity has been reported. Recurrence of CNS toxicity after several uneventful treatment courses has been reported.
CNS toxicity has been reported very commonly and appears to be dose dependent.
Other risk factors that have been demonstrated or discussed in the literature include:
- Renal dysfunction, elevated serum creatinine
- Low serum albumin

Hepatic dysfunction
- Low bilirubin, low haemoglobin levels, decreased white blood cell count
- Acidosis, low serum bicarbonate
- Electrolyte imbalances, hyponatraemia and inappropriate ADH (vasopressin) secretion, water intoxication, low fluid intake
- Presence of brain metastases, prior CNS disease, brain irradiation
- Cerebral sclerosis, peripheral vasculopathy
- Presence of tumour in lower abdomen, bulky abdominal disease
- Poor performance status, advanced age, younger age
- Obesity, female gender, individual predisposition
- Interactions with other medicines (e.g., aprepitant, CYP 3A4 inhibitors), alcohol, drug abuse, or pretreatment with cisplatin

Neurotoxicity often manifests in patients without identifiable risk factors.
If encephalopathy develops, administration of ifosfamide should be discontinued. Methylene blue may be a treatment option for the prevention and management of ifosfamide-associated encephalopathy, but its effectiveness is not well established. Inconsistent results have been reported.
Due to the potential for additive effects, drugs acting on the CNS (such as antiemetics, sedatives, narcotics, or antihistamines) must be used with particular caution or, if necessary, be discontinued in case of ifosfamide induced encephalopathy.

Renal and Urothelial Toxicity
Ifosfamide is both nephrotoxic and urotoxic.
Glomerular and tubular kidney function must be evaluated and checked before commencement of therapy, as well as during and after treatment.
Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity.
Close clinical monitoring of serum and urine chemistries, including phosphorus, potassium, and other laboratory parameters appropriate for identifying nephrotoxicity and urothelial toxicity is recommended.

Nephrotoxic Effects
Fatal outcome from nephrotoxicity has been documented.
Renal parenchymal and tubular necrosis have been reported in patients treated with ifosfamide.

Disorders of renal function (glomerular and tubular) following ifosfamide administration are very common. Manifestations include a decrease in glomerular filtration rate and an increase in serum creatinine, proteinuria, enzymuria, cylindruria, aminoaciduria, phosphaturia, and glycosuria as well as renal tubular acidosis. Fanconi syndrome, renal rickets, and growth retardation in children as well as osteomalacia in adults have also been reported.
Development of a syndrome resembling SIADH (syndrome of inappropriate antidiuretic hormone secretion) has been reported with ifosfamide.
Tubular damage may become apparent during therapy, months or even years after cessation of treatment.

Glomerular or tubular dysfunction may resolve with time, remain stable, or progress over a period of months or years, even after

completion of ifosfamide treatment. Acute tubular necrosis, acute renal failure, and chronic renal failure secondary to ifosfamide therapy have been reported.
The risk of developing clinical manifestations of nephrotoxicity is increased with, for example:
- large cumulative doses of ifosfamide,
- pre-existing renal impairment,
- prior or concurrent treatment with potentially nephrotoxic agents,
- younger age in children (particularly in children up to approximately 5 years of age), - reduced nephron reserve as in patients with renal tumours and those having undergone renal radiation or unilateral nephrectomy.

The risks and expected benefits of ifosfamide therapy should be carefully weighed when considering the use of ifosfamide in patients with pre-existing renal impairment or reduced nephron reserve.

Urothelial Effects
Ifosfamide administration is associated with urotoxic effects, which can be reduced by prophylactic use of mesna.
Hemorrhagic cystitis requiring blood transfusion has been reported with ifosfamide. The risk of hemorrhagic cystitis is dose-dependent and increased with administration of single high doses compared to fractionated administration.
Hemorrhagic cystitis after a single dose of ifosfamide has been reported.
Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions.
During or immediately after administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity.
For prophylaxis of hemorrhagic cystitis, ifosfamide should be used in combination with mesna.
Ifosfamide should be used with caution, if at all, in patients with active urinary tract infections.

Past or concomitant radiation of the bladder or busulfan treatment may increase the risk for hemorrhagic cystitis.
The following manifestations of urotoxicity from cyclophosphamide, another oxazaphosphorine cytotoxic agent have been reported:

- hemorrhagic cystitis (including severe forms with ulceration and necrosis), - fatal outcome of urothelial toxicity, as well as the need for cystectomy due to fibrosis, bleeding, or secondary malignancy.
- hematuria, which may be severe and recurrent; while hematuria usually resolves in a few days after treatment is stopped, it may persist.
- signs of urothelial irritation (such as painful micturition, a feeling of residual urine, frequent voiding, nocturia, urinary incontinence) as well as the development of bladder fibrosis, small-capacity bladder, telangiectasia, and signs of chronic bladder irritation.
- pyelitis and ureteritis

Cardiotoxicity, Use in Patients With Cardiac Disease

Fatal outcome of ifosfamide-associated cardiotoxicity has been reported. The risk of developing cardiotoxic effects is dose-dependent. It is increased in patients with prior or concomitant treatment with other cardiotoxic agents or radiation of the cardiac region and, possibly, renal impairment.

Particular caution should be exercised when ifosfamide is used in patients with risk factors for cardiotoxicity and in patients with pre-existing cardiac disease.

Manifestations of cardiotoxicity reported with ifosfamide treatment (see Section 4.8) and include:

- Supraventricular or ventricular arrhythmias, including atrial/supraventricular

tachycardia, atrial fibrillation, pulseless ventricular tachycardia

- Decreased QRS voltage and STsegment or T-wave changes
- Toxic cardiomyopathy leading to heart failure with congestion and hypotension
- Pericardial effusion, fibrinous pericarditis, and epicardial fibrosis

Pulmonary Toxicity

Pulmonary toxicity leading to respiratory failure as well as fatal outcome has been reported. Interstitial pneumonitis and pulmonary fibrosis have been reported with ifosfamide treatment. Other forms of pulmonary toxicity have also been reported.

Secondary Malignancies

As with all cytotoxic therapy, treatment with ifosfamide involves the risk of secondary tumours and their precursors .

The secondary malignancy may develop several years after chemotherapy has been discontinued.

The risk of myelodysplastic alterations, some progressing to acute leukemias, is increased. Other malignancies reported after use of

ifosfamide or regimens with ifosfamide include lymphoma, thyroid cancer, and sarcomas.

Malignancy has also been reported after in utero exposure with cyclophosphamide, another oxazaphosphorine cytotoxic agent.

Veno-occlusive Liver Disease

Veno-occlusive liver disease has been reported with chemotherapy that included ifosfamide and also is a known complication with cyclophosphamide, another oxazaphosphorine cytotoxic agent.

Genotoxicity

Ifosfamide is genotoxic and mutagenic in male and female germ cells. Therefore, women should not become pregnant and men should not father a child during therapy with ifosfamide.

Effects on Fertility

Men should not father a child for up to 6 months after the end of therapy.

Sexually active women and men should use effective methods of contraception during these periods of time.

Female Patients

Amenorrhea has been reported in patients treated with ifosfamide. In addition, with cyclophosphamide, another oxazaphosphorine cytotoxic agent, oligomenorrhea has been reported.

The risk of permanent chemotherapy-induced amenorrhea is increased in older women.

Girls treated with ifosfamide during prepubescence may develop secondary sexual characteristics normally and have regular menses.

Girls treated with ifosfamide during prepubescence subsequently have conceived. Girls who have retained ovarian function after completing treatment are at increased risk of developing premature menopause.

Male Patients

Men treated with ifosfamide may develop oligospermia or azoospermia.

Sexual function and libido generally are unimpaired in these patients.

Boys treated with ifosfamide during prepubescence may develop secondary sexual characteristics normally, but may have oligospermia or azoospermia.

Some degree of testicular atrophy may occur.
Azoospermia may be reversible in some patients, though the reversibility may not occur for several years after cessation of therapy.
Men treated with ifosfamide have subsequently fathered children.
Anaphylactic/Anaphylactoid Reactions, Cross-sensitivity
Anaphylactic/anaphylactoid reactions have been reported in association with ifosfamide.
Cross-sensitivity between oxazaphosphorine cytotoxic agents has been reported.
Impairment of Wound Healing
Ifosfamide may interfere with normal wound healing.

PRECAUTIONS Alopecia
Alopecia is a very common, dose dependent effect of ifosfamide administration.
Chemotherapy-induced alopecia may progress to baldness.
The hair can grow back, though it may be different in texture or colour.
Nausea and Vomiting
Administration of ifosfamide may cause nausea and vomiting.
Current guidelines on the use of antiemetics for prevention and amelioration of nausea and vomiting should be considered.
Alcohol consumption may increase chemotherapy-induced nausea and vomiting. Oral hygiene is important.

Stomatitis
Administration of ifosfamide may cause stomatitis (oral mucositis).
Current guidelines on measures for prevention and amelioration of stomatitis should be considered.

Paravenous Administration
The cytotoxic effect of ifosfamide occurs after its activation, which takes place mainly in the liver. Therefore, the risk of tissue injury from accidental paravenous administration is low.
In case of accidental paravenous administration of ifosfamide, the infusion should be stopped immediately, the extravascular ifosfamide solution should be aspirated with the cannula in place, and other measures should be instituted as appropriate.

Use in Patients With Renal Impairment
In patients with renal impairment, particularly in those with severe renal impairment, decreased renal excretion may result in increased

plasma levels of ifosfamide and its metabolites. This may result in increased toxicity e.g., neurotoxicity, nephrotoxicity, hematotoxicity.
Use in Patients With Hepatic Impairment
In patients with hepatic impairment, particularly in those with severe hepatic impairment, decreased activation of ifosfamide may alter the effectiveness of ifosfamide treatment.
Low serum albumin and hepatic impairment are also considered risk factors for the development of CNS toxicity. Hepatic impairment may increase the formation of a metabolite that is believed to cause or contribute to CNS toxicity and also contribute to nephrotoxicity.

The degree of renal and hepatic impairment should be considered when selecting the dose and interpreting the response.

F. Interaction with other medicinal products and other forms of interaction

Planned co administration or sequential administration of other substances or treatments that could increase the likelihood or severity of toxic effects (by means of Pharmacodyanmic or pharmacokinetic interactions) requires careful individual assessment of the expected benefit and the risks. Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.

Patients being treated with ifosfamide and agents that reduce its activation should be monitored for a potential reduction of therapeutic effectiveness and the need for dose adjustment.

Interaction Common to all Cytotoxic

Increased haematotoxicity and/or immunosuppression may result from a combined effect of ifosfamide and, for example:

- ACE inhibitors: ACE inhibitors can cause leukopenia.
- Carboplatin
- Cisplatin
- Natalizumab

Increased cardiotoxicity may result from a combined effect of ifosfamide and, for example: - Anthracyclines

- Irradiation of the cardiac region

Increased pulmonary toxicity may result from a combined effect of ifosfamide and, for example: - Amiodarone

- G-CSF, GM-CSF (granulocyte colonystimulating factor, granulocyte macrophage colony-stimulating factor)

Increased nephrotoxicity may result from a combined effect of ifosfamide and, for example: - Acyclovir

- Aminoglycosides
- Amphotericin B
- Carboplatin
- Cisplatin

Additive CNS effects may result from a combined effect of ifosfamide and, for example: - Antiemetics

- Antihistamines
- Narcotics - Sedatives

Inducers of human hepatic and extrahepatic microsomal enzymes (e.g., cytochrome P450 enzymes):

Aprepitant: Reports suggest increased ifosfamide neurotoxicity in patients receiving antiemetic prophylaxis with aprepitant, which is both an inducer and a moderate inhibitor of CYP 3A4.

Coumarin derivatives: Increased INR (increased international normalized ratio) has been reported in patients receiving ifosfamide and warfarin.

Contraindicated

An increased risk of developing hemorrhagic cystitis may result from a combined effect of ifosfamide and, for example:

- Busulfan
- Irradiation of the bladder

Docetaxel: Increased gastrointestinal toxicity has been reported when ifosfamide was administered before Docetaxel infusion.

Prohibited:

Vaccines: The immunosuppressive effects of ifosfamide can be expected to reduce the response to vaccination. Use of live vaccines may lead to vaccine induced infection. Cisplatin: Cisplatin-induced hearing loss can be exacerbated by concurrent ifosfamide therapy.

Theoretical interactions of ifosfamide and allopurinol resulting in an increased severity of bone marrow depression.

Interactions requiring Precautionary Measures

The potential for increased formation of metabolites responsible for cytotoxicity and other toxicities (depending on the enzymes induced) must be considered in case of prior or concomitant treatment with, for example:

- Carbamazepine
- Corticosteroids
- Rifampin
- Phenobarbital - Phenytoin
- St. John's Wort

Inhibitors of CYP 3A4: Reduced activation and metabolism of ifosfamide may alter the effectiveness of ifosfamide treatment. Inhibition of CYP 3A4 can also lead to increased formation of an ifosfamide metabolite associated with CNS and nephrotoxicity. CYP 3A4 inhibitors include:

- Ketoconazole
- Fluconazole
- Itraconazole
- Sorafenib

Tamoxifen: Concomitant use of tamoxifen and chemotherapy may increase the risk of thromboembolic complications.

Irinotecan: Formation of the active metabolite of irinotecan may be reduced when irinotecan is administered with ifosfamide.

Alcohol: In some patients, alcohol may increase ifosfamide-induced nausea and vomiting.

Concurrent administration of antidiabetic agents, such as sulfonylureas and ifosfamide may enhance the hypoglycaemic effects of the former drugs.

F. Pregnancy and lactation

Pregnancy

It is contraindicated in pregnant women.

The administration of ifosfamide during organogenesis has been shown to have a fetotoxic effect in mice, rats, and rabbits and therefore may cause fetal damage when administered to pregnant women.

There are only very limited data available on the use of ifosfamide during pregnancy in humans. Fetal growth retardation and neonatal anaemia have been reported following exposure to ifosfamidecontaining chemotherapy regimens during pregnancy. Multiple congenital deviations have been reported after use during the first trimester of pregnancy. Animal data generated with cyclophosphamide, another oxazaphosphorine cytotoxic agent suggest that an increased risk of failed pregnancy and malformations may persist after discontinuation of the agent as long as oocytes/follicles exist that were exposed to the agent during any of their maturation phases.

In addition, exposure to cyclophosphamide has been reported to cause miscarriage, malformations (following exposure during the first trimester), and neonatal effects, including leukopenia, pancytopenia, severe bone marrow hypoplasia, and gastroenteritis.

Based on the results of animal studies, human case reports and the substance's mechanism of action, the use of Ifosfamide during pregnancy, particularly in the first trimester, is advised against.

In every individual case, the benefits of the treatment will have to be weighed against possible risks for the fetus.

If ifosfamide is used during pregnancy, or if the patient becomes pregnant while taking this drug or after treatment, the patient should be apprised of the potential hazard to a fetus.

Lactation

It is contraindicated in lactating women.

Ifosfamide is passed into the breast milk and may cause neutropenia, thrombocytopenia, low haemoglobin concentrations and diarrhea in children. Women must not breastfeed during treatment with ifosfamide.

G. Effects on ability to drive and use machines

Potential side-effects on the central nervous system may transiently impair the ability to operate machinery and motor vehicles.

H. Undesirable effects

Treatment with ifosfamide may be associated with the following dose-related, generally reversible side-effects.

Urogenital tract - Urothelial toxicity is the usual dose-limiting factor. This can be largely prevented by the concurrent administration of mesna. Urotoxicity involving the efferent urinary tract as well as the bladder can lead to haemorrhagic cystitis and dysuria.

Nephrotoxicity may occur with oliguria, raised uric acid, increased blood urea and serum creatinine and decreased creatinine clearance. Glycosuria, proteinuria, aminoaciduria and hyperphosphaturia which may lead to renal rickets have been reported with changes in serum proteins and electrolytes. Nephrotoxicity is usually reversible, especially in the early stages but severe cases are recorded. Delay in the diagnosis and treatment of renal toxicity may, especially in children, lead to a full picture of Fanconi's Syndrome or diabetes insipidus. Patients with pre-existing renal dysfunction and/or prior treatment with nephrotoxic drugs such as cisplatin may be predisposed to nephrotoxicity.

Haematological reactions - large doses of ifosfamide give rise to a predictable bone marrow toxicity and consequent immunosuppression. The white cell count reaches its nadir 5-10 days after commencing treatment, recovery commencing after 10-14 days and usually returning to normal within 2-3 weeks. About 30% of patients would be expected to have a fall in haemoglobin of greater than 2 g/100 ml and a white cell count less than 2000/mm^3, but only 5% would be expected to have a platelet count less than 100,000/mm^3. There have been only occasional reports of coagulation disorders.

Central nervous system side-effects may occur. These may present as drowsiness, confusion, disorientation, restlessness, depressive psychoses and/or hallucinations, rarely convulsions. These will rarely persist beyond 2 days, and will usually resolve spontaneously after cessation of treatment. Occasionally tonic-clonic spasms, motor unrest and emotional lability have been noted.

A severe encephalopathy occurs less frequently. The symptoms may be preceded by EEG abnormalities. Clumsiness, confusion, disorientation, logorrhoea, echolalia, perseveration, aggression and depression of conscious level have been reported. Fever and tachycardia may be present. Occasionally recovery has been incomplete with persistent psychological disturbances, coma and death.
If central nervous system toxicity is suspected, ifosfamide should be stopped and supportive therapy given. There are indications of a higher incidence of CNS effects in elderly patients and those with cerebral metastases.
Special care should be taken in giving Ifosfamide to patients with reduced plasma albumin levels and/or impaired kidney function.

Gastrointestinal reactions - frequently nausea and vomiting, very occasionally anorexia, diarrhoea or constipation. Nausea and vomiting may be reduced by the prior administration of an anti-emetic.
Other side-effects include: frequent but reversible alopecia, stomatitis, dermatitis, impairment of gonadal function, hypersensitivity reactions, polyneuropathy, pneumonitis, impaired vision, increased reaction to radiation.

More rarely hepatic dysfunction (including jaundice and increased liver enzyme and/or bilirubin levels), thrombophlebitis at site of injection or syndrome of inappropriate antidiuretic hormone secretion may occur.

Isolated cases of acute pancreatitis have been reported. There have been isolated reports of cardiac arrhythmia or heart failure after very high doses of ifosfamide and/or prior or concurrent treatment with anthracyclines. As is the case with cytotoxic therapy in general, treatment with ifosfamide involves the risk of secondary tumours as late sequelae.

I. Overdose

The most serious consequences of overdosage are haemorrhagic cystitis and myelosuppression. The latter usually recovers spontaneously, but until it does, administration of a broad spectrum antibiotic may be advisable.
Transfusion of whole blood should be given as necessary. If the overdosage is recognised within the first 24 hours, i.v. mesna may be beneficial in ameliorating damage to the urinary system.

Normal supportive measures such as analgesics and maintenance of fluid balance should be instituted. If despite these measures the cystitis does not resolve, more intensive treatment may be necessary and a urological opinion should be sought. No further courses should be given until the patient has fully recovered.

5. Pharmacological properties

A. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents
ATC Code: L01AA06
Ifosfamide is an antineoplastic, a cytotoxic alkylating agent. It is a prodrug and shows no in vitro cytotoxic activity until activated by microsomal enzymes. The cytotoxic activity of Ifosfamide (alkylation of the nucleophilic centres in the cells) is associated with the activated oxazaphosphorine ring hydroxylated at the C4 atom which interacts with DNA-DNA cross linking. This activity manifests itself by blocking the late S and early G2 phases of the cell cycle.

B. Pharmacokinetic properties

Ifosfamide is rapidly absorbed from the site of administration, activation of Ifosfamide is primarily in the liver by microsomal mixed function oxidases.
Elimination of metabolised Ifosfamide is primarily via the kidneys. The serum halflife ranges between 4 - 8 hours depending on the dose and dosage regimen. Over 80% of a single dose of ifosfamide was excreted in the urine within 24 hours.
Approximately 80% of the dose was excreted as parent compound. Significant quantities of unchanged ifosfamide were found in the cerebrospinal fluid consistent with the high lipid solubility of the drug.

C. Preclinical safety data

Not relevant

6. *Pharmaceutical particulars*

A. List of excipients

Not applicable

B. Incompatibilities

Benzyl alcohol-containing solutions can reduce the stability of ifosfamide.

C. Shelf life: 2 Years

D. Special precautions for storage

Store at controlled room temperature 20°C -25°C. Protect from light. Do not freeze. Reconstituted or constituted and further diluted solutions of Ifosfamide should be refrigerated and used within 24 hours.

Note: As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solution showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

E. Nature and contents of container:

50ml Flint Glass vial with literature.

Pack containing 1 single-use vial.

G. Special precautions for disposal

The following protective recommendations are advised during handling due to the toxic nature of the substance:

Reconstitution and administration must be undertaken only by trained personnel. Pregnant staff and breastfeeding mothers should be excluded.

Protective clothing, goggles, masks and disposable PVC or latex gloves should be worn. A designated area should be defined for reconstitution (preferably under a laminar airflow system).

The work surface should be protected by a disposable, plastic backed absorbent paper. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water. Soap and water should then be used on non-mucous membranes. Spillage should be removed by dry or moist disposable towels.

Care must be taken in the disposal of all waste material (syringes, needles and disposable towels etc.) Used items should be placed in appropriate secure containers in readiness for destruction in an appropriate high-temperature incinerator with an afterburner.

7. Manufacturer

Getwell Pharmaceuticals

474, Udyog Vihar, Phase V,
Gurgaon-122016,
Haryana. INDIA
Tel. : +91-124-4014403/04
Fax : +91-124-4012497
Email: info@getwellpharma.org

MESNA INJECTION

200mg/2ml* 1. *Name of the medicinal product:

a) Product Name: MESNA INJECTION b) Strength: 200mg/2ml

c) Pharmaceutical Dosage Form: Solution for injection or infusion.

2. *Qualitative and quantitative composition*

Each ml contains

Mesna BP	100 mg
Water for Injection USP	q.s

3. **Pharmaceutical form**: Solution for Injection or Infusion

4. Clinical particulars

A. Therapeutic indications

For the prevention of urothelial toxicity including haemorrhagic cystitis, microhaematuria and macrohaematuria in patients treated with ifosfamide and cyclophosphamide, in doses considered to be urotoxic.

B. 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 non-toxic levels. This usually occurs within 8-12hours 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 ifosfamide or cyclophosphamide is used as an iv bolus: Mesna is given by intravenous injection over 15-30minutes 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 dosage schedule

	0hrs	**4hrs**	**8hrs**
Cyclophosphamide/Ifosfamide	2g	-	-
Mesna	400mg	400mg	400mg

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

	0hrs	**3hrs**	**6hrs**	**9hrs**
Cyclophosphamide/Ifosfamide	2g	-	-	-
Mesna	800mg	800mg	800mg	800mg

Where ifosfamide is used as a 24-hour infusion: Mesna can be used as a concurrent infusion. An initial 20% (w/w) of the total ifosfamide dose is given as an i.v. bolus, then an infusion of 100% (w/w) of the ifosfamide over 24 hours, followed by a further 12-hour infusion of 60% (w/w) of the ifosfamide dose. Total mesna dose = 180% of the ifosfamide dose. Example dosage schedule:

	0hrs	**0-24hrs**	**24hrs**	**28hrs**	**32hrs**	**36hrs**
Ifosfamide	-	5 g/m^2 infusion	-	-	-	-
Mesna	1 g/m^2 IV	5 g/m^2 infusion	3 g/m^2 infusion			
				1 g/m^2 IV	1 g/m^2 IV	1 g/m^2 IV

Where ifosfamide is used as a long-term infusion:
An initial 20% (w/w) of the first 24 hours ifosfamide dose is given as an i.v. bolus as the ifosfamide infusion starts.
Then each 24 hour infusion of ifosfamide 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 ifosfamide) should be commenced as the ifosfamidemesna infusion finishes. Example dosage schedule:

Day 1			**Day 2**	**Day 3**		**Day 4**		
	0hrs	**0-24hrs**	**0-24hrs**	**0-24hrs**	**24hrs**	**4hrs**	**8hrs**	**12hrs**

Ifosfamide	-	2 g/m^2 infusion	2 g/m^2 infusion	2 g/m^2 infusion	-	-	-	-
Mesna	1 g/m2 IV	2 g/m^2 infusion	2 g/m^2 infusion	2 g/m^2 infusion	1.2 g/m^2 infusion			
						0.4 g/m^2 iv	0.4 g/m^2 iv	0.4 g/m^2 iv

The final 12-hour infusion of mesna, after long-term or 24 hour infusion of ifosfamide, may be replaced by boluses at28, 32 and 36 hours, each of 20% (w/w) of the ifosfamide dose, or by oral mesna.

Mesna can be mixed in the same infusion bag as the ifosfamide.

Oral use of mesna ampoules: Mesna has been shown to be effective when taken orally. Compared with intravenous administration, overall availability of mesna in urine after oral administration is approximately 50%; the onset of urinary excretion is delayed by up to 2 hours and is more prolonged than following intravenous dosing.

With the exception of continuous long-term infusions of oxazaphosphorines with mesna, intravenously administered mesna may be replaced by oral administration of mesna. The dosage should be 40% w/w of the dosage of the oxazaphosphorines. The contents of the ampoule should be added to a flavoured soft drink (e.g. orange juice, cola).

This mixture is stable when refrigerated in a sealed container for 24 hours.

For intermittent oxazaphosphorine therapy following an initial intravenous injection of mesna at a dose of 20% (w/w) of the oxazaphosphorine dose, oral mesna (40% w/w) should be administered at 2 hours and again at 6 hours after the initial intravenous dose. Alternatively, three oral doses of mesna may be administered, replacing the i.v. dose with an oral dose (40% w/w) 2 hours prior to administration of oxazaphosphorines. Example dosage schedule:

	2hrs	**0hrs**	**2hrs**	**6hrs**
Ifosfamide/Cyclophosphamide	-	1 g iv	-	-
Mesna	400 mg PO	-	400mg PO	400mg PO
		200 mg iv	400mg PO	400mg PO

Where ifosfamide is used as a long-term continuous infusion with concomitant mesna, oral mesna may be taken as the infusion of ifosfamide and mesna finishes, then at 2 hours and 6 hours after the time at the finish of the infusion. All oral mesna doses should be 40% (w/w) of the final 24 hour ifosfamide dose.

	0hrs	**0-24hrs**	**24hrs**	**26hrs**	**30hrs**
Cyclophosphamide/Ifosfamide	-	5 g/m^2 infusion	-		
Mesna	400mg	5 g/m^2 infusion	2 g/m^2 PO	2 g/m^2 PO	2 g/m^2 PO

Example dosage schedule:
Children
Children generally micturate 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.

Elderly
No specific information is available. Clinical trials have included patients over 65 and no adverse reactions specific to this age group have been reported.

C. Contraindications

Absolute contraindication:

It is contraindicated in patients who are having known hypersensitivity to mesna or any thiol-containing compounds.

Relative Contraindication

During Pregnancy and Lactation

It is contraindicated in pregnant and lactating women.

There are no adequate data from the use of mesna in pregnant or lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing mesna.

Pregnancy and lactation are contraindications for cytostatic treatment, and consequently Mesna is not likely to be used under these circumstances.

Should an individual patient be undergoing oxazaphosphorine therapy during pregnancy then Mesna should be administered to this patient. Mothers should not breast-feed whilst being treated with these drugs.

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

D. Special warnings and precautions for use

WARNINGS Hypersensitivity

Hypersensitivity reactions to mesna have been reported following administration of mesna as an uroprotectant. These include:

Various skin and subcutaneous tissue symptoms

Cases of severe bullous and ulcerative skin and mucosal reactions were reported. Some reactions were considered to be consistent with Stevens-Johnson Syndrome, toxic epidermal necrolysis, or erythema exudativum multiforme.

In some cases, skin reactions were accompanied by one or more other symptoms, such as _ fever,
_ cardiovascular symptoms
_ signs consistent with acute renal impairment,
_ pulmonary symptoms
_ laboratory signs of disseminated intravascular coagulopathy (DIC)
_ haematological abnormalities
_ increased liver enzymes,
_ nausea, vomiting,
_ pain in the extremities, arthralgia,
myalgia, malaise, _ stomatitis, and _
conjunctivitis.

Some reactions have presented as anaphylaxis.

Fever accompanied by, e.g., hypotension but no skin manifestations has also been reported.

Severe as well as minor reactions were reported with the use of mesna in regimens to treat both severe systemic autoimmune disorders and malignancy.

In most cases, reactions occurred during or after a first treatment occasion or after several weeks of mesna exposure. In other cases, the initial reaction was observed only after several months of exposure.

In many cases, symptoms appeared on the day of exposure, with a tendency to shorter intervals following subsequent exposures.

In some patients, the occurrence and/or severity of reaction appeared to vary with the dose administered.
Recurrence of reactions, in some cases with increasing severity, has been reported with re-exposure. However, in some cases, a reaction did not recur with re-exposure.

Some patients with a history of a reaction have shown positive delayed-type skin test results. However, a negative delayed reaction does not exclude hypersensitivity to mesna. Positive immediate-type skin test reactions have occurred in patients regardless of previous mesna exposure or history of hypersensitivity reactions, and may be related to the concentration of the mesna solution used for testing.

Prescribers should
- be aware of the potential for such reactions and that reactions may worsen with reexposure and may in some cases be life-threatening,

- be aware that hypersensitivity reactions to mesna were interpreted to resemble the clinical picture of sepsis and, in patients with autoimmune disorders, resemble an exacerbation of the underlying disease.

Thiol Compounds:
Mesna is a thiol compound, i.e., a sulfhydryl (SH) group-containing organic compound. Thiol compounds show some similarities in their adverse reaction profile, including a potential to elicit severe skin reactions. Examples of drugs that are thiol compounds include amifostine, penicillamine, and captopril.

It is not clear whether patients who experienced an adverse reaction to such a drug are at increased risk for any reactions, or similar reactions, to another thiol compound. However, when considering subsequent use of another thiol compound in such patients, the possibility of an increased risk should be taken into account.

PRECAUTIONS

Mesna does not prevent haemorrhagic cystitis in all patients. Patients should be monitored accordingly.

Sufficient urinary output should be maintained, as required for oxazaphosphorine treatment.

Sodium content

Mesna solution for injection contains approximately 59 mg of sodium per 400 mg mesna.

Lab test interferences

Mesna treatment may cause false positive reactions in nitroprusside sodium-based urine tests (including dipstick tests) for ketone bodies. The addition of glacial acetic acid can be used to differentiate between a false positive result (cherryred colour that fades) and a true positive result (red-violet colour that intensifies).

Mesna treatment may cause false positive reactions in Tillman's reagent-based urine screening tests for ascorbic acid.

In pharmacokinetics studies in healthy volunteers, serum creatine phosphokinase (CPK) values were lower in samples taken 24 hours after mesna dosing than in predosing samples. While available data are insufficient to determine the cause of this phenomenon, it might be considered to represent a significant interference with thiol (e.g., Nacetylcysteine) dependent enzymatic CPK tests.

Paediatric use

Safety and effectiveness of Mesna in paediatric patients (<16 years of age) have not been established in clinical studies performed. However, the use of mesna in paediatric patients is referenced in the medical literature.

E. 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 ifosfamide 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.

Food does not influence the absorption and urinary elimination of mesna.

Common to all Cytotoxic:

No clinical significant interactions have been observed during studies.

Contraindicated

No clinical significant interactions have been observed during studies.

Prohibited

No clinical significant interactions have been observed during studies.

Precautionary Measures

Mesna is a thiol compound, i.e., a sulfhydryl (SH) group-containing organic compound. Thiol compounds show some similarities in their adverse reaction profile, including a potential to elicit severe skin reactions. Examples of drugs that are thiol compounds include amifostine, penicillamine, and captopril.

Severe as well as minor reactions were reported with the use of mesna in regimens to treat both severe systemic autoimmune disorders and malignancy.

F. Pregnancy and lactation

It is contraindicated in pregnant and lactating women.

There are no adequate data from the use of mesna in pregnant or lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing mesna.

Pregnancy and lactation are contraindications for cytostatic treatment, and consequently Mesna is not likely to be used under these circumstances.

Should an individual patient be undergoing oxazaphosphorine therapy during pregnancy then Mesna should be administered to this patient. Mothers should not breast-feed whilst being treated with these drugs.
Animal studies have shown no evidence of embryotoxic or teratogenic effects of mesna.

G. Effects on ability to drive and use machines

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

H. Undesirable effects

Because patients receive potent cytotoxic agents concurrently, the side-effect profile of mesna is difficult to define.
However, in healthy volunteers the following side-effects occurred at single doses of 60-70 mg/kg per day: nausea, vomiting, colic, diarrhoea, headache, fatigue, limb and joint pains, depression, irritability, lack of energy, rash, hypotension and tachycardia. In rare cases, pseudoallergic reactions (rash, pruritus, blistering of skin and mucous membranes, urticarial oedema, sudden hypotension, tachycardia and a transient rise of liver transaminases) have been reported. These pseudoallergic reactions appear to be more common in patients with autoimmune disorders.

I. 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

A. Pharmacodynamic properties

Pharmacotherapeutic group: detoxifying agent for antineoplastic treatment
ATC Code: VO3AF01.

Mesna is an antidote, and offers the possibility of reliably preventing urotoxic sideeffects associated with aggressive cancer chemotherapy using oxazaphosphorine cytostatics. Extensive and wide-ranging pharmacological and toxicological investigations have shown that mesna has no intrinsic pharmacodynamics and low toxicity.

The pharmacological and toxicological inertness of mesna administered systemically and its excellent detoxifying effect in the efferent urinary tract and bladder, are due to the nature of its pharmacokinetics.

B. Pharmacokinetic properties

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

C. Preclinical safety data

Not relevant

6. *Pharmaceutical particulars*

A. List of excipients

Not applicable

B. Incompatibilities

Mesna is incompatible with platinum derivatives (e.g. Cisplatin and nitrogen mustard) and must not be mixed in the same infusion solution.

C. Shelf life: 2 Years

Once opened, vials should be used immediately.

Chemical and physical in use stability have been demonstrated as follows:

Mesna is chemically compatible with 0.9 % saline or 5.0 % dextrose for 36 hours and in dextrose/saline for 24 hours at room temperature.

Mesna and ifosfamide are chemically compatible with:

(i) 0.9 % saline and dextrose/saline solution for one week at room temperature.

(ii) Water for Injections for one week under refrigeration.

(iii) 5% dextrose solution for 24 hours at room temperature.

(iv) 0.9% saline solution for 28 days at room temperature.

Mesna and cyclophosphamide are chemically compatible with:

(i) 10% dextrose solution for 2 hours at room temperature.

Mesna does not contain a preservative.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hour (less when combined with cyclophosphamide in dextrose, see above) at 2 to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

Mesna can also be stored in cola drinks or orange juice. Once opened and mixed for drinking, the mixture should be kept in the fridge in a sealed container for not more than 24 hours.

D. Special precautions for storage

Store at controlled room temperature 20°C -25°C. Protect from light. Do not freeze.

E. Nature and contents of container: 2 ml glass ampoule with literature.

Pack containing 1 single-ampoule

F. Special precautions for disposal

The following protective recommendations are advised during handling due to the toxic nature of the substance:

Reconstitution and administration must be undertaken only by trained personnel. Pregnant staff and breastfeeding mothers should be excluded.

Protective clothing, goggles, masks and disposable PVC or latex gloves should be worn. A designated area should be defined for reconstitution

(preferably under a laminar airflow system). The work surface should be protected by a disposable, plastic backed absorbent paper. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water. Soap and water should then be used on non-mucous membranes. Spillage should be removed by dry or moist disposable towels.

Care must be taken in the disposal of all waste material (syringes, needles and disposable towels etc.) Used items should be placed in appropriate secure containers in readiness for destruction in an appropriate high-temperature incinerator with an afterburner.

7. Manufacturer

Getwell Pharmaceuticals
474, Udyog Vihar, Phase V,
Gurgaon-122016,
Haryana. INDIA
Tel. : +91-124-4014403/04
Fax : +91-124-4012497
Email: info@getwellpharma.org