Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mitoxana 2 g Powder for Sterile Concentrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 g of ifosfamide.

When reconstituted as directed, each millilitre of concentrate contains 80 mg Ifosfamide.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion or injection. (Powder for Sterile Concentrate).

White powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mitoxana 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. Mitoxana is also frequently used in combination with other cytotoxic drugs, radiotherapy and surgery.

Children and adolescents – see section 5.1 - Paediatric Population.

4.2 Posology and method of administration

Ifosfamide should be administered only by physicians experienced with this drug.

Dosage must be individualised. Doses and duration of treatment and/or treatment intervals depend on the therapeutic indication, the scheme of a combination therapy, the patient's general state of health and organ function, and the results of laboratory monitoring.

Method of administration

A guide to the dosage regimens used for most indications is given below:

a) 8 - 12 g/m^2 equally fractionated as single daily doses over 3 - 5 days every 2 - 4 weeks.

b) 5 - 6 g/m^2 (maximum 10 g) given as a 24 hour infusion every 3 - 4 weeks.

The frequency of dosage is determined by the degree of myelosuppression and the time taken to recover adequate bone marrow function. The usual number of courses given is 4, but up to 7 (6 by 24 hour infusion) courses have been given. Re-treatment has been given following relapse.

In combination with other agents of similar toxicity, a dose reduction or extension of the therapy-free intervals may be necessary.

During or immediately after administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urothelial toxicity (see section 4.4).

For prophylaxis of hemorrhagic cystitis, ifosfamide should be used in combination with mesna.

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

Before parenteral administration, the substance must be completely dissolved. For instructions on dilution of the medicinal product before administration, see section 6.6.

For storage conditions of Mitoxana reconstituted in Water for Injection and further diluted in 0.9% Sodium Chloride, refer to section 6.3.

Patients with Renal Impairment:

The dose may need to be adjusted in patients with decreased renal function (see sections 4.3 and 4.4).

Ifosfamide and its metabolites are dialyzable. In patients requiring dialysis, use of a consistent interval between ifosfamide administration and dialysis should be considered.

Patients with Hepatic Impairment:

The dose may need to be adjusted in patients with decreased hepatic function (see sections 4.3 and 4.4).

Elderly:

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 (see section 5.2).

Paediatric:

In children, the dosage and administration should be determined by the tumour type, tumour stage, the general condition of the patient, any previous cytotoxic therapy, and whether chemotherapy or radiotherapy is to be administered concurrently. Clinical trials have involved doses of:

a) 5 g/m^2 over 24 hours

b) 9 g/m^2 equally fractionated as single daily doses over 5 days

c) 9 g/m^2 as a continuous infusion over 72 hours - repeated at three weekly intervals.

4.3 Contraindications

Ifosfamide is contra-indicated in patients with:

• Known hypersensitivity to ifosfamide. See section 4.4
• Urinary outflow obstruction.

Mitoxana 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.

Mitoxana is contra-indicated in patients with known hypersensitivity to ifosfamide, bone marrow aplasia, myelosuppression, urinary tract obstruction, acute infections including urinary tract infection, or with acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy.

Mitoxana 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.

4.4 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 (see section 4.5).

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 colony-stimulating factor, granulocyte macrophage colony-stimulating factor) (see section 4.5)

The risk of myelosuppression is dose dependent 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.

Encephalopathy and CNS toxicity

Administration of ifosfamide can cause encephalopathy and other neurotoxic effects

An ifosfamide-induced CNS toxicity may become manifest within a few hours to a few days after 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. If CNS toxicity develops, administration of ifosfamide should be discontinued.

CNS toxicity seems to be dose dependent. Risk factors for the development of ifosfamide associated encephalopathy include hypoalbuminaemia, impaired renal function, poor performance status, pelvic disease (e.g. presence of tumour in lower abdomen, bulky abdominal disease), and previous or concomitant nephrotoxic treatments including cisplatin.

Due to the potential for additive effects, drugs acting on the CNS (such as antiemetics, sedatives, narcotics, or antihistamines) or substances (such as alcohol) acting on the CNS must be used with particular caution or, if necessary, be discontinued in case of ifosfamide induced encephalopathy.
Patients treated with ifosfamide should be closely monitored for symptoms of encephalopathies in particular if patients are at increased risk for encephalopathies.

The use of methylene blue may be considered for the treatment and prophylaxis of ifosfamide-associated encephalopathies.

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 (see section 4.8). 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 (see section 4.8).

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 (see section 4.3).

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 (see section 4.3).

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 ST segment 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 (see section 4.8). 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

(See section 4.6 and 5.3)

Effects on Fertility

(See section 4.6)

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 and should be considered when determining the dosage in such patients (see section 4.3).

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.

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

4.5 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 pharmacodynamic 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.

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 colony-stimulating 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

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

- Busulfan
- Irradiation of the bladder

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):

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

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

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

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.

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

Cisplatin: Cisplatin-induced hearing loss can be exacerbated by concurrent ifosfamide therapy (see also interactions above).

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
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, aother oxazaphosphorine cytotoxic agent 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.

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

Fertility
Ifosfamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Ifosfamide may cause transient or permanent amenorrhea in women and oligospermia or azoospermia in boys during pre-pubescence. Men treated with Ifosfamide are informed prior to treatment about the possibility to save and keep in proper condition pre-produced sperm.

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.
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 (see Section 5.3).

4.7 Effects on ability to drive and use machines

Manifestations of CNS toxicity may impair a patients's ability to operate an automobile or other heavy machinery. See Section 4.4

4.8 Undesirable effects

The adverse reactions and frequencies below are based on publications describing clinical experience with fractionated administration of ifosfamide as monotherapy with a total dose of 4 to 12 g/m2 per course.

ADR frequency is based upon the following scale: Very common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very rare (<1/10,000), Unknown (adverse reactions reported in the post-marketing experience).

System Organ Class (SOC)	Adverse Reaction	Frequency Category
INFECTIONS AND INFESTATIONS	Infection* Pneumonia Sepsis (septic shock)**	Common Not known Not known
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYCTS AND POLYPS)	Secondary tumors - Urinary tract carcinoma	Not known Not known

	- Myelodysplastic syndrome	Not known
	- Acute leukaemia***	Not known
	- Acute lymphocytic leukemia**	Not known
	- Lymphoma (Non-Hodgkin's lymphoma)	Not known
	- Sarcomas**	Not known
	- Renal cell carcinoma	Not known
	- Thyroid cancer	Not known
	Progressions of underlying malignancies*	Not known
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Leukopenia[1] (any)	Very common
	Thrombocytopenia[2] (any)	Very common
	Anemia[3]	Very common
	Hematotoxicity**	Not known
	Myelosuppression ****	Not known
	Agranulocytosis	Not known
	Febrile bone marrow aplasia	Not known
	Disseminated intravascular coagulation	Not known
	Hemolytic uremic syndrome	Not known
	Hemolytic anemia	Not known
	Neonatal anemia	Not known
	Methaemoglobinaemia	Not known
IMMUNE SYSTEM DISORDERS	Angioedema**	Not known
	Anaphylactic reaction	Not known
	Immunosuppression	Not known
	Urticaria	Not known
	Hypersensitivity reaction	Not known
ENDOCRINE DISORDERS	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Not known
METABOLISM AND NUTRITION DISORDERS	Decreased Appetite	Common
	Tumor lysis syndrome Metabolic acidosis	Not known
	Hypokalemia	Not known
	Hypocalcemia	Not known
	Hypophosphatemia	Not known
	Hyperglycemia	Not known
	Polydipsia	Not known
PSYCHIATRIC DISORDERS	Panic attack	Not known
	Catatonia	Not known
	Mania	Not known
	Paranoia	Not known
	Delusion,	Not known
	Delirium	Not known
	Bradyphrenia	Not known
	Mutism	Not known
	Mental status change	Not known
	Echolalia	Not known
	Logorrhea	Not known
	Perseveration	Not known
	Amnesia	Not known
NERVOUS SYSTEM DISORDERS	Neurotoxicity [4,5]	Not known
	Central nervous system toxicity	Not known
	Peripheral neuropathy	Not known
	Dysarthria	Not known
	Convulsion**	Not known
	Status epilepticus (convulsive and nonconvulsive)	Not known
	Reversible posterior leukoencephalopathy	Not known
	syndrome	Not known
	Leukoencephalopathy	Not known
	Extrapyramidal disorder	Not known
	Asterixis	Not known
	Movement disorder	Not known

	Polyneuropathy	Not known
	Dysesthesia	Not known
	Hypoesthesia	Not known
	Paresthesia	Not known
	Neuralgia	Not known
	Gait disturbance	Not known
	Fecal incontinence	Not known
EYE DISORDERS	Vision blurred	Not known
	Visual impairment	Not known
	Conjunctivitis	Not known
	Eye irritation	Not known
EAR AND LABYRINTH DISORDERS	Deafness	Not known
	Hypoacusis	Not known
	Vertigo	Not known
	Tinnitus	Not known
CARDIAC DISORDERS	Cardiotoxicity[6]	Uncommon
	Arrythmia	Not known
	Ventricular arrhythmia	Not known
	Ventricular fibrillation**	Not known
	Ventricular tachycardia**	Not known
	Ventricular extrasystoles	Not known
	Supraventricular arrhythmia	Not known
	Atrial fibrillation	Not known
	Atrial flutter	Not known
	Supraventricular extrasystoles	Not known
	Premature atrial contractions	Not known
	Bradycardia	Not known
	Cardiac arrest**	Not known
	Myocardial infarction	Not known
	Cardiogenic shock**	Not known
	Cardiac failure**	Not known
	Bundle branch block left	Not known
	Bundle branch block right	Not known
	Pericardial effusion	Not known
	Myocardial hemorrhage	Not known
	Angina pectoris	Not known
	Left ventricular failure	Not known
	Cardiomyopathy**	Not known
	Congestive cardiomyopathy	Not known
	Myocarditis**	Not known
	Pericarditis	Not known
	Myocardial depression	Not known
	Palpitations	Not known
	Ejection fraction decreased**	Not known
	Electrocardiogram ST-segment abnormal	Not known
	Electrocardiogram T- wave inversion	Not known
	Electrocardiogram QRS complex abnormal	Not known
VASCULAR DISORDERS	Hypotension[7]	Uncommon
	Pulmonary embolism	Not known
	Deep vein thrombosis	Not known
	Capillary leak syndrome	Not known
	Vasculitis	Not known
	Hypertension	Not known
	Flushing	Not known
	Blood pressure decreased	Not known
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Respiratory failure**	Not known
	Acute respiratory distress syndrome**	Not known
	Pulmonary hypertension**	Not known
	Interstitial lung disease** (as manifested by	Not known

	Pulmonary fibrosis)	Not known
	Alveolitis allergic,	Not known
	Interstitial pneumonitis	Not known
	Pneumonitis**	Not known
	Pulmonary edema**	Not known
	Pleural effusion	Not known
	Bronchospasm	Not known
	Dyspnea	Not known
	Hypoxia	Not known
	Cough	Not known
GASTROINTESTINAL DISORDERS	Nausea/Vomiting	Very common
	Diarrhea	Uncommon
	Stomatitis	Uncommon
	Cecitis	Not known
	Colitis	Not known
	Enterocolitis	Not known
	Pancreatitis	Not known
	Ileus	Not known
	Gastrointestinal hemorrhage	Not known
	Mucosal ulceration	Not known
	Constipation	Not known
	Abdominal pain	Not known
	Salivary hypersecretion	Not known
HEPATOBILIARY DISORDERS	Hepatotoxicity[8]	Common
	Hepatic failure**	Not known
	Hepatitis fulminant**	Not known
	Veno-occlusive liver disease	Not known
	Portal vein thrombosis	Not known
	Cytolytic hepatitis	Not known
	Cholestasis	Not known
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Alopecia	Very common
	Dermatitis	Rare
	Papular rash	Rare
	Toxic epidermal necrolysis	Not known
	Stevens-Johnson syndrome	Not known
	Palmar-plantar erythrodysesthesia syndrome	Not known
	Radiation recall dermatitis	Not known
	Skin necrosis	Not known
	Facial swelling	Not known
	Petechiae	Not known
	Rash	Not known
	Macular rash	Not known
	Pruritus	Not known
	Erythema	Not known
	Skin hyperpigmentation	Not known
	Hyperhidrosis	Not known
	Nail disorder	Not known
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Rhabdomyolysis	Not known
	Osteomalacia	Not known
	Rickets	Not known
	Growth retardation	Not known
	Myalgia	Not known
	Arthralgia	Not known
	Pain in extremity	Not known
	Muscle twitching	Not known
RENAL AND URINARY DISORDERS	Hemorrhagic cystitis	Very common
	Hematuria	Very common
	Macrohematuria	Very common
	Renal dysfunction[10]	Very common

	Renal structural damage	Very common
	Fanconi syndrome	Not known
	Tubulointerstitial nephritis	Not known
	Nephrogenic diabetes insipidus	Not known
	Phosphaturia	Not known
	Aminoaciduria	Not known
	Polyuria	Not known
	Enuresis	Not known
	Feeling of residual urine	Not known
	Acute renal failure**	Not known
	Chronic renal failure**	Not known
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	Infertility	Not known
	Ovarian failure	Not known
	Premature menopause	Not known
	Amenorrhea	Not known
	Ovulation disorder	Not known
	Azoospermia	Not known
	Oligospermia	Not known
	Blood estrogen decreased	Not known
	Blood gonadotrophin increased	Not known
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	Fetal growth retardation	Not known
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS	Phlebitis[11]	Common
	Neutropenic fever[12]	Common
	Fatigue	Uncommon
	Malaise	Not known
	Multiorgan failure**	Not known
	General physical deterioration	Not known
	Injection/Infusion site reactions*****	Not known
	Chest pain	Not known
	Edema	Not known
	Mucosal inflammation	Not known
	Pain	Not known
	Pyrexia	Not known
	Chills	Not known

* including as well as reactivation of latent infections, including viral hepatitis, Pneumocystis jiroveci, herpes zoster, Strongyloides, progressive multifocal leukoencephalopathy, and other viral and fungal infections.
** including fatal outcomes
*** including acute myeloid leukemia, acute promyelocytic leukemia , acute lymphocytic leukemia*,
**** Myelosuppression manifested as Bone marrow failure,
***** including swelling, inflammation, pain, erythema, tenderness, pruritus;

1 The following adverse reaction terms have been reported for leukopenia: neutropenia, granulocytopenia, lymphopenia, and pancytopenia. For neutropenic fever, see point 12 below.
2 Thrombocytopenia may also be complicated by bleeding. Bleeding with fatal outcome has been reported.
3 Includes cases reported as anemia and decrease in hemoglobin/hematocrit.
4 Encephalopathy with coma and death has been reported.
5 Central nervous system toxicity was reported to be manifested by the following signs and symptoms: Abnormal behavior, Affect lability, Aggression, Agitation, Anxiety, Aphasia, Asthenia, Ataxia, Cerebellar syndrome, Cerebral function deficiency, Cognitive disorder, Coma, Confusional state, Cranial nerve dysfunction, Depressed state of consciousness, Depression, Disorientation, Dizziness, Electroencephalogram abnormal, Encephalopathy, Flat affect, Hallucinations, Headache, Ideation, Lethargy, Memory impairment, Mood change, Motor dysfunction, Muscle spasms, Myoclonus, Progressive loss of brainstem reflexes, Psychotic reaction, Restlessness, Somnolence, Tremor, Urinary incontinence.
6 Cardiotoxicity was reported as congestive heart failure, tachycardia, pulmonary edema. Fatal outcome has been reported.
7 Hypotension leading to shock and fatal outcome has been reported.

8 Hepatotoxicity was reported as increases in liver enzymes, i.e., serum alanine aminotransferase, serum aspartate aminotransferase, alkaline phosphatase, gamma¬glutamyltransferase and lactate dehydrogenase, increased bilirubin, jaundice, hepatorenal syndrome.
9 Frequency of hemorrhagic cystitis is estimated based on the frequency of hematuria. Reported symptoms of hemorrhagic cystitis included dysuria and pollakiuria.
10Renal dysfunction was reported to be manifested as: Renal failure (including acute renal failure, irreversible renal failure; fatal outcomes have been reported), Serum creatinine increased, BUN increased, Creatinine clearance decreased, Metabolic acidosis, Anuria, Oliguria, Glycosuria, Hyponatremia, Uremia, Creatinine clearance increased. Renal structural damage was reported to be manifested as: Acute tubular necrosis, Renal parenchymal damage, Enzymuria, Cylindruria, Proteinuria.
11 Includes cases reported as phlebitis and irritation of the venous walls.
12 Frequency of neutropenic fever: Includes cases reported as granulocytopenic fever.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Serious consequences of overdosage include manifestations of dose-dependent toxicities such as CNS toxicity, nephrotoxicity, myelosuppression, and mucositis (see section 4.4).

Patients who received an overdose should be closely monitored for the development of toxicities.

No specific antidote for ifosfamide is known.

Overdosage should be managed with supportive measures, including appropriate, state-of-the-art treatment for any concurrent infection, myelosuppression, or other toxicity, should it occur.

Ifosfamide as well as ifosfamide metabolites are dialyzable. Consider haemodialysis in cases of severe overdose presenting early, particularly in patients with renal impairment.

Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with overdose.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mitoxana 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 Mitoxana (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.

A variety of dosage schedules and regimens of ifosfamidein combination with other antitumor agents, are used. The prescriber should refer to chemotherapy regimens for specific tumour type in choosing a specific dosage, mode of administration and schedules.

Usually the doses of ifosfamide in pediatric tumors range from 0.8 to 3 g/m2/day for 2-5 days for a total dose of 4-12 g/m2 for chemotherapy course.

Fractionated administration of ifosfamide is performed as intravenous infusion over a period ranging between 30 minutes and 2 hours, depending on the infusion volume or recommendations of protocol:

Uroprotection with mesna is mandatory during ifosfamide administration with a dose equivalent to 80-120 % of ifosfamide. It is recommended to prolong Mesna infusion to 12-48 hours after the end of ifosfamide infusion. 20 % of the whole Mesna dose should be given as i.v start bolus. Hyperhydration with at least 3000 ml/m2 is required during ifosfamide infusion and for 24-48 hours after the end of ifosfamide administration.

Under treatment with ifosfamide, especially in case of long-term treatment, sufficient diuresis and regular control of renal function will be required. Children 5 years of age or younger may be more susceptible to ifosfamide-induced renal toxicity than older children or adults. Severe nephrotoxicity leading to Fanconi's syndrome has been reported. Progressive tubular damage resulting in potentially debilitating hypophosphatemia and rickets has been reported rarely but should be taken into consideration.

Paediatric population

Ewing's sarcoma

In a randomized controlled trial, 518 patients (87% under 17 years of age) with Ewing's Sarcoma, primitive neuroectodermal tumour of bone or primitive sarcoma of bone were randomized to ifosfamide/etoposide alternating with standard treatment, or to standard treatment alone. In those with no metastases at baseline, there was a statistically significant improvement in 5 year survival for those receiving ifosfamide /etoposide (69%) compared to those on standard treatment alone (54%). Overall survival at 5 years was 72% in the ifosfamide/etoposide group compared to 61% in the standard treatment group. Similar toxicities were observed in both treatment arms. In those with metastases at baseline, there was no difference in 5 year event-free survival or 5 year overall survival between treatment groups.

In a randomized comparative study of ifosfamide (VAIA regimen) and cyclophosphamide (VACA regimen) in 155 patients with standard risk Ewing's sarcoma (83% under 19 years of age), no difference in event free survival or overall survival was demonstrated. Less toxicity was demonstrated for the ifosfamide regimen.

Other paediatric cancers

Ifosfamide has been widely investigated in uncontrolled prospective exploratory studies in children. Various dosage schedules and regimens, in combination with other antitumour agents, have been used. The following paediatric cancers have been investigated: rhabdomyosarcoma, nonrhabdomyosarcoma soft tissue sarcoma, germ cell tumours, osteosarcoma, non-Hodgkins lymphoma, Hodgkins Lymphoma , acute lymphoblastic leukaemia, neuroblastoma, Wilms tumour, and malignant CN tumours. Favourable partial responses, complete responses and survival rates have been documented.

A variety of dosage schedules and regimens of ifosfamide in combination with other antitumor agents, are used. The prescriber should refer to chemotherapy regimens for specific tumour type in choosing a specific dosage, mode of administration and schedules.

Usually the doses of ifosfamide in pediatric tumors range from 0.8 to 3 g/m2/day for 2-5 days for a total dose of 4-12 g/m2 for chemotherapy course.

Fractionated administration of ifosfamide is performed as intravenous infusion over a period ranging between 30 minutes and 2 hours, depending on the infusion volume or recommendations of protocol: Uroprotection with mesna is mandatory during ifosfamide administration with a dose equivalent to 80-120 % of ifosfamide. It is recommended to prolong Mesna infusion to 12-48 hours after the end of ifosfamide infusion. 20 % of the whole Mesna dose should be given as i.v start bolus. Hyperhydration with at least 3000 ml/m2 is required during ifosfamide infusion and for 24-48 hours after the end of ifosfamide administration.

Under treatment with ifosfamide, especially in case of long-term treatment, sufficient diuresis and regular control of renal function will be required. Children 5 years of age or younger may be more susceptible to ifosfamide-induced renal toxicity than older children or adults. Severe nephrotoxicity leading to Fanconi's syndrome has been reported. Progressive tubular damage resulting in potentially debilitating hypophosphatemia and rickets has been reported rarely but should be taken into consideration.

Paediatric data from randomized controlled clinical studies are limited.

5.2 Pharmacokinetic properties

Mitoxana is rapidly absorbed from the site of administration. Activation of Mitoxana is primarily in the liver by microsomal mixed function oxidases. Elimination of metabolised Mitoxana is primarily via the kidneys. The serum half-life 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.

5.3 Preclinical safety data

Not relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Benzyl alcohol-containing solutions can reduce the stability of ifosfamide. It is recommended that ifosfamide is not reconstituted in Water for Injection containing Benzyl alcohol as a preservative.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 5 years.

<u>After dilution</u>

Chemical and physical in use stability has been demonstrated for 17 hours at 25°C in Sodium Chloride 0.9%.

In circumstances where the diluted solution cannot be used immediately, chemical and physical in-use stability has been demonstrated with storage at refrigerated conditions for a number of days with additional storage at 25°C for the durations indicated in the table below:

Storage at 2°C to 8°C (days)	**Subsequent in-use shelf-life at 25°C (hours)**
0	17 h
1	16 h
7	13 h

From a microbiological point of view, the infusion solution should be administered immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution/dilution has been taken place in controlled and validated aseptic condition.

6.4 Special precautions for storage

Do not store above 25°C.

Keep container in outer carton.

See section 6.3 for storage requirements after dilution.

6.5 Nature and contents of container

Type I or Type III clear glass injection vial with bromobutyl rubber closure and beading cap. Vials are packed singly in a cardboard box.

Vials are packed with or without a protective plastic overwrap. Protective plastic overwrap does not come into contact with the medicinal product and provides additional transport protection, which increases the safety for the medical and pharmaceutical personnel.

6.6 Special precautions for disposal and other handling

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

Before parenteral administration, the substance must be completely dissolved.

Administration:

Ifosfamide is inert until activated by enzymes in the liver. However, safe handling is required and advice is included under Pharmaceutical Precautions. The dry contents of a vial should be dissolved in Water for Injections as follows:

2 g vial: add 25 ml of Water for Injections

The resultant solution of 8% of ifosfamide should not be injected directly into the vein. The solution may be:

1. diluted to less than a 4% solution in Sodium Chloride 0.9% and injected directly into the vein, with the patient supine.
2. infused in Sodium Chloride 0.9% over 30-120 mins.
3. injected directly into a fast-running infusion,
4. made up in 3 x 1 litres of Sodium Chloride 0.9% and infused over 24 hours. Each litre should be given over eight hours.

See section 6.3 for storage requirements.

Repeated intravenous injections of large doses of Ifosfamide have resulted in local irritation.

Where Ifosfamide is used as an i.v. bolus, increased dosages of mesna are recommended in children, patients whose urothelium may be damaged from previous therapies and those who are not adequately protected by the standard dose of mesna.

The fluid intake of patients on the intermittent regimen should be at least 2 litres in 24 hours. As Ifosfamide may exert an antidiuretic effect, a diuretic may be necessary to ensure an adequate urinary output.

Urine should be sent for laboratory analysis before, and at the end of, each course of treatment, and the patient should be monitored for output and evidence of proteinuria and haematuria at regular intervals (4-hourly if possible) throughout the treatment period. The patient should be instructed to report any signs or symptoms of cystitis. Ifosfamide should be avoided in patients with cystitis from any cause until it has been treated.

If leucocyte count is below 4,000/mm^3 or the platelet count is below 100,000/mm^3, treatment with Ifosfamide should be withheld until the blood count returns to normal.

The handling and preparation of ifosfamide should always be in accordance with current guidelines on safe handling of cytotoxic agents.

Skin reactions associated with accidental exposure to ifosfamide may occur.

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 a chemical incinerator equipped with an after-burner.

For instructions on dilution of the product before administration, see section 4.2.
Appearance following reconstitution: clear and colourless solution.

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2299/028/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd December 1996

Date of last renewal: 3rd December 2006

10 DATE OF REVISION OF THE TEXT

September 2023