

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Mitoxana 1 g Powder for Sterile Concentrate

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 g of ifosfamide.

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

For the 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<sup>2</sup> equally fractionated as single daily doses over 3 - 5 days every 2 - 4 weeks.
- b) 5 - 6 g/m<sup>2</sup> (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.

*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<sup>2</sup> over 24 hours
- b) 9 g/m<sup>2</sup> equally fractionated as single daily doses over 5 days
- c) 9 g/m<sup>2</sup> 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  $\mu\text{mol/l}$  or 1.5  $\text{mg}/100\text{ ml}$ ) or hepatic impairment (bilirubin greater than 17  $\mu\text{mol/l}$  or 1  $\text{mg}/100\text{ ml}$ ), 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.

#### 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 (see section 4.8).

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. The possibility to reintroduce ifosfamide should be determined after careful assessment of the benefits and risks for the individual patient.

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 (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)

#### 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 (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. 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 (see section 4.3).

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

See also aprepitant below.

**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

See also aprepitant below.

**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.

**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 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 azospermia 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.

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

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

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/m<sup>2</sup> per course.

[illegible]

[illegible]

| System Organ Class (SOC)    | Adverse Reaction                                  | Frequency Category |
|-----------------------------|---------------------------------------------------|--------------------|
| NERVOUS SYSTEM DISORDERS    | Neurotoxicity <sup>4,5</sup>                      | 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 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     |
| 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          |

| System Organ Class (SOC)  | Adverse Reaction                       | Frequency Category |
|---------------------------|----------------------------------------|--------------------|
| <b>CARDIAC DISORDERS</b>  | Cardiotoxicity <sup>6</sup>            | Uncommon           |
|                           | Arrhythmia                             | 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          |
| <b>VASCULAR DISORDERS</b> | Hypotension <sup>7</sup>               | 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          |

| System Organ Class (SOC)                                | Adverse Reaction                                                                                                                                                                                                                                                                                                             | Frequency Category                                                                                                                                                        |
|---------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS</b> | Respiratory failure**<br>Acute respiratory distress syndrome**<br>Pulmonary hypertension**<br>Interstitial lung disease** (as manifested by Pulmonary fibrosis)<br>Alveolitis allergic,<br>Interstitial pneumonitis<br>Pneumonitis**<br>Pulmonary edema**<br>Pleural effusion<br>Bronchospasm<br>Dyspnea<br>Hypoxia<br>Cough | Not known<br>Not known<br>Not known<br>Not known<br><br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known |
| <b>GASTROINTESTINAL DISORDERS</b>                       | Nausea/Vomiting<br>Diarrhea<br>Stomatitis<br>Cecitis<br>Colitis<br>Enterocolitis<br>Pancreatitis<br>Ileus<br>Gastrointestinal hemorrhage<br>Mucosal ulceration<br>Constipation<br>Abdominal pain<br>Salivary hypersecretion                                                                                                  | Very common<br>Uncommon<br>Uncommon<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known     |
| <b>HEPATOBIILIARY DISORDERS</b>                         | Hepatotoxicity <sup>8</sup><br>Hepatic failure**<br>Hepatitis fulminant**<br>Veno-occlusive liver disease<br>Portal vein thrombosis<br>Cytolytic hepatitis<br>Cholestasis                                                                                                                                                    | Common<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known                                                                                      |

[illegible]

| System Organ Class (SOC)                                    | Adverse Reaction                                                                                                                                                                                                                                                 | Frequency Category                                                                                                                                             |
|-------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>             | Infertility<br>Ovarian failure<br>Premature menopause<br>Amenorrhea<br>Ovulation disorder<br>Azoospermia<br>Oligospermia<br>Blood estrogen decreased<br>Blood gonadotrophin increased                                                                            | Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known                                              |
| <b>CONGENITAL, FAMILIAL AND GENETIC DISORDERS</b>           | Fetal growth retardation                                                                                                                                                                                                                                         | Not known                                                                                                                                                      |
| <b>GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS</b> | Phlebitis <sup>11</sup><br>Neutropenic fever <sup>12</sup><br>Fatigue<br>Malaise<br>Multiorgan failure**<br>General physical deterioration<br>Injection/Infusion site reactions*****<br>Chest pain<br>Edema<br>Mucosal inflammation<br>Pain<br>Pyrexia<br>Chills | Common<br>Common<br>Uncommon<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>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.
- 10 Renal 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,  
Earlsfort Terrace,  
IRL - Dublin 2.  
Tel: +353 1 6764971  
Fax: +353 1 6762517  
Website: [www.hpra.ie](http://www.hpra.ie)  
E-mail: [medsafety@hpra.ie](mailto:medsafety@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 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/m<sup>2</sup>/day for 2-5 days for a total dose of 4-12 g/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup>/day for 2-5 days for a total dose of 4-12 g/m<sup>2</sup> 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/m<sup>2</sup> 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.

Chemical and physical in-use stability has been demonstrated for ifosfamide as a 4% solution in Water for Injections, 0.9% saline, dextrose/saline and dextrose solutions at room temperature for 7 days. Ifosfamide and mesna when prepared under strict aseptic conditions at the recommended dilutions are chemically stable with:

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

(ii) Water for Injections for one week under refrigeration

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

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

From a microbiological point of view, the reconstituted solution 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 not normally be longer than 24 hours at 2-8°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

### **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 reconstitution.

#### **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:

1 g vial: add 12.5 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 and injected directly into the vein, with the patient supine.
2. infused in 5% dextrose-saline or normal saline over 30-120 mins.
3. injected directly into a fast-running infusion,
4. made up in 3 x 1 litres of dextrose-saline or normal saline and infused over 24 hours. Each litre should be given over eight hours, and should be freshly made up immediately before infusion.

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<sup>3</sup> or the platelet count is below 100,000/mm<sup>3</sup>, 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**

PA 2299/028/001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 3<sup>rd</sup> December 1996

Date of last renewal: 3<sup>rd</sup> December 2006

**10. DATE OF REVISION OF THE TEXT**

April 2019