Baxter

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the proprietary medicinal product

Ifosfamide Injection 2g

2. Qualitative and quantitative composition

Each vial contains 2g of ifosfamide.

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

3. Pharmaceutical form (including route of administration)

Powder for concentrate for solution for infusion.

White powder.

4. Clinical particulars

4.1 Therapeutic indications

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

Children and adolescents - see section 5.1-Paediatric population

4.2 Posology and method of administration

For intravenous use as a diluted solution only - by infusion, or if solution is less than 4% by direct injection. Ifosfamide should only be used by clinicians experienced in the use of cancer chemotherapy.

Dosage: Ifosfamide should not be used without the concurrent administration of Mesna to protect against urothelial toxicity that can occur with the oxazaphosphorine alkylating agents. The dose and frequency of administration should be determined by the tumour type, tumour stage, the general condition of the patient, the extent of any previous cytotoxic therapy, and whether other chemotherapy or radiotherapy is to be administered concurrently.

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

a) 8 - 12 g/m² equally fractionated as single daily doses over 3 - 5 days every 2 - 4 weeks.

b) 5 - 6 g/m² (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.

Children:

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/m² over 24 hours
b) 9 g/m² equally fractionated as single daily doses over 5 days
c) 9 g/m² as a continuous infusion over 72 hours

- repeated at three weekly intervals**.**

Elderly:

No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

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
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 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.

Care should be taken that extravasation does not take place, however, should it occur local tissue damage is unlikely and no specific measures need be taken. Repeated intravenous injections of large doses of Ifosfamide have resulted in local irritation.

Mesna should be used to prevent urothelial toxicity.

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 patient should be well hydrated and maintained in fluid balance, replacement fluids being given as necessary to achieve this. 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.

Antiemetics given before, during and after therapy may reduce nausea and vomiting. Oral hygiene is important.

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.

There should be no signs or symptoms of urothelial toxicity or renal or hepatic impairment prior to the start of each course of Ifosfamide.

4.3 Contraindications

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

Ifosfamide 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.

Ifosfamide is contra-indicated in patients with renal impairment (serum creatinine greater than 120 mcmol/l or 1.5 mg/100 ml) or hepatic impairment (bilirubin greater than 17 mcmol/l or 1 mg/100 ml), or serum transaminases or alkaline phosphatase more than 2.5 times the upper limit of normal.

Contraception in both sexes is advised during and for at least 6 months after Ifosfamide therapy. Patients should receive counselling with respect to subsequent pregnancies.

4.4 Special warnings and special precautions for use

Care should be exercised in patients who are elderly, debilitated, have diabetes mellitus or evidence of myelosuppression or who have recently received or are receiving concurrent treatment with radiotherapy or cytotoxic agents. Any electrolyte imbalances should be corrected before treatment is started.

Caution is necessary in patients who have previously received platinum compounds or undergone a nephrectomy.

In children, high cumulative doses of ifosfamide and continued treatment in the presence of renal tubular dysfunction may be associated with increased frequency or severity of renal damage.

Ifosfamide is a potent immunuosuppressive drug and the increased risk to the patient should be borne in mind.

Amenorrhoea and azoospermia can occur. Patients should be warned of a potential risk to future progeny.

Ifosfamide has been shown to be mutagenic, teratogenic and carcinogenic in laboratory tests and there is a risk of drug-induced neoplasia following long-term treatment.

4.5 Interaction with other medicaments and other forms of interaction

Concurrent administration of anticoagulants, especially warfarin, can result in disturbance of anticoagulant control and an increased risk of bleeding.

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.

The prior or concurrent administration of nephrotoxic agents like cisplatin, aminoglycosides, acyclovir or amphotericin B may enhance the nephrotoxic, haemotoxic and neurotoxic (CNS) effects of ifosfamide. Enhanced neurotoxicity may occur with concurrent use of barbiturates.

Prior treatment with enzyme inducing drugs may result in a faster metabolism of ifosfamide.

4.6 Pregnancy and lactation

Contraception is advised in both sexes during Ifosfamide therapy and for at least six months following treatment. Patients should receive counselling with respect to subsequent pregnancies. Mothers should not breast-feed while being treated with Ifosfamide as ifosfamide has been shown to be teratogenic in animals and is excreted in breast milk.

Ifosfamide should not be used in pregnancy especially the first trimester, unless the expected benefit is thought to outweigh the substantial risk to the foetus.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Nephrotoxicity may occur with oliguria, raised uric acid, increased blood urea and serum creatinine and decreased creatinine clearance. Glycosuria, proteinuria, aminoaciduria and hyperphosphaturia which may lead to renal rickets have been reported with changes in serum proteins and electrolytes. Nephrotoxicity is usually

reversible, especially in the early stages but severe cases are recorded. Delay in the diagnosis and treatment of renal toxicity may, especially in children, lead to a full picture of Fanconi's Syndrome or diabetes insipidus. Patients with pre-existing renal dysfunction and/or prior treatment with nephrotoxic drugs such as cisplatin may be predisposed to nephrotoxicity.

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

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

A severe encephalopathy occurs less frequently. The symptoms may be preceded by EEG abnormalities. Clumsiness, confusion, disorientation, logorrhoea, echolalia, perseveration, aggression and depression of conscious level have been reported. Fever and tachycardia may be present. Occasionally recovery has been incomplete with persistent psychological disturbances, coma and death.

If central nervous system toxicity is suspected, ifosfamide should be stopped and supportive therapy given. There are indications of a higher incidence of CNS effects in elderly patients and those with cerebral metastases. Special care should be taken in giving Ifosfamide to patients with reduced plasma albumin levels and/or impaired kidney function.

Gastrointestinal reactions - frequently nausea and vomiting, very occasionally anorexia, diarrhoea or constipation. Nausea and vomiting may be reduced by the prior administration of an anti-emetic.

Other side-effects include: frequent but reversible alopecia, stomatitis, dermatitis, impairment of gonadal function, hypersensitivity reactions, polyneuropathy, pneumonitis, impaired vision, increased reaction to radiation.

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

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

4.9 Overdose

The most serious consequences of overdosage are haemorrhagic cystitis and myelosuppression. The latter usually recovers spontaneously, but until it does, administration of a broad spectrum antibiotic may be advisable.

Transfusion of whole blood should be given as necessary. If the overdosage is recognised within the first 24 hours, i.v. mesna may be beneficial in ameliorating damage to the urinary system.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

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 CNS tumours.
Favourable partial responses, complete responses and survival rates have been documented.

Paediatric data from randomized controlled clinical studies are limited.

5.2 Pharmacokinetic properties

Ifosfamide is rapidly absorbed from the site of administration, activation of Ifosfamide is primarily in the liver by microsomal mixed function oxidases. Elimination of metabolised Ifosfamide is primarily via the kidneys. The serum 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

None known.

6.3 Shelf life

Five years.

The reconstituted solution should be used immediately. The product does not contain a preservative, therefore microbial stability cannot be guaranteed. When prepared under strict aseptic conditions, ifosfamide is, as a 4% solution, however, chemically stable for 7 days at room temperature with Water for Injections, 0.9% saline, dextrose/saline and dextrose solutions. 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.

6.4 Special precautions for storage

Do not store above 25°C.

Keep container in outer carton.

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.

6.6 Instructions for use and handling

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

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

Protective clothing, goggles, masks and disposable PVC or latex gloves should be worn.

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

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

7. Marketing Authorisation Holder

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8. Marketing authorisation number

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10. Date of revision of the Text

10th July 2012