



**IFOSFAMIDE 40 MG/ML SOLUTION FOR INFUSION
PL 00116/0421**

UKPAR

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**IFOSFAMIDE 40 MG/ML SOLUTION FOR INFUSION
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LAY SUMMARY

The MHRA granted Baxter Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Ifosfamide 40mg/ml solution for infusion (PL 00116/0421). This is a prescription only medicine (POM) for the treatment of various cancers.

Ifosfamide 40mg/ml solution for infusion contains the active ingredient ifosfamide which is a cytotoxic drug.

No unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Ifosfamide 40mg/ml solution for infusion outweigh the risks, hence a Marketing Authorisation has been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Ifosfamide 40mg/ml solution for infusion (PL 00116/0421) to Baxter Healthcare Limited on 18 December 2006. The product is a prescription only medicine.

The application was submitted as a line extension of the existing product Mitoxana Lyophilisate (Baxter Healthcare Limited) for a new pharmaceutical form.

The product contains the active ingredient ifosfamide, a nitrogen mustard analogue that is metabolised and activated enzymatically in the liver by the P450 cytochrome system. The alkylating metabolites of ifosfamide have been shown to interact with DNA. Other metabolites produced in the process are responsible for the demonstrated toxicity of ifosfamide.

Ifosfamide 40mg/ml solution for infusion is indicated for the treatment of malignant disease and may be used in combination with other cytotoxic drugs, radiotherapy and surgery.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The product is formulated as an aqueous based solution for infusion containing the active pharmaceutical ingredient ifosfamide at a strength of 40 mg/ml. The excipients present are sodium chloride (NaCl), sodium phosphate dibasic decahydrate ($\text{Na}_2\text{HPO}_4 \cdot 10\text{H}_2\text{O}$), sodium phosphate monobasic dihydrate ($\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$), 10% phosphoric acid ($\text{o-H}_3\text{PO}_4$) and water for injections.

The solution is presented in colourless moulded type I glass vials with bromobutyl grey rubber stoppers, sealed with aluminium crimping caps and a plastic cap. Vials are available in 25ml or 50ml sizes.

DRUG SUBSTANCE

Ifosfamide

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Ifosfamide is stored in appropriate packaging.

Appropriate stability data have been generated which support a retest period of 12 months when stored in the proposed packaging.

DRUG PRODUCT

Other ingredients

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

Manufacture

A full description and a detailed flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation has been carried out.

Finished product specification

The finished product specification is acceptable and the analytical methods used have been suitably validated. Certificates of analysis have been provided for all reference standards used. Batch analysis data have demonstrated compliance with the release specification.

Container Closure System

Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 18 months has been set, which is satisfactory. Storage conditions are “Store between 2°C and 8°C.”

SPC, PIL and LABELS

The SPC, PIL and labels are pharmaceutically acceptable.

CONCLUSION

It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

This is a line extension of the product Mitoxana Lyophilisate, a powder for injection after reconstitution, which was initially granted to Asta Medica Limited. A change of ownership was subsequently granted to Baxter Healthcare Limited and the current application seeks the authorisation for a solution for injection with the active ingredient left unchanged.

Ifosfamide is a cytotoxic agent which is chemically related to nitrogen mustard and is a synthetic analogue of cyclophosphamide. Since ifosfamide's first approval, a large variety of malignancies have been studied to assess their responses. Solid tumours (e.g. those of the lung, cervix, endometrium, ovary, breast, testes, pancreas and thymus) have been shown to respond to intravenous administration of ifosfamide as well as sarcomas and malignant lymphoma.

INDICATIONS

The proposed indications are:

Ifosfamide solution for infusion 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 solution for infusion is also frequently used in combination with other cytotoxic drugs, radiotherapy and surgery.

These are considered satisfactory and to be consistent with the SPC for Mitoxana Lyophilisate.

DOSE AND DOSE SCHEDULE

The proposed dose and dose schedule for this product to be used for the above indications are the same as for Mitoxana Lyophilisate.

CLINICAL PHARMACOLOGY

No studies or new data were presented in this application and none are required.

CLINICAL EFFICACY

No new efficacy data were presented in this application and none are required.

CLINICAL SAFETY

Additional adverse drug event data was collected which was consistent with the known toxicity of ifosfamide. As a result, additional undesirable effects were included in the SPC which have been supported by the International Core Data Sheet and the Clinical Expert Report.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified medical doctor. It is an adequate summary of the clinical data provided in the dossier.

SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSIONS

The risk benefit of the proposed formulation is considered to be no different to that of the existing product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ifosfamide 40mg/ml solution for infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

As this is a new formulation of an existing product using the same active ingredient no bioequivalence data was required for Ifosfamide 40mg/ml solution for infusion.

No unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and are based on those for Mitoxana Lyophilisate.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the Marketing Authorisation application on 01 June 2005.
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 12 July 2005.
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 06 February 2006 and further information relating to the clinical dossier on 19 May 2006.
- 4 The applicant responded to the MHRA's requests, providing further information on 12 May 2006 relating to the quality sections and on 24 July 2006 relating to the clinical sections.
- 5 The application was determined on 18 December 2006.

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STEPS TAKEN AFTER AUTHORISATION – SUMMARY

Date submitted	Application type	Scope	Outcome
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ifosfamide 40 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Ifosfamide

1 vial with 25 ml solution for infusion contains: Ifosfamide 1 g (40 mg/ml)

1 vial with 50 ml solution for infusion contains: Ifosfamide 2 g (40 mg/ml)

For full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Galenical form and amount of active ingredient per unit dose

Solution for infusion: vials containing 1g/25ml and 2g/50ml solution

Clear, colourless solution, practically free of foreign particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ifosfamide solution for infusion is to be administered exclusively by physicians with experience in oncology.

Ifosfamide solution for infusion 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 solution for infusion is also frequently used in combination with other cytotoxic drugs, radiotherapy and surgery.

4.2 Posology and method of administration

Dosage must always be adapted to the individual needs and under consideration of the general state of health and the blood picture.

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.

Compared to fractionated administration, administration of ifosfamide as a high single dose may lead to more severe haematological, urological, nephrological and CNS toxicities.

Note:

The dosage recommendations mentioned above shall mainly apply in case of monotherapy with ifosfamide. When used together with other cytostatic agents as combination chemotherapy, the dosage instructions of the appropriate therapy scheme must be observed.

When used in combination with other chemotherapeutic substances of similar toxicity, dose reduction and/or extension of the treatment-free intervals might become necessary.

Special dosage recommendations:

Children and adolescents

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 or weak patients

In general, dose selection for elderly patients should be cautious, reflecting the higher frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

Patients with impaired renal function

Use of ifosfamide is contra-indicated in patients with renal impairment.

Patients with impaired hepatic function

Use of ifosfamide is contra-indicated in patients with hepatic impairment.

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Use of ifosfamide is contra-indicated in patients with hepatic impairment.

4.3 Contraindications

Ifosfamide is contraindicated in patients with

- known hypersensitivity to ifosfamide
- severely impaired bone-marrow function (especially in patients previously treated with cytotoxic agents or radiotherapy)
- inflammation of the urinary bladder (cystitis)
- impaired renal function and/or obstructions of the urine flow
- hepatic impairment
- acute infections
- pregnancy and lactation (see separate section 'Pregnancy and lactation').

4.4 Special warnings and precautions for use

Blood and lymphatic system disorders / Investigations

Until normalization, the blood picture must be controlled on a regular basis. Fairly severe myelosuppression must be expected in patients pre-treated with chemotherapy and/or radiation therapy or in patients with impaired renal function. Therefore, a close haematological monitoring is recommended. White blood cell (WBC) count, platelet (Pt) count and haemoglobin (Hb) values should be obtained prior to each administration and at appropriate intervals if necessary every day. Unless essential, ifosfamide should not be given to patients with a WBC count below 2.500/ μ l. In case of fever and/or leukopenia antibiotics and/or antimycotics must be given prophylactically.

Immune system disorders

Patients with weak immune defence (e.g. in case of diabetes mellitus or chronic liver or kidney disorders) need to be closely monitored.

Psychiatric disorders / Nervous system disorders

Patients with brain metastases and/or cerebral symptoms must be monitored on a regular basis.

The risk of toxic effects of ifosfamide on the CNS necessitates careful monitoring of the patient. In case of encephalopathy development, treatment with ifosfamide is to be discontinued and must not be restarted.

Risk factors to develop an encephalopathy are impaired renal function (creatinine > 1.5 mg/dl), pre-treatment with nephrotoxic drugs (e.g. cisplatin) and post-renal obstructions (e.g. pelvic tumours).

Further risk factors for encephalopathy include a poor general state of health, old age, a history of alcohol abuse, decreased levels of serum albumin or serum hydrogen carbonate, acidosis and hepatic dysfunction.

Drugs acting on the CNS (such as antiemetics, tranquillizers, narcotics or antihistamines) are to be used with particular caution in the case of ifosfamide-induced encephalopathy or should be discontinued, if possible.

Cardiac disorders / Investigations

Special caution must be exercised in patients with pre-existent cardiac disorders. There is a need for regular electrolyte controls. Furthermore, there is evidence that the cardiotoxic effect of ifosfamide may be enhanced in patients who have received previous radiation treatment of the heart region and/or adjuvant treatment with anthracyclines.

Gastrointestinal disorders

To reduce stomatitis attention should be paid to thorough oral hygiene.

Antiemetics must be administered in time to reduce frequency and severity of nausea and vomiting.

Renal and urinary disorders

Use in patients who already suffer from renal impairment before treatment is initiated shall be subject to appraisal of the individual case. Close monitoring of these patients is recommended (see also special dosing recommendations).

Under treatment, renal function, urinary status as well as urinary sediment must be checked regularly.

It is recommended that a urine analysis should be obtained prior to each dose of ifosfamide. Outflow disturbances in the efferent urinary tract, cystitis as well as infections and electrolyte imbalances must be ruled out or eliminated before start of therapy. In case, cystitis

accompanied by gross haematuria or microhaematuria is present under the treatment with ifosfamide, therapy must be interrupted until normalization is obtained.

Under treatment with ifosfamide, special attention should be paid to sufficient hydration, regular drain of the bladder and the use of mesna (refer to "Posology/Administration").

Especially in case of long-term treatment with ifosfamide, sufficient diuresis and regular control of renal function will be required. In particular, this shall apply to children. In case of onset of nephropathy, irreversible kidney damage must be expected if treatment with ifosfamide is continued. Careful appraisal of the risk-benefit ratio will be required.

Predisposing factors for nephrotoxicity include large cumulative doses of ifosfamide (in particular for children below 3 years of age). Therefore, glomerular and tubular kidney function must be evaluated and checked before commencement of therapy, as well as during and after treatment.

Caution is required in nephrectomised patients, in patients with impaired renal function and in patients pre-treated with nephrotoxic drugs (such as cisplatin). In these patients, frequency and intensity of myelotoxicity, nephrotoxicity and cerebral toxicity are increased.

Reproductive system and breast disorders / Congenital, familial and genetic disorders

Ifosfamide has a mutagenic potential and genotoxic effect. Men to be treated with ifosfamide should be informed about sperm preservation before treatment starts and should not father a child, neither during therapy nor until up to six months after end of such therapy.

General disorders and administration site conditions

As the cytostatic effect of ifosfamide occurs only after its activation in the liver, there is no risk of injuring the tissue in case of accidental paravenous administration of an ifosfamide solution. However, in case of extravasation, it is recommended to stop infusion immediately, to aspirate the paravasate with the needle in place, to irrigate with saline solution and to immobilize the extremity.

Investigations

The blood sugar level should be checked regularly in diabetic patients in order to adjust antidiabetic therapy on time. See also interactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products and other forms of interaction:

Potiation of the myelotoxicity due to interaction with other cytostatic agents or irradiation must be considered. Concomitant administration of ifosfamide and allopurinol or hydrochlorothiazide may also increase the myelosuppressive effect.

Due to the immunosuppressant effects of ifosfamide a reduced response to the respective vaccines must be expected. In case of live vaccines a vaccine-induced infection may develop.

The concurrent use of ifosfamide with warfarin may increase the anticoagulant effect of warfarin and thus raise the risk of haemorrhage.

The prior or concomitant administration of nephrotoxic drugs, such as cisplatin, aminoglycosides, acyclovir or amphotericin B may intensify the nephrotoxic effects of ifosfamide and consequently hematotoxicity and CNS toxicity.

Drugs acting on the CNS (e.g. antiemetics, tranquillizers, narcotics or antihistamines) are to be used with particular caution in the case of ifosfamide-induced encephalopathy or, if possible, discontinued.

The treatment may increase the blood glucose-lowering (hypoglycaemic) effect of sulfonylureas.

Findings from in vitro experiments indicate that bupropion is mainly catabolised via the microsomal enzyme cytochrome P450 IIB6 (CYP2B6). Therefore, caution must be exercised in case of concomitant administration of bupropion and preparations that act on the isoenzyme CYP2B6 (such as orphenadrine, cyclophosphamide and ifosfamide). In case of previous or concomitant treatment with phenobarbital, phenytoin, benzodiazepines, primidone, carbamazepine, rifampicin or chloralhydrate there is a risk to induce the ubiquitous microsomal CYP isoenzymes, which are particularly present in the liver.

Grapefruits contain a substance which leads to an inhibition of CYP isoenzymes and therefore may reduce metabolic activation of ifosfamide and consequently its efficacy. For this reason, patients treated with ifosfamide should avoid eating grapefruits and/or the consumption of food or beverages containing this fruit.

Ifosfamide may intensify dermal radiation reaction (radiation recall syndrome).

The following interactions are conceivable in analogy to cyclophosphamide: The therapeutic effect and the toxicity of ifosfamide may be enhanced by the concurrent administration of chlorpromazine, triiodothyronine or aldehyde dehydrogenase

inhibitors such as disulfiram (Antabus). Potentiation of the muscle-relaxant effect of suxamethonium

4.6 Pregnancy and lactation

Women should not become pregnant during treatment with ifosfamide.

Animal studies indicate that treatment with ifosfamide may have a genotoxic effect and may cause foetal damage when administered to pregnant women. In case of vital indication during the first trimester of pregnancy a medical consultation regarding abortion is absolutely necessary. After the first trimester of pregnancy, if therapy cannot be delayed, chemotherapy may be undertaken after informing the patient of the minor but possible risk of teratogenic effects and the potential hazard for the foetus.

If treatment should be required in women with childbearing potential a reliable contraceptive method must be used during the therapy as well as for up to six months after the end of treatment. If ifosfamide is used during pregnancy, or if the patient becomes pregnant while taking ifosfamide, the patient should be apprised of.

Mothers should not breast-feed while being treated with Ifosfamide solution for infusion as ifosfamide has been shown to be teratogenic in animals and is excreted in breast milk.

4.7 Effects on ability to drive and use machines

Ifosfamide can lead to impairment of the ability to drive a vehicle or to operate machinery, directly by inducing encephalopathy and indirectly by inducing nausea and vomiting - particularly in the case of concomitant administration of medical products acting on the CNS or consumption of alcohol.

4.8 Undesirable effects

In patients receiving ifosfamide as a single agent, the dose-limiting toxicities are myelosuppression and urotoxicity. An uroprotector such as mesna, vigorous hydration and dose fractionation can significantly reduce the incidence of haematuria, especially gross haematuria, associated with hemorrhagic cystitis. Leukopenia, when it occurs, is usually mild to moderate. Other significant side effects include alopecia, nausea, vomiting, and central nervous system toxicities.

Undesirable effects: Incidence

Primary SOC	Very common > 1/ 10	Common > 1/ 100 - < 1/ 10	Uncommon > 1/ 1000 - < 1/ 100	Rare >1/ 10 000 - < 1/ 1000	Very rare > 1/ 10 000, incl. isolated reports
Infections and		Infections	Pneumonia		

infestations			Sepsis		
Neoplasm benign and malignant (incl. cysts and polyps)			Secondary tumours Urinary tract carcinoma Myelodysplastic syndrome Acute leukaemia		
Blood and lymphatic system disorders	Myelosuppression Leukopenia Neutropenia	Thrombocytopenia		Anaemia Pancytopenia	Haemolytic uremic syndrome Disseminated intravascular coagulation
Immune system disorders				Hypersensitivity reactions	Anaphylactic shock
Endocrine disorders			Irreversible ovulation disturbances	SIADH (Syndrome of inadequate ADH secretion)	
Metabolism and nutrition disorders		Metabolic acidosis	Anorexia	Hyponatremia Dehydration Water retention Electrolyte imbalance	Hypokalaemia
Psychiatric disorders			Hallucinations Depressive psychosis Disorientation Restlessness Confusion		
Nervous system disorders	Encephalopathy Drowsiness		Somnolence Forgetfulness Dizziness	Cerebellar syndrome	Coma Seizures Polyneuropathy Tachycardia
Eye disorders				Blurred vision	Visual impairment
Cardiac disorders			Arrhythmia Ventricular arrhythmia		Cardiac arrest Myocardial infarction

			Supraventricular arrhythmia Cardiac failure		
Vascular disorders			Bleeding	Hypotension	Thromboembolism
Respiratory disorders				Pulmonary disorder Cough Dyspnea	Interstitial pneumonitis Interstitial pulmonary fibrosis Respiratory failure Toxic allergic pulmonary oedema
Gastrointestinal disorders	Nausea Vomiting		Diarrhoea Constipation	Stomatitis Faecal incontinence	Acute pancreatitis
Hepatobiliary disorders			Liver function disturbances		Jaundice
Skin and subcutaneous tissue disorder	Alopecia			Rash Dermatitis	Toxic skin reactions
Musculoskeletal and connective tissue disorders				Cramps	Rickets Osteomalacia Rhabdomyolysis
Renal and urinary disorders	Haematuria Micro-haematuria	Hemorrhagic cystitis Nephropathies Tubular dysfunction Macro-haematuria Increased creatinine Decreased creatinine clearance	Incontinence Dysuria Disturbed urinary frequency Bladder irritation	Glomerular dysfunctions Tubular acidosis Proteinuria Acute renal failure Chronic renal failure Urinary incontinence	Fanconi Syndrome
Reproductive system and breast disorders		Impairment of spermatogenesis	Amenorrhoea Reduced levels of female sex hormones	Azoospermia Persistent oligospermia	
General disorders and administration	Fever	Asthenic conditions Fatigue		Mucositis Injection site reactions	Death

site conditions		Weakness Malaise			
Investigations			Elevation of the ST segment Increase in liver enzymes Increase in SGOT Increase in SGPT Increase in gamma-GT Increase in ALP Increase in bilirubin	Phosphaturia	
Injury poisoning and procedural complications					Intensified reaction on radiotherapy
Congenital, familial and genetic disorders				Aminoaciduria	

Infections and infestations / Respiratory disorders

Uncommonly, pneumonia has been reported.

Very rarely interstitial pneumonitis and chronic interstitial pulmonary fibrosis may occur.

Rarely pulmonary disorders are accompanied with clinical signs such as cough, dyspnea, progressing very rarely into respiratory failure.

Very rare cases of toxic-allergic pulmonary oedema were described.

Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)

As generally with alkylating agents, therapy with ifosfamide also uncommonly involves a risk of development of secondary tumours or their precursors as a late sequelae: Urinary tract carcinomas and myelodysplastic syndrome culminating in acute leukaemia have been reported amongst others. Animal studies proved that the risk of bladder cancer can be markedly reduced by an adequate administration of mesna.

Blood and lymphatic system disorders / Infections and infestations / Vascular disorders / General disorders and administration site conditions

Myelosuppression is very common, dose-related and dose-limiting. It consists mainly of leukopenia and, to a lesser extent of thrombocytopenia associated with a higher risk of bleeding. At higher dosages, leukopenia is almost universal. In general, anemia is a rare complication and does not develop until several treatment cycles have been given.

Myelosuppression is usually reversible and treatment can be given every 3 to 4 weeks. When ifosfamide is used in combination with other myelosuppressive agents,

adjustments in dosing may be necessary. Fever can occur in context of neutropenia and may be accompanied with infections. Patients who experience severe myelosuppression are potentially at increased risk for infection that may progress into a life threatening sepsis.

There are certain complications, such as thromboembolism, DIC (disseminated intravascular coagulation), or haemolytic uremic syndrome (HUS), that may be induced by the underlying disease, but that might occur with an increased frequency under chemotherapy that includes ifosfamide.

Immune system disorders / Vascular disorders / Skin and subcutaneous tissue disorders

In rare cases, hypersensitivity reactions have been reported. Common clinical signs are rash, fever hypotension etc. Very rarely allergic reactions may progress to anaphylactic shock.

Endocrine disorders / Metabolism and nutrition disorders

In rare cases, SIADH (syndrome of inadequate ADH secretion) with hyponatraemia and water retention and associated symptoms (confusion, cramps) have been observed.

Musculoskeletal and connective tissue disorders

In very rare cases ifosfamide containing combination chemotherapy may be a contributing factor in the development of rhabdomyolysis.

Psychiatric disorders / Nervous system disorders

Very commonly, encephalopathy may occur. It may develop within a few hours up to a few days after the treatment with ifosfamide was initiated. The encephalopathy and associated symptoms are usually reversible and disappear spontaneously within a few days after the last administration of ifosfamide.

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.

There are reports about a more rapid symptom relief when methylene blue is used in patients who have developed ifosfamide induced encephalopathy. Other reports, however, do not support the use of methylene blue in this situation. Therefore methylene blue should be considered as a treatment option only for those patients who have developed very severe ifosfamide induced encephalopathies after a concise risk-benefit analysis.

Rarely, polyneuropathy may occur.

Eye disorders

Rarely, transient blurred vision and isolated cases of visual impairment were reported.

Cardiac disorders / Investigations

Uncommonly, arrhythmias such as ventricular and supraventricular arrhythmia, elevations of the ST segment and cardiac failure have been reported, especially following administration of extremely high doses of ifosfamide. In very rare cases arrhythmias may progress to fatal cardiac arrest. In very rare cases myocardial infarction has been reported, which however cannot be clearly attributed to ifosfamide treatment.

Gastrointestinal disorders / Metabolism and nutrition disorders / General disorders and administration site conditions

Nausea and vomiting are very common dose-dependent side effects. Moderate to severe forms occur in about 50% of the patients and may lead to dehydration. Uncommonly anorexia, diarrhoea, constipation and rarely mucositis/stomatitis have been seen.

In very rare cases acute pancreatitis may develop.

Hepatobiliary disorders/ Investigations

Uncommonly, liver function disturbances accompanied by increases in liver enzymes such as SGOT, SGPT, gamma-GT, ALP and/or bilirubin may occur.

Skin and subcutaneous tissue disorders

Alopecia is a very common side effect. Depending on the dose administered and the duration of treatment, it may occur in up to 100% of the patients, but is reversible in general.

Rare cases of dermatitis and very rare cases of toxic skin reactions may develop.

Very rare cases of intensified skin reactions on radiotherapy (radiation recall syndrome) have been reported.

Renal and urinary disorders / Metabolism and nutrition disorders / Musculoskeletal and connective tissue disorders / Congenital, familial and genetic disorders

Bladder

Haematuria following administration of ifosfamide is a very common dose-dependent complication. Dependent on severity of micro-, macro- haematuria or hemorrhagic cystitis, it requires discontinuation of treatment.

Further clinical signs are dysuria, disturbed urinary frequency and other symptoms of bladder irritation.

Kidneys

Ifosfamide induces nephropathies which commonly manifest as tubular and rarely as glomerular dysfunctions. Common clinical signs of an ifosfamide nephropathy are a decrease in creatinine clearance or elevation of BUN and serum creatinine - being usually transient.

Tubular kidney dysfunction under ifosfamide is rarely accompanied by aminoaciduria, phosphaturia, tubular acidosis, proteinuria and/or electrolyte imbalance.

Ifosfamide induced acidosis is commonly reported as metabolic acidosis.

In very rare cases, however, commonly in children, patients with chronic tubular kidney dysfunction may develop a Fanconi syndrome. This can result in rickets as well as in osteomalacia in adults. Nephropathies progressing into acute and chronic renal failure particularly in combination with nephrotoxic drugs are very rare, either.

In very rare cases hypokalaemia is reported.

Reproductive system disorders / Endocrine disorders

Due to its mechanism of action, ifosfamide, as an alkylating agent, commonly causes impairment of spermatogenesis –rarely irreversible - resulting in azoospermia and/or persistent oligospermia.

Uncommonly, irreversible ovulation disturbances resulting in amenorrhoea and reduced levels of female sex hormones have been reported. This is more likely to happen in women over 30 years of age. In younger women, periods may stop temporarily, but re-start again after finishing ifosfamide.

General disorders and administration site conditions

Fever occurs very common under ifosfamide treatment in context of neutropenia and associated with infections or in context of hypersensitivity reactions sometimes with an unknown origin.

Asthenic conditions like fatigue, weakness, as well as malaise etc. are common complications in cancer patients. However, ifosfamide as other cytostatic treatments may intensify such symptoms.

Rarely, injection site reactions may occur.

4.9 Overdose

Since no specific antidote for ifosfamide is known, special caution is advised each time it is used.

Management of overdosage would include general supportive measures to sustain the patient through any period of toxicity that might occur.

Ifosfamide is dialyzable *in vitro*. Therefore, rapid haemodialysis is indicated when treating any suicidal or accidental overdose or intoxication. In the case of overdose, myelosuppression, mostly in form of leukopenia, is to be expected, among other reactions. Severity and duration of myelosuppression depends on the extent of the overdose. Frequent checks of the blood picture as well as close monitoring of the patient are required. If neutropenia develops, infection prophylaxis must be given and infections must be treated adequately with antibiotics. If thrombocytopenia develops, thrombocyte replacement should be ensured according to need. For the purpose to avoid urotoxic conditions, uroprotection using mesna is absolutely necessary. The use of methylene blue may be considered in cases of ifosfamide-associated encephalopathy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: L01AA06

Ifosfamide is a cytostatic agent of the group of oxazaphosphorines. Chemically, it is related to the nitrogen-mustard and it is a synthetic analogue of cyclophosphamide.

Ifosfamide is inactive *in vitro* and is *in vivo* preferably activated in the liver by microsomal enzymes to 4-hydroxy-ifosfamide, which is in equilibrium with aldoifosfamide, its tautomer. Aldoifosfamide disintegrates spontaneously into acrolein and the alkylating metabolite isofosfamide-mustard. Acrolein is blamed for the urotoxic effects of ifosfamide.

The cytotoxic effect of ifosfamide is due to interaction between its alkylating metabolites and the DNA. The preferred point of attack is the phosphodiester bridges of the DNA. Alkylation results in strand fracture and cross-linking of the DNA.

In the cell cycle the passage through the G₂ phase is slowed down. The cytotoxic effect is not specific to the phase of the cell cycle; however it is specific to the cell cycle.

Cross-resistance, mainly with structurally related cytostatic agents such as cyclophosphamide, but also with other alkylating agents, cannot be ruled out. On the other hand, it has been found that tumours being resistant to cyclophosphamide or which recur after cyclophosphamide therapy often still respond to treatment with ifosfamide.

5.2 Pharmacokinetic properties

Absorption

After intravenous administration, ifosfamide is detectable in organs and tissues after a few minutes. There is a linear relationship between the plasma concentrations reached and the administered dose of ifosfamide.

Distribution

Ifosfamide and its metabolites distribute in the body among tissues and the organs, including the brain. The distribution volume comes to 0.5 -0.8 l/kg. The plasma half-life of ifosfamide is between 4 and 7 hours.

Unchanged ifosfamide may cross the blood-brain barrier. In children, metabolites of ifosfamide were also detected in the cerebrospinal fluid, whereas this is still under controversial discussion for adults.

There are no confirmed data about passage of ifosfamide through the placenta or excretion into breast milk. Because of the teratogenicity of the substance which was confirmed in animal experiments and the structural resemblance with cyclophosphamide it must be expected that ifosfamide also passes the placenta and is excreted into breast milk.

Ifosfamide is bound to about 20% to plasma protein.

Metabolism

Within a few minutes, metabolisation of ifosfamide starts.

Ifosfamide is hydroxylated to active 4-hydroxy-ifosfamide. The process is mainly catalysed by the cytochrome P450 isoenzyme CYP3A4. By ring opening reaction, 4-hydroxy-ifosfamide is transformed into active aldoifosfamide. Further decomposition of aldoifosfamide proceeds by cleavage of acrolein to active isophosphoramidomustard. Moreover, ifosfamide is being deactivated to 25 - 60% by dealkylation of the chloroethyl side chains. This seems to be catalysed by CYP2B6. Alternatively, aldoifosfamide can be oxidized to the inactive carboxyifosfamide.

Metabolism of ifosfamide is characterized by a wide inter-individual variability.

Elimination

Ifosfamide and its metabolites are mainly eliminated via the kidneys. At a fractionated dose of 1.6 - 2.4 g/m² body surface/day on three consecutive days, 57% of the dose administered, and at a high single dose of 3.8 - 5 g/m² body surface, 80% of the dose administered was eliminated in form of metabolites or unchanged ifosfamide within 72 hours. The unmetabolised excreted amount came to 15% and 53%, respectively, for the above-mentioned doses.

Renal clearance is 6 - 22 ml/min.

Pharmacokinetics in special clinical situations/populations

Children

The pharmacokinetic properties of ifosfamide seen in children do not vary essentially from the ones observed in adults, with a shorter elimination half-life period and where it seems that renal elimination of ifosfamide and its metabolites might be slightly higher.

Elderly and obese patients

In case of elderly and/or obese patients, serum half-life period of ifosfamide is prolonged.

Renal impairment

No formal studies were conducted in patients with impaired renal function. However, due to the fact that renal clearance of ifosfamide is low, it is not expected that a slightly impaired renal function will have any influence on the pharmacokinetic properties of ifosfamide. In case of renal failure, neurotoxicity of ifosfamide may be increased because of impaired renal elimination. Therefore, dose reduction is recommended in these patients.

Hepatic impairment

Ifosfamide is mainly metabolised in the liver. Impaired hepatic function may slow down metabolism of ifosfamide. Hepatic failure led to complete blockage of ifosfamide metabolism and thus excretion took place exclusively in form of ifosfamide.

5.3 Preclinical safety data

Acute toxicity

Following intraperitoneal administration, LD₅₀ values are ranging between 520 and 760 mg/kg in mice and between 150 and 300 mg/kg in rats. Repeated intravenous administration of doses of 100 mg/kg or more caused signs of toxicity in rats.

Chronic toxicity

Corresponding to the clinical side effects, studies concerning chronic toxicity tests did result in damage to the lymphohematopoietic system, the gastrointestinal tract, the urinary bladder, the kidneys, the liver and the gonads.

Mutagenic and carcinogenic potential

Being an alkylating agent, ifosfamide belongs to the genotoxic substances and possesses the corresponding mutagenic potential. In long-term studies in rats and mice, ifosfamide proved to have a carcinogenic effect.

Reproductive toxicity

Ifosfamide has embryotoxic and teratogenic effects. Teratogenic effects were observed in three animal species (mice, rats, rabbits) at doses between 3 and 7.5

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium monohydrogen phosphate dodecahydrate
Sodium dihydrogen phosphate dehydrate
Phosphoric acid
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store between +2°C and +8°C.

Do not use Ifosfamide solution for infusion after the expiry date indicated on the package.

Store in the original packaging.

6.5 Nature and contents of container

Ifosfamide solution for infusion in a pack containing 1 vial of 25ml or 50ml solution for infusion (40mg/ml).

6.6 Special precautions for disposal

When handling Ifosfamide solution for infusion, the safety regulations concerning handling of cytostatic agents must be observed.

Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation of the infusion solution

For the purpose of infusion, it is recommended to dilute Ifosfamide solution for infusion with a 0.9%-conc. NaCl solution. The following can be used as a guideline: Dilution to 250 ml for an infusion over a period of 30 - 60 minutes and dilution to 500 ml for an infusion administered over one to two hours. For continuous 24-hours infusion with high doses of Ifosfamide solution for infusion, it is recommended to dilute the total dose (e.g. 5 g/m²) in three litres of 0.9%-conc. NaCl solution.

For the diluted solutions, a chemical and physical stability of 24 hours at 25°C was demonstrated.

For microbiological reasons, it is recommended to use the diluted solutions immediately after their preparation. In case they will not be used immediately, the user will be responsible to observe the instructions given concerning shelf life and storage requirements; however, 24 hours at 2 - 8°C should not be exceeded.

7 MARKETING AUTHORISATION HOLDER

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Baxter

PATIENT INFORMATION LEAFLET

IFOSFAMIDE 40 mg/ml Solution for Infusion

Please read this leaflet carefully. This leaflet provides some useful information for you about your medicine. Keep this leaflet, you may need to read it again. If you have any questions or are not sure about anything, please ask your doctor or pharmacist.

In this leaflet:

1. What is IFOSFAMIDE 40 mg/ml and what is it used for?
2. Before using IFOSFAMIDE 40 mg/ml
3. How to use IFOSFAMIDE 40 mg/ml
4. Possible side effects
5. Storing IFOSFAMIDE 40 mg/ml
6. Further Information

1. WHAT IS IFOSFAMIDE 40 mg/ml AND WHAT IS IT USED FOR?

IFOSFAMIDE 40 mg/ml is a clear, colourless solution for infusion.

IFOSFAMIDE is a cytotoxic drug used to treat a wide variety of different cancers. It works by killing cancer cells (this is sometimes called "chemotherapy"). It is often used together with other anti-cancer drugs or radiotherapy.

It is presented in a glass vial containing either 25 ml or 50 ml of IFOSFAMIDE 40 mg/ml solution for infusion.

2. BEFORE USING IFOSFAMIDE 40 MG/ML

DO NOT TAKE IFOSFAMIDE

- If you have ever experienced an allergic reaction (shortness of breath, wheezing, skin rashes, itching or swelling) after taking IFOSFAMIDE or any of the other ingredients before.
- If you are pregnant.

At the moment do you have:

- any very bad infections?
- problems with your bone marrow?
- any problems with your bladder (e.g. cystitis or blood in your urine)?
- any problems with your liver function?
- any problems with your kidney function?

If the answer is yes to any of these questions you must tell your doctor - your treatment may need to be altered.

TAKE SPECIAL CARE WHEN BEING GIVEN IFOSFAMIDE

As IFOSFAMIDE is a very powerful drug your doctor will want to do a number of tests, such as blood or urine tests, before you start your treatment and to monitor your condition during treatment. Careful monitoring of your condition may also be required if you suffer from or are at risk of certain medical conditions. Examples of some of these medical conditions are:

- Blood and Lymphatic system disorders. Blood tests will be done to check that your blood count is high enough (the number of red blood cells, white blood cells and platelets).
- Problems with your immune system such as diabetes, long terms liver or kidney disorders.
- If you suffer from cancer effecting the brain or other symptoms effecting the brain.
- If you have a heart condition.
- You will be given advice on oral hygiene to help reduce inflammation in your mouth.

- You will be given drugs called antiemetics to reduce the frequency and level of nausea and vomiting.

WHAT ABOUT OTHER MEDICINES THAT YOU MAY BE TAKING?

IFOSFAMIDE can interact with certain medicines. The effectiveness of the medicines or the risk of undesirable effects may change.

- The toxicity of other chemotherapy drugs, allopurinol and hydrochlorothiazide and, radiation therapy may be increased.
- The effectiveness of some vaccines may be reduced or a vaccine induced infection may develop.
- The blood thinning effect of warfarin may increase therefore raising the risk of bleeding.
- Drugs which are toxic to the kidneys such as cisplatin, aminoglycosides, acyclovir and amphotericin may increase the toxic effects of IFOSFAMIDE on the kidneys.
- Drugs which act on the brain such as antiemetics, tranquillisers, narcotics and antihistamines should be used with caution and may need to be discontinued.
- The blood glucose lowering effects of some diabetes treatments (sulphonylureas) may be increased.
- The toxicity of IFOSFAMIDE may be increased if you are taking chlorpromazine, triiodothyronine or aldehyde dehydrogenase inhibitors.
- The muscle relaxant effect of suxamethonium is increased.
- You need to consult your Doctor before taking bupropion, a drug used to help smoking cessation.

Consumption of alcohol should generally be avoided during treatment with IFOSFAMIDE.

TAKING IFOSFAMIDE WITH FOOD AND DRINK

Avoid eating grapefruit or any food or drinks which have it as an ingredient when being treated with IFOSFAMIDE. The effectiveness of IFOSFAMIDE may be reduced by a substance in grapefruit.

PREGNANCY AND BREASTFEEDING

- Men or women having must use contraception during therapy and the following six months as IFOSFAMIDE can damage an unborn child.
- You should not breast feed while taking IFOSFAMIDE or for 36 hours after completely stopping this treatment.

DRIVING AND USING MACHINES

- IFOSFAMIDE may induce swelling in the brain and cause nausea and vomiting.
- Do not drive or operate and tools or machines.

3. HOW TO USE IFOSFAMIDE 40 mg/ml

Before it is given to you IFOSFAMIDE 40 mg/ml will be diluted with 0.9% w/v Sodium Chloride solution. It will normally be given to you in a large bag of intravenous drip solution directly into a vein. The drip containing your IFOSFAMIDE may need to continue for several hours - sometimes even several days. The drip can go into a vein through a small needle usually in the arm or back of the hand. Some people have special "long lines" put into a large vein under the collar bone, and IFOSFAMIDE can be given into this long line. You will usually have your IFOSFAMIDE treatment every two to four weeks. The amount of IFOSFAMIDE given to you will depend on the type of cancer you have, how big you are (a combination of your height and weight), your general condition and whether you are being given other anti-cancer drugs or having radiotherapy.

4. POSSIBLE SIDE EFFECTS

As IFOSFAMIDE is a very powerful anti-cancer drug, it has some side-effects. The most common side effects are:

- Nausea and Vomiting**

Feeling sick and occasionally being sick for about 24 hours after a IFOSFAMIDE injection. However, there are very effective anti-sickness medicines which your doctor will prescribe for you. This means that most patients are not sick.

- **Loss of hair**

You may just notice this as a little extra loss of hair when you are combing or washing your hair, or you may lose most or all of your hair. The amount of hair which you lose will depend on the dose of IFOSFAMIDE, the thickness of your hair and whether you are also having other anti-cancer drugs. If you are having IFOSFAMIDE in combination with other anti-cancer drugs, you are much more likely to lose your hair than if you are having IFOSFAMIDE alone.

Other side-effects which you may not notice, but for which your doctor will check are:

- **Damage to the lining of the bladder**

IFOSFAMIDE produces a compound which can damage the lining of the bladder, causing bleeding into your urine. Your doctor knows this and he will give you a medicine called mesna which will protect your bladder. Most people having IFOSFAMIDE with mesna do not develop any problems with their bladder, but your doctor may want to test your urine for the presence of blood. If you notice that you have blood in the urine, then you must tell your doctor.

- **Damage to the kidneys**

Sometimes IFOSFAMIDE can damage the kidneys so that they do not work properly. This is more likely to happen if you only have one kidney, or if your kidneys are already damaged. Usually there are no symptoms from kidney damage, but your doctor will be able to detect any damage by looking at your test results. Often the damage caused by IFOSFAMIDE to kidneys is only temporary, and they will return to normal after you stop IFOSFAMIDE therapy. Occasionally kidney damage is permanent and can be severe.

- **A lowering of the blood count (blood cell numbers)**

IFOSFAMIDE works by killing cancer cells, but it will also kill some of your normal cells. The normal cells that are most affected are your bone marrow cells. Bone marrow makes the red blood cells, white blood cells which fight infection and platelets which help your blood to clot. Your doctor will check that the number of red blood cells, white blood cells and platelets is high enough before you start your IFOSFAMIDE treatment. After an injection of IFOSFAMIDE your blood count will drop. This is an unavoidable side-effect of IFOSFAMIDE because it is such a powerful drug. Your blood count will reach its lowest level about 5-10 days after your IFOSFAMIDE injection. Most people recover to a normal blood count within 21-28 days. If you have had a lot of chemotherapy in the past, it may take a little longer to return to normal.

You may not notice anything at all when your blood count drops. Some people feel a bit tired. Because your white blood cell count is low it is important that you should take care not to come into contact with any infectious people, as without white blood cells, you cannot fight infection. Unfortunately, some infections are carried in the air, which you cannot avoid. If you think you have an infection (a high temperature, feeling cold and shivery, or hot and sweaty, or any signs of infection such as a cough, or stinging on passing water) you must contact your doctor immediately. Without your white blood cells, you may need antibiotics to fight infection.

Sometimes, people having IFOSFAMIDE become anaemic (a lack of red blood cells). Usually, no treatment is required, your body will eventually replace the red blood cells. If you are very anaemic, you may need a blood transfusion.

If your platelet count is low, your blood will not clot very well. Most people on IFOSFAMIDE do not have problems with blood clotting, but you may notice that if you cut yourself, for instance, while shaving, that it takes a long time to stop bleeding. Women may notice that their periods are heavier than normal.

If you find that you are getting bruises without knocking yourself, or that you are bleeding from the gums - then you must contact your doctor immediately. You may have to have a special platelet transfusion to replace your platelets.

- **Changes in mental state**

In a few people, IFOSFAMIDE can affect the central nervous system (brain). Usually the effects are mild, such as slight confusion or abnormal sleepiness. Sometimes people on IFOSFAMIDE therapy do not realise that they have been affected but friends and relatives may notice a change in them. These mild effects rarely last for more than two days, and usually go away completely after stopping IFOSFAMIDE. Very rarely a more serious form of these effects can occur with IFOSFAMIDE. These serious forms are called "encephalopathy" and can involve having fits, becoming very confused and sometimes aggressive, and also a loss of consciousness. If any of these effects occurs, your IFOSFAMIDE treatment will be stopped. Most people then return to normal in a few days. Very, very rarely people on IFOSFAMIDE have gone into a coma.

Your doctor will be well aware of these possible problems. Although they sound very frightening, he will not prescribe IFOSFAMIDE unless he thinks that your cancer is more of a risk to you than the possible side-effects.

- **Infertility**

Men on IFOSFAMIDE often become infertile because their sperm count drops. Usually, they will regain normal fertility (and a normal sperm count) about 3 months to 1 year after finishing treatment. Sometimes IFOSFAMIDE causes permanent infertility. Although this does not happen very often, your doctor may advise you to bank your sperm before you start IFOSFAMIDE. If you do not regain your fertility, this banked sperm can be used in the future if you want to have children. IFOSFAMIDE has no effect on your libido (your desire to have sex) or on your ability to have sex.

Women on IFOSFAMIDE may also become infertile. This is more likely to happen in women over 30 years of age. You may notice that your periods stop altogether, and you may develop menopausal symptoms e.g. "hot flushes". In younger women, periods may stop temporarily, but re-start again after finishing IFOSFAMIDE. If your periods re-start or if they are not affected at all, you may be able to have children in the future.

- **Damage to unborn children**

Although both men and women having IFOSFAMIDE may remain fertile during their treatment, women must not get pregnant at this time. This is because IFOSFAMIDE can damage your unborn baby, leading to stillbirth, or a permanently damaged or deformed child. Women on IFOSFAMIDE must take care not to get pregnant during their treatment and for at least 6 months after the end of treatment. Some doctors recommend not trying to get pregnant for one year after the end of treatment as babies conceived before this have a higher chance of being born prematurely or being of low birthweight.

Men on IFOSFAMIDE should not make their wives or girlfriends pregnant during treatment with IFOSFAMIDE or for at least 6 months after the end of treatment. This is because damaged sperm can also cause damage to an unborn child.

However, both men and women on IFOSFAMIDE can have sex if they want to, if contraception is used.

- **Other side effects**

IFOSFAMIDE has other side-effects which occur in a small number of patients. Your doctor will check for these. They include fluid retention, allergic reactions, diarrhoea, loss of appetite, constipation, liver disorders, acute inflammation of the pancreas (which results in severe upper abdominal pain), inflammation of the lungs, impaired vision, muscle weakness, numbness or abnormal sensations, skin rashes and mouth problems, such as ulcers and swelling, increased reaction to radiation treatment, inflammation in the vein at the site of treatment and possible effects on the heart.

Although these side-effects can be serious and may sound frightening, your doctor has balanced the risk of these side-effects with the risk to you of your cancer. If you have any questions about these side-effects or if you notice any other side-effects or problems, you should tell your doctor or pharmacist.

5. STORING IFOSFAMIDE 40mg/ml

- Your medicine will be stored a safe place where children cannot see or reach it. Your medicine could harm them.
- Do not use your medicine after the expiry date on the box or vial, even if there is some medicine left after this date. Ask your doctor to replace it with a new prescription.
- Your medicine will be stored between 2°C and 8°C (in a refrigerator) and kept in its outer container before use. Once it has been diluted ready for use it should not be stored above 25°C and should be used within 24 hours.
- Any unused medicine or waste material from its use must be disposed of in accordance with local requirements.

6. FURTHER INFORMATION**◆ NAME OF MEDICINAL PRODUCT**

The name of your medicine is IFOSFAMIDE 40 mg/ml solution for infusion.

◆ WHAT IS IN YOUR MEDICINE

Each vial of contains either 25 ml or 50 ml of IFOSFAMIDE 40 mg / ml solution which equals 1 g or 2 g of the active ingredient IFOSFAMIDE. It also contains the inactive ingredients: Sodium chloride, sodium monohydrogen phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, phosphoric acid and water for injections.

◆ WHO PRODUCES YOUR MEDICINE

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For information about IFOSFAMIDE 40 mg/ml or to request this leaflet in formats such as audio or large print please contact the Marketing Authorisation Holder: Tel: 01635 206345.

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LABELLING



