SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Holoxan 1g
Holoxan 2g

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1g, 2g of ifosfamide.
When reconstituted as directed, each milliliter of concentrate contains 80 mg Ifosfamide.

3 PHARMACEUTICAL FORM
Powder for solution for infusion/ injection. White powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Testicular tumor
For combination chemotherapy in patients with advanced stage II to IV tumours according to the TNM classification (seminomas and non-seminomas), which do not respond or adequately respond to initial chemotherapy.

Cervical cancer
Palliative cisplatin/ifosfamide combination chemotherapy (without any other combination partners) of cervical carcinoma, FIGO stage IV B (when curative therapy of the disease is not possible with surgery or radiotherapy) – as an alternative to palliative radiotherapy.

Breast cancer
For palliative therapy in advanced, therapy-refractory or recurrent breast cancer.

Non-small-cell lung cancer
For mono- or combination chemotherapy of patients with inoperable or metastatic tumours.

Small-cell lung cancer
For combination chemotherapy.

Soft-tissue sarcoma (incl. osteosarcoma and rhabdomyosarcoma)
For mono- or combination chemotherapy of rhabdomyosarcoma or osteosarcoma after failure of standard therapies. For mono- or combination chemotherapy of other soft-tissue sarcomas after failure of surgery and radiation therapy.

Ewing's sarcoma
For combination chemotherapy after failure of primary cytostatic therapy.

Non-Hodgkin's lymphoma
For combination chemotherapy in patients with highly malignant non-Hodgkin's lymphoma which does not respond, or only insufficiently responds, to the initial therapy. For combination therapy of patients with recurrent tumours.

Hodgkin's lymphoma
For the treatment of patients with primary progressive forms and early relapse of Hodgkin's lymphoma (duration of complete remission shorter than one year) after failure of primary chemotherapeutic or radio-chemotherapeutic treatment – as part of a recognised combination chemotherapy regimen, such as the MINE protocol.

4.2 Posology and method of administration

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 by physicians experienced with this drug.

Dosage must be individualized. 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.

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

Method of administration

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.

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.

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

Ifosfamide and its metabolites are dialyzable.

Use in Patients with Hepatic Impairment
Hepatic impairment, particularly if severe, may be associated with decreased activation of ifosfamide. This 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. This should be considered when selecting the dose and interpreting response to the dose selected (see section 4.3).

Use in Paediatric Patients
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
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).

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:
Holoxan 1 gram vial: add 25 ml of Water for Injections
Holoxan 2 gram vial: add 50 ml of Water for Injections

The resultant solution contains 4% of ifosfamide.

The solution may then be:

- For intravenous infusion (30-120min) – diluted in 250ml of Ringer's solution or 5% strength glucose solution or 0.9% strength physiological solution
- For prolonged administration (60-120min) - diluted in 500ml of Ringer's solution or 5% strength glucose solution or 0.9% strength physiological solution
- For continuous 24-hour infusion - diluted in 3000ml of 5% strength glucose solution or 0.9% strength physiological solution

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/mm³ or the platelet count is below 100,000/mm³, 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 is contra-indicated in patients with:
- known hypersensitivity to ifosfamide (see section 4.4).
- urinary outflow obstruction.
- severely impaired bone-marrow function (especially in patients previously treated with cytotoxic agents or radiotherapy)
- inflammation of the urinary bladder (cystitis)
- impaired renal function
- hepatic impairment
- acute infections
- Breastfeeding

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.

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 (colonystimulating factors and erythropoiesis-stimulating agents) may be considered to reduce the risk of myelosuppressive complications and/or help facilitate the delivery of the intended dosing. For information on a potential interaction with G-CSF and GM-CSF (granulocyte colonystimulating factor, granulocyte macrophage colony-stimulating factor) (see section 4.5).

The risk of myelosuppression is dosedependent and is increased with administration of a single high dose compared to fractionated administration.

The risk of myelosuppression is increased in patients with reduced renal function.

Severe immunosuppression has led to serious, sometimes fatal, infections. Infections reported with ifosfamide include pneumonias, as well as other bacterial, fungal, viral, and parasitic infections. Sepsis and septic shock also have been reported.

Latent infections can be reactivated. In patients treated with ifosfamide, reactivation has been reported for various viral infections.

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 (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 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, 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
— Obesity, female gender
— Interactions with other medicines (e.g., aprepitant, CYP 3A4 inhibitors), alcohol, drug abuse, or pretreatment with cisplatin

If encephalopathy develops, administration of ifosfamide should be discontinued.

Publications report both successful and unsuccessful use of methylene blue for the treatment and prophylaxis of ifosfamide-associated encephalopathy.

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.

Close clinical monitoring of serum and urine chemistries, including phosphorus, potassium, and other laboratory parameters appropriate for identifying nephrotoxicity and urothelial toxicity is recommended (see section 4.3).

Nephrotoxic Effects

Fatal outcome from nephrotoxicity has been documented.

Disorders of renal function (glomerular and tubular) following ifosfamide administration are very common (see section 4.8).

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.

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
— reduced nephron reserve as in patients with renal tumours and those having undergone renal radiation or unilateral nephrectomy.

Urothelial Effects

Ifosfamide administration is associated with urotoxic effects, which can be reduced by prophylactic use of mesna.

Hemorrhagic cystitis requiring blood transfusion has been reported with ifosfamide.

The risk of hemorrhagic cystitis is dose-dependent and increased with administration of single high doses compared to fractionated administration.

Hemorrhagic cystitis after a single dose of ifosfamide has been reported.

Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions.

During or immediately after administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity.

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.

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.

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.

Veno-occlusive Liver Disease

Veno-occlusive liver disease has been reported with chemotherapy that included ifosfamide and also is a known complication with 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 another oxazaphosphorine cytotoxic agent, oligomenorrhea has been reported (see section 4.6).

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

Male Patients

Men treated with ifosfamide may develop oligospermia or azoospermia (see section 4.6).

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.

Paravenous Administration

The cytotoxic effect of ifosfamide occurs after its activation, which takes place mainly in the liver. Therefore, the risk of tissue injury from accidental paravenous administration is low.

In case of accidental paravenous administration of ifosfamide, the infusion should be stopped immediately, the extravascular ifosfamide solution should be aspirated with the cannula in place, and other measures should be instituted as appropriate.

Use in Patients with Renal Impairment

In patients with renal impairment, particularly in those with severe renal impairment, decreased renal excretion may result in increased plasma levels of ifosfamide and its metabolites. This may result in increased toxicity (e.g., neurotoxicity, nephrotoxicity, hematotoxicity) and should be considered when determining the dosage in such patients.

Use in Patients with Hepatic Impairment

Hepatic impairment, particularly if severe, may be associated with decreased activation of ifosfamide. This 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.

This should be considered when selecting the dose and interpreting response to the dose selected.

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 colonystimulating factor, granulocyte macrophage colony-stimulating factor)

Increased nephrotoxicity may result from a combined effect of ifosfamide and, for example:
– Cyclovir
– 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. Ifosfamide is contra-indicated for breast-feeding (see section 4.3).

Fertility
Ifosfamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Development of sterility appears to depend on the dose of ifosamide, duration of therapy, and state of gonadal function at the time of treatment.
Ifosfamide may cause transient or permanent amenorrhea in women and oligospermia or azoospermia in men.

Female patients
Women treated with ifosamide should be informed prior to treatment about the possibility to save and preserve their eggs.
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 should be informed prior to treatment about the possibility to save pre-produced sperm kept in proper conditions.
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.

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.
Women treated with ifosfamide should take contraceptive measures for at least 1 year after discontinuation of ifosfamide therapy.
Men should not father a child for up to 6 months after the end of therapy.

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

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

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

ADR frequency is based upon the following scale: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), and very rare (< 1/10,000), Not known (adverse reactions reported in the post-marketing experience).

System Organ Class (SOC)	Adverse Reaction	Frequency Category
Infections and Infestations	Infections (including reactivation of latent infections)	Common
	Sepsis (septic shock)*	Not known
Neoplasms Benign, Malignant and Unspecified (INCL Cycts and Polyps)	Secondary tumors* (including Urinary tract carcinoma, Myelodysplastic syndrome, Acute leukaemia, Acute lymphocytic leukemia, Lymphoma [Non-Hodgkin's lymphoma], Sarcomas, Renal cell carcinoma, Thyroid cancer)	Not known
	Progressions of underlying malignancies*	Not known
Blood and Lymphatic System Disorders	Myelosuppression	Very common
	- Leukopenia	Very common
	- Thrombocytopenia*	Very common
	- Anemia	Not known
	- Agranulocytosis	Not known
	Hematotoxicity*	Not known
	- Hemolytic anemia	Not known
	- Methaemoglobinaemia	Not known
	Febrile bone marrow aplasia	Not known
	Disseminated intravascular coagulation	Not known
	Hemolytic uremic syndrome	Not known
	Neonatal anemia	Not known
Immune System Disorders	Angioedema*	Not known
	Anaphylactic reaction	Not known
	Immunosuppression	Not known
	Urticaria	Not known
	Hypersensitivity reaction	Not known
Endocrine Disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Not known
Metabolism and Nutrition Disorders	Decreased Appetite	Common
	Tumor lysis syndrome	Not known
	Metabolic acidosis	Not known
	Hypokalemia	Not known
	Hypocalcemia	Not known
	Hypophosphatemia	Not known
	Hyperglycemia	Not known
	Polydipsia	Not known
Psychiatric Disorders	Mutism	Not known
	Mental status change (including mania, paranoia, delusion, delirium, catatonia, amnesia, panic attack)	Not known
	Echolalia	Not known
	Perseveration	Not known
Nervous System Disorders	Central nervous system toxicity	Not known
	- Encephalopathy	Not known
	- Faecal incontinence	Not known
	- Status epilepticus* (convulsive and nonconvulsive)	Not known
	- Movement disorder	Not known
	- Extrapyramidal disorder	Not known
	- Gait disturbance	Not known
	- Dysarthria	Not known
	Peripheral neuropathy	Not known
	- Hypoesthesia	Not known
	- Paresthesia	Not known
	Asterixis	Not known
	Neuralgia	Not known
Eye Disorders	Visual impairment	Not known
	Conjunctivitis	Not known
	Eye irritation	Not known
Ear and Labyrinth Disorders	Deafness	Not known
	Vertigo	Not known
	Tinnitus	Not known
Cardiac Disorders	Cardiotoxicity*	Uncommon
	Arrythmia (including supraventricular and ventricular arrhythmia)	Not known
	Atrial fibrillation	Not known
	Premature atrial contractions	Not known
	Bradycardia	Not known
	Cardiac arrest*	Not known
	Myocardial infarction	Not known
	Cardiac failure*	Not known
	Myocardial hemorrhage	Not known
	Angina pectoris	Not known
	Cardiomyopathy* (including congestive cardiomyopathy)	Not known
	Electrocardiogram ST-segment abnormal	Not known
	Electrocardiogram T- wave inversion	Not known
	Electrocardiogram QRS complex abnormal	Not known
Vascular Disorders	Hypotension	Uncommon
	Pulmonary embolism	Not known
	Deep vein thrombosis	Not known
	Capillary leak syndrome	Not known
	Vasculitis	Not known
	Hypertension	Not known
	Flushing	Not known
Respiratory, Thoracic and Mediastinal Disorders	Respiratory failure*	Not known
	Acute respiratory distress syndrome*	Not known
	Pulmonary hypertension	Not known
	Interstitial lung disease* (as manifested by Pulmonary fibrosis)	Not known
	Pneumonitis*	Not known
	Pulmonary oedema*	Not known
	Pleural effusion	Not known
	Dyspnea	Not known
	Hypoxia	Not known
	Cough	Not known
Gastrointestinal Disorders	Nausea/Vomiting	Very Common
	Diarrhea	Uncommon
	Stomatitis	Uncommon
	Enterocolitis	Not known
	Pancreatitis	Not known
	Ileus	Not known
	Gastrointestinal hemorrhage	Not known
	Mucosal ulceration	Not known
	Constipation	Not known
	Abdominal pain	Not known
	Salivary hypersecretion	Not known
Hepatobiliary Disorders	Hepatotoxicity	Common
	- Hepatic failure	Not known
	Veno-occlusive liver disease	Not known
	Portal vein thrombosis	Not known
	Cytolytic hepatitis	Not known
Skin and Subcutaneous Tissue Disorders	Alopecia	Very common
	Dermatitis	Rare
	Papular rash	Rare
	Toxic epidermal necrolysis	Not known
	Stevens-Johnson syndrome	Not known
	Palmar-plantar erythrodysesthesia syndrome	Not known
	Radiation recall dermatitis	Not known
	Skin necrosis	Not known
	Facial swelling	Not known
	Rash	Not known
	Pruritus	Not known
	Erythema	Not known
	Skin hyperpigmentation	Not known
	Hyperhidrosis	Not known
	Nail disorder	Not known
Musculoskeletal and Connective Tissue Disorders	Rhabdomyolysis	Not known
	Osteomalacia	Not known
	Rickets	Not known
	Growth retardation	Not known
	Myalgia	Not known
	Arthralgia	Not known
	Muscle twitching	Not known
Renal and Urinary Disorders	Hemorrhagic cystitis	Very common
	Hematuria	Very common
	Renal dysfunction*	Very common
	- Acute renal failure	Very common
	- Chronic renal failure	Not known
	- Aminoaciduria	Not known
	- Phosphaturia	Not known
	- Fanconi syndrome	Not known
	- Tubulointerstitial nephritis	Not known
	Renal structural damage	Not known
	Nephrogenic diabetes insipidus	Not known
	Polyuria	Not known
	Enuresis	Not known
	Feeling of residual urine	Not known
Reproductive System and Breast Disorders	Infertility	Not known
	Ovarian failure	Not known
	Premature menopause	Not known
	Amenorrhea	Not known
	Ovulation disorder	Not known
	Azoospermia	Not known
	Oligospermia	Not known
Congenital, Familial and Genetic Disorders	Fetal growth retardation	Not known
General Disorders and Administrative Site Conditions	Phlebitis	Common
	Fatigue	Uncommon
	Malaise	Not known
	Multiorgan failure*	Not known
	General physical deterioration	Not known
	Injection/Infusion site reactions	Not known
	Oedema	Not known
	Pain	Not known
	Pyrexia	Not known
	Chills	Not known

* including fatal outcomes

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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.

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, non-rhabdomyosarcoma soft tissue sarcoma, germ cell tumours, osteosarcoma, non-Hodgkins lymphoma, Hodgkins Disease, acute lymphoblastic leukaemia, neuroblastoma, Wilms tumour, and malignant CNS 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 3g/m²/day for 2-5 days for a total dose of 4-12 g/m² for chemotherapy course.
Fractionated administration of ifosfamide is performed as intravenous infusion over a period ranging between 30 minutes and 2 hours, depending on the infusion volume or recommendations of protocol:
Uroprotection with mesna is mandatory during ifosfamide administration with a dose equivalent to 80-120% of ifosfamide. It is recommended to prolong Mesna infusion to 12-48 hours after the end of ifosfamide infusion. 20 % of the whole Mesna dose should be given as i.v start bolus.
Hyperhydration with at least 3000 ml/m² is required during ifosfamide infusion and for 24-48 hours after the end of ifosfamide administration.

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

Paediatric data from randomized controlled clinical studies are limited.

5.2 Pharmacokinetic properties

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 Pre-clinical 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.

6.3 Shelf-life
Five years.

The chemical and physical stability ready-to-use preparation was proven for 48 hours at 25°C. From a micro-biological point of view, the ready-to-use preparation should be used immediately. If the ready-to-use preparation is not used immediately, the user is responsible for the duration and the condition of storage. If the production of the ready-to-use preparation does not take place under controlled and validated aseptic conditions, it must not be stored for longer than 24 hours between 2°C and 8°C.

6.4 Special Precautions for Storage
Store below 25°C.
Store in original carton box in order to protect from light.

6.5 Nature and Content of Container
Glass vials type III with nominal volume 50ml with bromobutyl rubber closure and beading cap.
Packages:
1 vial
5 vials
5 x 10 vials (50 vials)

6.6 Special precautions for disposal

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

Before parenteral administration, the substance must be completely dissolved.

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
Baxter Oncology GmbH, Halle, Westfalen, Germany

8 LICENSE HOLDER
Megapharm Ltd., P.O. Box 519 Hod Hasharon 4510501

9 MARKETING AUTHORIZATION NUMBER
Holoxan 1 gram: 156-22-34017
Holoxan 2 gram: 156-23-34019

This leaflet format has been determined by the Ministry of Health and its content was checked and approved in May 2016.

Holoxan SPC 052016 P.4