Baxter

Patient Information Leaflet Please read carefully!

Holoxan®

Active substance: Ifosfamide

Composition: 1 vial	Holoxan 200 mg	Holoxan 500 mg	Holoxan 1 g	Holoxan 2 g
	contains:			
Ifosfamide	200 mg	500 mg	1 g	2 g

as dry substance for preparing an injectable solution. White powder for solution for injection or infusion.

Indications:

Holoxan is to be administered exclusively by physicians with experience in oncology. It is indicated in inoperable malignant tumours that are sensitive to ifosfamide, e.g. bronchial carcinoma, ovarian carcinoma, testicular tumours, soft-tissue sarcoma, breast cancer, pancreatic carcinoma, hyper- nephroma, endometrial carcinoma, malignant lymphomas.

Special remark:

Should during treatment with Holoxan a cystitis in connection with macro- or microhaematuria appear, Holoxan therapy has to be interrupted until normalization.

Contraindications:

Holoxan is contraindicated in cases of

- known hypersensitivity to ifosfamide
- severely depressed bone-marrow function (especially in patients previously treated with cytotoxic agents or radiotherapy)
- active infections
- impaired renal function and/or obstructions of the urine flow
- cystitis
- pregnancy (see special comments)
- lactation

Adverse Reactions:

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

ADR frequency is based upon the following scale: Very common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very rare (<1/10,000), 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) Sepsis (septic shock)*	Common Not known
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYCTS AND POLYPS)	Secondary tumors* (including Urinary tract carcinoma, Myelodysplastic syndrome, Acute leukaemia, Acute lymphocytic leukaemia, Lymphoma [Non-Hodgkin's lymphoma], Sarcomas, Renal cell carcinoma, Thyroid cancer) Progressions of underlying malignancies*	Not known Not known
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Myelosuppression - Leukopenia - Thrombocytopenia* - Anaemia - Agranulocytosis Haematotoxicity* - Haemolytic anaemia - Methaemoglobinaemia Febrile bone marrow aplasia Disseminated intravascular coagulation Haemolytic uremic syndrome Neonatal anaemia	Very common Very common Very common Not known Not known Not known Not known Not known Not known Not known Not known Not known
IMMUNE SYSTEM DISORDERS	Angioedema* Anaphylactic reaction Immunosuppression Urticaria Hypersensitivity reaction	Not known Not known Not known Not known Not known
ENDOCRINE DISORDERS	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Not known

System Organ Class (SOC)	Adverse Reaction	Frequency Category
METABOLISM AND NUTRITION DISORDERS	Decreased Appetite	Common
	Tumor lysis syndrome	Not known
	Metabolic acidosis	Not known
	Hypokalaemia	Not known
	Hypocalcaemia	Not known
	Hypophosphataemia	Not known
	Hyperglycaemia	Not known
	Polydipsia	Not known
PSYCHIATRIC DISORDERS	Mutism	Not known
	Mental status change (includine 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 haemorrhage	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

System Organ Class (SOC)	Adverse Reaction	Frequency Category
GASTROINTESTINAL DISORDERS	Nausea/Vomiting	Very common
	Diarrhoea	Uncommon
	Stomatitis	Uncommon
	Enterocolitis	Not known
	Pancreatitis	Not known
	Ileus	Not known
	Gastrointestinal haemorrhage	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	Haemorrhagic cystitis	Very common
	Haematuria	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

System Organ Class (SOC)	Adverse Reaction	Frequency Category
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.

Overdose:

Serious consequences of overdosage include manifestations of dose-dependent toxicities such as CNS toxicity, nephrotoxicity, myelosuppression, and mucositis. See Section on Special Warnings and Precautions for Use

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.

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

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 including pneumonias, as well as other bacterial, fungal, viral, parasitic infections, sepsis, and septic shock. Fatal outcome of ifosfamide-associated myelosuppression has been reported.**
- **Ifosfamide-induced myelosuppression can cause leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding events), and anemia.**
- 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 must be expected particularly in patients pre-treated with and/or receiving concomitant chemotherapy/hematotoxic agents, and/or radiation therapy. See Section on Interactions with Other Medicinal Products and Other Forms of Interaction
- **The risk of myelosuppression is dose-dependent and is increased with administration of a single high dose compared to fractionated administration.**
- **The risk of myelosuppression is increased in patients with reduced renal function or diabetes mellitus.**
- **Latent infections can be reactivated. In patients treated with ifosfamide reactivation has been reported for various viral infections.**
- Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician.
- In case of neutropenic fever, antibiotics and/or antimycotics must be given.
- **Close hematologic monitoring is recommended.** White blood cell count, platelet count, and hemoglobin levels should be obtained prior to each administration and at appropriate intervals after administration.
- Ifosfamide should be used with caution, if at all, in patients with severe impairment of bone marrow function, severe immunosuppression, and in the presence of an infection.

Encephalopathy and CNS toxicity
- **Administration of ifosfamide can cause encephalopathy and other neurotoxic effects.**
- **An ifosfamide-induced CNS toxicity may become manifest within a few hours to a few days after 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. If CNS toxicity develops, administration of ifosfamide should be discontinued.**
- **The symptoms may include the following: confusion, somnolence, coma, hallucination, blurred vision, psychotic behavior, extrapyramidal symptoms, urinary incontinence, and seizures.**
- **CNS toxicity seems to be dose dependent. Risk factors for the development of ifosfamide associated encephalopathy include hypoalbuminaemia, impaired renal function, poor performance status, pelvic**

disease (e.g. presence of tumour in lower abdomen, bulky abdominal disease), and previous or concomitant nephrotoxic treatments including cisplatin.

- **Due to the potential for additive effects, drugs acting on the CNS (such as antiemetics, sedatives, narcotics, or antihistamines) or substances (such as alcohol) acting on the CNS must be used with particular caution or, if necessary, be discontinued in case of ifosfamide-induced encephalopathy.**
- **Patients treated with ifosfamide should be closely monitored for symptoms of encephalopathies in particular if patients are at increased risk for encephalopathies.**
- **The use of methylene blue may be considered for the treatment and prophylaxis of ifosfamide-associated encephalopathies.**
- **Recurrence of CNS toxicity after several uneventful treatment courses has been reported.**

Renal and Urothelial Toxicity

- **Ifosfamide is both nephrotoxic and urotoxic.**
- **Glomerular and tubular kidney function must be evaluated and checked before commencement of therapy, as well as during and after treatment.**
- Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity.
- **Close clinical monitoring of serum and urine chemistries, including phosphorus, potassium, and other laboratory parameters appropriate for identifying nephrotoxicity and urothelial toxicity is recommended.**
- Appropriate replacement therapy should be administered as indicated.

Nephrotoxic Effects

- **Renal parenchymal and tubular necrosis have been reported in patients treated with ifosfamide.**
- **Disorders of renal function (glomerular and tubular) following ifosfamide administration are very common. Manifestations include a decrease in glomerular filtration rate and an increase in serum creatinine, proteinuria, enzymuria, cylindruria, aminoaciduria, phosphaturia, and glycosuria as well as renal tubular acidosis. Fanconi syndrome, renal rickets, and growth retardation in children as well as osteomalacia in adults have also been reported.**
- Distal tubular dysfunction impairs the ability of the kidney to concentrate urine.
- **Development of a syndrome resembling SIADH (syndrome of inappropriate antidiuretic hormone secretion) has been reported with ifosfamide.**
- **Tubular damage may become apparent during therapy, months or even years after cessation of treatment.**
- **Glomerular or tubular dysfunction may resolve with time, remain stable, or progress over a period of months or years, even after completion of ifosfamide treatment. Acute tubular necrosis, acute renal failure, and chronic renal failure secondary to ifosfamide therapy have been reported and fatal outcome from nephrotoxicity has been documented.**
- **The risk of developing clinical manifestations of nephrotoxicity is increased with, for example:**
  - **large cumulative doses of ifosfamide,**
  - **preexisting renal impairment,**
  - **prior or concurrent treatment with potentially nephrotoxic agents,**
  - **younger age in children** (particularly in children up to approximately 5 years of age)**,**
  - **reduced nephron reserve as in patients with renal tumors and those having undergone renal radiation or unilateral nephrectomy.**
  - The risks and expected benefits of ifosfamide therapy should be carefully weighed when considering the use of ifosfamide in patients with preexisting renal impairment or reduced nephron reserve.

Urothelial Effects

- **Ifosfamide administration is associated with urotoxic effects, which can be reduced by prophylactic use of mesna.**
- **Hemorrhagic cystitis requiring blood transfusion has been reported with ifosfamide.**
- **The risk of hemorrhagic cystitis is dose-dependent and increased with administration of single high doses compared to fractionated administration.**
- **Hemorrhagic cystitis after a single dose of ifosfamide has been reported.**
- **Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions.** See Section on Contraindications
- **During or immediately after administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity.**
- For prophylaxis of hemorrhagic cystitis, ifosfamide should be used in combination with mesna.
- **Ifosfamide should be used with caution, if at all, in patients with active urinary tract infections.**
- **Past or concomitant radiation of the bladder or busulfan treatment may increase the risk for hemorrhagic cystitis.**
- **The following manifestations of urotoxicity from** cyclophosphamide**, another oxazaphosphorine cytotoxic agent have been reported:**
  - fatal outcome of urothelial toxicity, as well as the need for cystectomy due to fibrosis, bleeding, or secondary malignancy;
  - hemorrhagic cystitis (including severe forms with ulceration and necrosis);
  - hematuria, which may be severe and recurrent; while hematuria usually resolves in a few days after treatment is stopped, it may persist;
  - signs of urothelial irritation (such as painful micturition, a feeling of residual urine, frequent voiding, nocturia, urinary incontinence) as well as the development of bladder fibrosis, small-capacity bladder, telangiectasia, and signs of chronic bladder irritation;
  - pyelitis and ureteritis.

Cardiotoxicity, Use in Patients With Cardiac Disease

- **Manifestations of cardiotoxicity reported with ifosfamide treatment 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
  - 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 preexisting cardiac disease.**

Pulmonary Toxicity

- **Pulmonary toxicity leading to respiratory failure as well as fatal outcome has been reported. Interstitial pneumonitis and pulmonary fibrosis as well as other forms of pulmonary toxicity have been reported with ifosfamide treatment.**

Secondary Malignancies

- **As with all cytotoxic therapy, treatment with ifosfamide involves the risk of secondary tumors and theirprecursors.**
- **The risk of myelodysplastic alterations, some progressing to acute leukemias, is increased. Other malignancies reported after use of ifosfamide or regimens with ifosfamide include lymphoma, thyroid cancer, and sarcomas.**
- **The secondary malignancy may develop several years after chemotherapy has been discontinued.**
- **Malignancy has also been reported after in utero exposure with** cyclophosphamide, **other oxazaphosphorine cytotoxic agent**

Veno-occlusive Liver Disease

- **Veno-occlusive liver disease has been reported with chemotherapy that included ifosfamide and also is a known complication with** cyclophosphamide, **another oxazaphosphorine cytotoxic agent.**

Genotoxicity

- **Ifosfamide is genotoxic and mutagenic in male and female germ cells. Therefore, women should not become pregnant and men should not father a child during therapy with ifosfamide.**
- **Men should not father a child for up to 6 months after the end of therapy.**
- **Animal data generated with** cyclophosphamide, **another oxazaphosphorine cytotoxic agent indicate that exposure of oocytes during follicular development may result in a decreased rate of implantations and viable pregnancies and in an increased risk of malformations. This effect should be considered in case of intended fertilization or pregnancy after discontinuation of ifosfamide therapy. The exact duration of follicular development in humans is not known, but may be longer than 12 months.**
- **Sexually active women and men should use effective methods of contraception during these periods of time.**
  See also Section on Pregnancy and Lactation

Effects on Fertility

- **Ifosfamide interferes with oogenesis and spermatogenesis. Amenorrhea, azoospermia, and sterility in both sexes have beenreported.**
- **Development of sterility appears to depend on the dose of ifosfamide, duration of therapy, and state of gonadal function at the time of treatment. Sterility may be irreversible in somepatients.**

Female Patients

- **Amenorrhea has been reported in patients treated with ifosfamide. In addition, with** cyclophosphamide, **another oxazaphosphorine cytotoxic agent, oligomenorrhea has beenreported.**
- **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 areat increased risk of developing premature menopause.**

Male Patients

- **Men treated with ifosfamide may develop oligospermia or azoospermia.**
- **Sexual function and libido generally are unimpaired in these patients.**
- **Boys treated with ifosfamide during prepubescence may develop secondary sexual characteristics normally, but may have oligospermia or azoospermia.**
- **Some degree of testicular atrophy mayoccur.**
- **Azoospermia may be reversible in some patients, though the reversibility may not occur for several years after cessation of therapy.**
- **Men treated with ifosfamide have subsequently fathered children.**

Anaphylactic/Anaphylactoid Reactions, Cross-sensitivity

- **Anaphylactic/anaphylactoid reactions have been reported in association with ifosfamide.**
- **Cross-sensitivity between oxazaphosphorine cytotoxic agents hasbeen reported.**

Impairment of Wound Healing

- **Ifosfamide may interfere with normal wound healing.**

PRECAUTIONS

Alopecia
- Alopecia is a very common, dose-dependent effect of ifosfamide administration.
- Chemotherapy-induced alopecia may progress to baldness.
- The hair can grow back, though it may be different in texture or color.

Nausea and Vomiting
- Administration of ifosfamide may cause nausea and vomiting.
- Current guidelines on the use of antiemetics for prevention and amelioration of nausea and vomiting should be considered.
- Alcohol consumption may increase chemotherapy-induced nausea and vomiting.

Stomatitis
- Administration of ifosfamide may cause stomatitis (oral mucositis).
- Current guidelines on measures for prevention and amelioration of stomatitis should be considered.

Paravenous Administration
- **The cytotoxic effect of ifosfamide occurs after its activation, which takes place mainly in the liver. Therefore, the risk of tissue injury from accidental paravenous administration is low.**
- **In case of accidental paravenous administration of ifosfamide, the infusion should be stopped immediately, the extravascular ifosfamide solution should be aspirated with the cannula in place, and other measures should be instituted as appropriate.**

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

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

Interactions 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 hematotoxicity and/or immunosuppression may result from a combined effect of ifosfamide and, for example:**
  - **ACE inhibitors: ACE inhibitors can cause leukopenia.**
  - **Carboplatin**
  - **Cisplatin**
  - **Natalizumab**

- **Increased cardiotoxicity may result from a combined effect of ifosfamide and, for example:**
  - **Anthracyclines**
  - **Irradiation of the cardiac region**

- **Increased pulmonary toxicity may result from a combined effect of ifosfamide and, for example:**
  - **Amiodarone**
  - **G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor)**

- **Increased nephrotoxicity may result from a combined effect of ifosfamide and, for example:**
  - **Acyclovir**
  - **Aminoglycosides**
  - **Amphotericin B**
  - **Carboplatin**
  - **Cisplatin**
- **An increased risk of developing hemorrhagic cystitis may result from a combined effect of ifosfamide and, for example:**
  - **Busulfan**
  - **Irradiation of the bladder**

- **Additive CNS effects may result from a combined effect of ifosfamide and, for example:**
  - **Antiemetics**
  - **Antihistamines**
  - **Narcotics**
  - **Sedatives**

- **Inducers of human hepatic and extrahepatic microsomal enzymes (e.g., cytochrome P450 enzymes): The potential for increased formation of metabolites responsible for cytotoxicity and other toxicities (depending on the enzymes induced) must be considered in case of prior or concomitant treatment with, for example:**
  - **Carbamazepine**
  - **Corticosteroids**

  - **Rifampin**
  - **Phenobarbital**
  - **Phenytoin**
  - **St. John's Wort**
- **Inhibitors of CYP 3A4: Reduced activation and metabolism of ifosfamide may alter the effectiveness of ifosfamide treatment. Inhibition of CYP 3A4 can also lead to increased formation of an ifosfamide metabolite associated with CNS and nephrotoxicity. CYP 3A4 inhibitors include:**
  - **Ketoconazole**
  - **Fluconazole**
  - **Itraconazole**
  - **Sorafenib**

- **Docetaxel: Increased gastrointestinal toxicity has been reportedwhen 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.**

Pregnancy and Lactation:

- **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.**
- **Fetal growth retardation and neonatal anemia have been reported following exposure to ifosfamide-containing chemotherapy regimens during pregnancy. In addition, exposure to** cyclophosphamide, **another oxazaphosphorine cytotoxic agent, has been reported to cause miscarriage, malformations (following exposure during the first trimester), and neonatal effects, including leukopenia, pancytopenia, severe bone marrow hypoplasia, and gastroenteritis.**
- **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. See Genotoxicity under Section on Special Warnings and Precautions for Use.**
- **If ifosfamide is used during pregnancy, or if the patient becomes pregnant while taking this drug or after treatment (see Genotoxicity under Section on Special Warnings and Precautions for Use), the patient should be apprised of the potential hazard to afetus.**
- **Ifosfamide may pass into the breast milk. Ifosfamide toxicity may occur in a breast-fed child. These toxicities include neutropenia, thrombocytopenia, low hemoglobin, and diarrhea. Women must not breastfeed during treatment withifosfamide.**

Effects on Ability to Drive and Use Machines:
Manifestations of CNS toxicity may impair a patient's ability to operate an automobile or other heavy machinery. See Section on Special Warnings and Precaution for Use

Dosage and administration:

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

Dosage

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.
Where indicated, use of haematopoiesis-stimulating agents (colony stimulating factors and erythropoiesis-stimulating agents) may be considered to reduce the risk of myelosuppressive complications and/or help facilitate the delivery of the intended dosing. For information on a potential interaction with G-CSF and GM-CSF (granulocyte colony stimulating factor, granulocyte macrophage colony-stimulating factor) see Interactions With Other Medicinal Products and Other Forms of Interaction.
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 Special Warnings and Precautions for Use.
For prophylaxis of haemorrhagic cystitis, ifosfamide should be used in combination with mesna.

Fractionated administration is the most common dosage form for monotherapy in adult patients. Fractionated application (duration of infusion between 30 and 120 min, depending on volume) usually implies 1.2 - 2.4 g ifosfamide/m2 of body surface area (BSA; up to 60 mg/kg body weight) daily, on five consecutive days in the form of intravenous infusion.
Holoxan can also be administered as a high single dose, usually in the form of a 24-hour continuous infusion. Dosage is usually 5 g/m2 body surface area (125 mg/kg body weight) and should not exceed 8 g/m2 body surface area (200 mg/kg body weight) per cycle. Administration of high single doses may lead to more severe haematological, urological, nephrological and CNS toxicities.
The ready-to-use ifosfamide solution must not exceed a concentration of 4 %. When applying ifosfamide, as with any other cytostatic drug, monitoring of blood count is required prior to each chemotherapy cycle and in the intervals between

cycles. Dosage adjustment may be necessary depending on blood count results.

Patients with Renal Impairment
In patients with renal impairment, particularly in patients 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, hemotoxic effects and nephrotoxic effects) and should be considered when determining the dosage in such patients.
Ifosfamide and its metabolites are dialyzable. In patients requiring dialysis, use of a consistent interval between ifosfamide administration and dialysis should be considered.

Patients with Hepatic Impairment
In patients with hepatic impairment, particularly in patients with severe hepatic impairment,
a decreased activation of ifosfamide may occur. This may alter the effectiveness of ifosfamide treatment. Low levels of serum albumin or hepatic impairment are counted as risk factors for CNS toxicity. Hepatic impairment may increase accumulation of a metabolite that is assumed to cause CNS toxicity. This should be considered when selecting the dose and interpreting response to the dose selected.

Elderly
In elderly patients, it may occur commonly that the function of liver, kidney, heart or other organs are impaired and that concomitant diseases occur or that concomitant therapies are necessary. Therefore, Ifosfamide should be used with particular caution in these patients. Increased monitoring for toxicities is necessary and the need for possible dose adjustment should also be considered.

Guidelines for dose reduction in the case of myelosuppression

White blood cells/µl	Platelets/µl	
>4,000	>100,000	100 % of the planned dose
4,000 – 2,500	100,000 to 50,000	50 % of the planned dose
<2,500	<50,000	Postponement until normalisation or individual decision

When used together with other cytostatic agents as a combination chemotherapy, the dosage should be adapted to the respective treatment regimen. When used in combination with other myelotoxic drugs, the dosage may have to be adapted as appropriate.

Note:
Given its urotoxic effect ifosfamide should always be combined with mesna. Other toxicities and the therapeutic effects of ifosfamide are not influenced by mesna. If cystitis accompanied by micro- or macrohaematuria occurs under treatment with ifosfamide, therapy must be interrupted until normalisation is obtained.

Method of administration

For instructions on preparing and handling the product, see Special Precautions for Disposal and Other Handling.
The therapy cycles may be repeated every 3 to 4 weeks. The intervals depend on factors including blood count and recovery from any undesirable effects or accompanying symptoms.

Notes:
Blood count, renal function, urinary status as well as urinary sediment must be checked regularly. Antiemetics should be administered in time, taking into account any undesirable effects on the CNS when combined with ifosfamide. In case of fever and/or leukopenia antibiotics and/or antimycotics should be given prophylactically. Sufficient diuresis is required. Attention should be paid to meticulous oral hygiene.

In case of long-term treatment with ifosfamide, sufficient diuresis and regular control of renal function will be required. This applies in particular to children. In case of onset of nephropathy, irreversible kidney damage must be expected if treatment with ifosfamide is continued. Appraisal of the risk-benefit ratio will be required. Caution is indicated in unilaterally 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 may be increased.

Special note:
Due to its alkylating effect, ifosfamide is a mutagenic and potentially carcinogenic substance. Contact with skin and mucous membranes must therefore be avoided.

Special Precautions for Disposal and Other Handling
For handling or disposal of ifosfamide the guidelines on safe use and safe handling of cytotoxic agents must be observed.

Skin reactions associated with accidental exposure to ifosfamide may occur. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and solutions containing ifosfamide. If ifosfamide solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water.

Preparation of the solution from Holoxan:
For preparation of the 4 % strength, ready-to-inject solution, the following amount of water for injections is added to the powder, depending on the pack size:

Powder	200 mg	500 mg	1 g	2 g
Water for injections	5 ml	13 ml	25 ml	50 ml

The substance dissolves readily when the injection vials are shaken vigorously for ½ to 1 minute after adding the water for injections. If complete dissolution does not occur immediately, it is expedient to allow the solution to stand for a few minutes.

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

Before parenteral administration, the substance must be completely dissolved.

For intravenous infusion (approx. 30 – 120 min) the solution is diluted in 250 ml of Ringer's solution or 5 % strength glucose solution or 0.9 % strength physiological saline solution.

For prolonged administration, over one to two hours, dilution with 500 ml Ringer's solution or 5 % glucose or 0.9 % physiological saline solution is recommended.

For continuous 24-hour infusion with high doses of ifosfamide, the solution, e.g. 5 g/m², is diluted in 3 litres of 5 % glucose solution and/or 0.9 % physiological saline.

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.

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.

Storage and Stability note:
Holoxan should not be stored above +25 °C
Holoxan should not be used after the expiry date stated on the package.
The reconstituted solution should be used within 24 hours after preparation (do not store above + 8°C!).

Keep drugs out of children´s reach!

Name and permanent address of the manufacturer
Baxter Oncology GmbH Kantstrasse 2
D-33790 Halle/Westfalen, Germany

Date of last revision of the text

Oct 2024

Presentation:

200 mg vials – Packs of 10 vials

500 mg vials – Packs of 1 and 10 vials

1g vials – Packs of 1 and 10 vials

2g vials – Packs of 1 and 10 vials

Holoxan® is available on prescription only