Patient Information Leaflet
Please read carefully!
HOLOXAN
Active substance: Ifosfamide

Composition:	1 vial	HOLOXAN 500 mg	HOLOXAN 1 g	HOLOXAN 2 g
		contains:		
	Ifosfamide	500 mg	1 g	2 g

as dry substance for preparing an injectable solution.

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, hypernephroma, 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.
Remarks:
Before starting treatment, it is necessary to exclude or correct any obstruction of the efferent urinary tract, cystitis, infections and electrolyte imbalances. In general, HOLOXAN, like other cytostatics, should be used with care in weakened or elderly patients and in patients who have had previous radiotherapy. Patients with a weakened immune system, e.g. those with diabetes mellitus, chronic hepatic and renal impairments, also require special care. Patients with brain metastases, cerebral symptoms and/or deteriorated renal function must be kept under close observation.

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.

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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 and immunosuppression must be expected particularly in patients pretreated with and/or receiving concomitant chemotherapy/hematotoxic agents, immunosuppressants and/or radiation therapy. See Section Interactions with Other Medicinal Products.
- 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.
- 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.

Central Nervous System Toxicity, Neurotoxicity

- Administration of ifosfamide can cause CNS toxicity and other neurotoxic effects.
- Manifestations of CNS toxicity reported with ifosfamide treatment include:
  - Confusion
  - Somnolence
  - Coma
  - Hallucinations
  - Blurred vision
  - Psychotic behavior
  - Extrapyramidal symptoms
  - Urinary incontinence
  - Seizures
- There also have been reports of peripheral neuropathy associated with ifosfamide use.
- Ifosfamide neurotoxicity may become manifest within a few hours to a few days after first administration and in most cases resolves within 48 to 72 hours of ifosfamide discontinuation. Symptoms may persist for longer periods of time. Occasionally, recovery has been incomplete. Fatal outcome of CNS toxicity has been reported.
- Recurrence of CNS toxicity after several uneventful treatment courses has been reported.
- CNS toxicity has been reported very commonly and appears to be dosedependent.

- 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 hemoglobin levels, decreased white blood cell count
  - Acidosis, low serum bicarbonate
  - Electrolyte imbalances, hyponatremia and inappropriate ADH (vasopressin) secretion, water intoxication, low fluid intake
  - Presence of brain metastases, prior CNS disease, brain irradiation
  - Cerebral sclerosis, peripheral vasculopathy
  - Presence of tumor in lower abdomen, bulky abdominal disease
  - Poor performance status, advanced age, younger age
  - Obesity, female gender, individual predisposition
  - Interactions with other medicines (e.g., aprepitant, CYP 3A4 inhibitors), alcohol, drug abuse, or pretreatment with cisplatin
- Neurotoxicity often manifests in patients without identifiable risk factors.
- The risk of CNS toxicity and other neurotoxic effects necessitates careful monitoring of the patient.
- If encephalopathy develops, treatment with ifosfamide should be discontinued. The possibility to reintroduce ifosfamide should be determined after careful assessment of the benefits and risks for the individual patient.
- 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 ifosfamideinduced encephalopathy.

Renal and Urothelial Toxicity

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

Nephrotoxic Effects

- Renal parenchymal and tubular necrosis, and fatal outcome from nephrotoxicity 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.
- 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.
- 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

- Fatal outcome of ifosfamide-associated cardiotoxicity has been reported.
- 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
- 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 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. Other malignancies reported after use of ifosfamide or regimens with ifosfamide include lymphoma, thyroid cancer, and sarcomas.
- Malignancy has also been reported after in utero exposure with cyclophosphamide, another oxazaphosphorine cytotoxic agent.

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

Genotoxicity
- 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.

Female Patients
- Amenorrhea has been reported in patients treated with ifosfamide. In addition, with cyclophosphamide, another oxazaphosphorine cytotoxic agent, oligomenorrhea has been reported.
- The risk of permanent chemotherapy-induced amenorrhea is increased in older women.
- Girls treated with ifosfamide during prepubescence may develop secondary sexual characteristics normally and have regular menses.
- Girls treated with ifosfamide during prepubescence subsequently have conceived.

- Girls who have retained ovarian function after completing treatment are at increased risk of developing premature menopause.

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

Anaphylactic/Anaphylactoid Reactions, Cross-sensitivity
- Anaphylactic/anaphylactoid reactions have been reported in association with ifosfamide.
- Cross-sensitivity between oxazaphosphorine cytotoxic agents has been reported.

Impairment of Wound Healing
- Ifosfamide may interfere with normal wound healing.

PRECAUTIONS

The following measures and/or tests are indicated in order to limit or alleviate adverse reactions:
– Timely administration of antiemetics.
– Regular blood counts,
– Regular checks of renal function parameters,
– Regular checks of urinalysis and urinary sediment.
In cases of hepatic or renal impairment before the start of therapy, the use of HOLOXAN has to be individually weighed for each patient. It is recommended that patients under HOLOXAN therapy are monitored more frequently.
The blood sugar level should be checked regularly in diabetics in order to modify the antidiabetic therapy on time.
It is essential to ensure adequate diuresis.
Fever and/or severe leucopenia require prophylactic administration of antibiotics and/or antimycotics.
Attention should be paid to meticulous oral hygiene.

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.

- Ifosfamide and its metabolites are dialyzable. In patients requiring dialysis, use of a consistent interval between ifosfamide administration and dialysis should be considered.

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.

Use in Elderly Patients

In elderly patients, monitoring for toxicities and the need for dose adjustment should reflect the higher frequency of decreased hepatic, renal, cardiac, or other organ function, and concomitant diseases or other drug therapy in this population.

Used during 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 Section Genotoxicity.
- If ifosfamide is used during pregnancy, or if the patient becomes pregnant while taking this drug or after treatment (see Section Genotoxicity), the patient should be apprised of the potential hazard to a fetus.

- In a vital indication during the first trimester of pregnancy a medical consultation regarding abortion is absolutely necessary.
- After the 1st trimester of pregnancy, if therapy cannot be delayed and the patient wishes to continue with her pregnancy, chemotherapy may be undertaken after informing the patient of the minor but possible risk of teratogenic effects.
- 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. Mothers must not breast feed during treatment with HOLOXAN.

Effects on Fertility
- Ifosfamide interferes with oogenesis and spermatogenesis. Amenorrhea, azoospermia, and sterility in both sexes have been reported.
- 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 some patients.

Contraceptive measures
Ifosfamide can cause congenital anomalies. Conception during treatment is not advisable. Men to be treated with HOLOXAN should be informed about sperm preservation before treatment. Women should not become pregnant during treatment. Should they still conceive during treatment, they should seek genetic consultation. The duration of contraception after the end of chemotherapy depends on the prognosis of the primary disease and on the intensity of the parents' desire for a child. The possibility of a genetic consultation should be used.

Adverse Reaction :
Patients on HOLOXAN therapy may experience the following adverse reaction:
Myelosuppression:
Different degrees of myelosuppression (leucocytopenia, thrombocytopenia and anaemia) can occur, depending on the dose. Frequently leucocytopenia with the risk of life-threatening infections and thrombocytopenia with the risk of bleeding have to be taken into consideration. The lowest leucocyte and thrombocyte counts normally occur one to two weeks after start of treatment and recover within 3 to 4 weeks. Anaemia usually occurs after several cycles of treatment. A combination treatment with other myelosuppressive agents may require dose adjustments. Single high-dose treatment leads more frequently to leucocytopenia than fractionated dose-regimen. In pretreated (chemotherapy and/or radiotherapy) patients or patients with renal function impairment, a more severe myelosuppression can be expected. With ifosfamide as with other cytostatics, blood counts have to be taken before each chemotherapy cycle as well as during the intervals between cycles.
Depending on the blood picture, appropriate dose adaptations (see table) should be made.
Remark: Guidelines for dose reduction in myelosuppression

Leucocyte Count	Thrombocyte Count	
>4000	>100.000	100% of planned dose

Urotoxicity and nephrotoxicity:

Haemorrhagic cystitis (macro- and microhaematuria) is a frequent, dose-dependent complication of ifosfamide.

Remark:

Fractionated dosing, adequate hydration, maintenance of fluid balance and particularly concomitant treatment with mesna (UROMITEXAN) can markedly reduce the frequency and severity of haemorraghic cystitis.

Disorders of glomerular renal function with an increase in serum creatinine, a decrease in creatinine clearance and proteinuria can occasionally occur, or more frequently disorders of tubular renal function with hyperaminoaciduria, phosphaturia, acidosis or proteinuria. Severe nephropathies are rare. Possible risk factors for disorders of glomerular renal function are high doses of the drug and additional treatment with platinum containing drugs.

Risk factors for disorders of tubular renal function are previous nephrectomy, additional treatment with platinum containing drugs or concomitant irradiation of the abdomen with inclusion of the kidneys or the remaining kidney. Caution is advisable when potentially nephrotoxic drugs such as aminoglycosides, acyclovir or amphotericin B are used concomitantly. These drugs do not potentiate the tubular kidney disorder, but may cause further deterioration of glomerular function.

In rare cases, patients with chronic tubular kidney disorder may develop Fanconi's syndrome resulting in rickets or, in adults, osteomalacia. Predisposing factors are high cumulative doses of the drug and young age (particularly younger than 3 years). Glomerular and tubular kidney function must therefore be evaluated and checked before start of therapy, during and after therapy.

During long-term treatment with ifosfamide, sufficient diuresis and regular control of renal function is necessary. This applies especially to children. In case of beginning nephropathy, irreversible kidney damage has to be expected if treatment with ifosfamide is continued. A careful risk benefit evaluation is required.

Caution is required in unilaterally nephrectomized patients, in patients with impaired renal function and in patients pre-treated with nephrotoxic drugs (e.g. cisplatin). In these patients frequency and intensity of myelotoxicity, nephro and cerebral toxicity are increased.

Central nervous system:

In 10-20% of cases, encephalopathy occurs and develops within a few hours up to a few days after start of treatment. Risk-factors are a poor state of health, impaired renal function (creatinine > 1.5 mg/dl), pre-treatment with nephrotoxic drugs (e.g. cisplatin) and post-renal obstructions (e.g. pelvic tumours). Other possible risk-factors are old age, a history of alcohol abuse, decreased levels of serum albumin or hydrogen carbonate, hepatic dysfunction or concurrent high dose treatment with antiemetic drugs. The most common symptom of encephalopathy is drowsiness which can progress to somnolence and coma. Other symptoms can be weakness, forgetfulness, depressive psychoses, disorientation, restlessness, confusion, hallucinations, cerebellar symptoms, incontinence and convulsions. The encephalopathies are usually reversible and disappear spontaneously within a few days after the last ifosfamide administration. Severe course are rare, and deaths were only seen in isolated cases and in connection with very high doses of the drug. With a fractionated dose-regimen, encephalopathies are less frequent and less severe.

Remarks:

Due to the CNS-toxicity of ifosfamide, patients must be carefully monitored. In the event of encephalopathy, ifosfamide treatment has to be discontinued and must not be resumed. In case of ifosfamide induced encephalopathy, drugs acting on the CNS (e.g., antiemetics, tranquilizers, narcotics or antihistamines) should be discontinued if possible, or used with special caution.

Other adverse effects:

Nausea and vomiting are dose-dependent side-effects. Moderate to severe forms can be seen in about 50% of the cases. Another frequent side-effect is reversible alopecia which occurs in up to 100% of patients, depending on dosage and duration of treatment. Because of its alkylating

mechanism of action, HOLOXAN can cause partly irreversible impairment of spermatogenesis with resulting azoospermia or persistent oligospermia, respectively less frequently irreversible ovulation disturbances with resulting amenorrhea and reduced levels of female sex hormones.

Additionally, there can occur:

- in isolated cases chronic interstitial pulmonary fibrosis. Toxic- allergic pulmonary oedema was reported in one single case.
- in isolated cases SIADH (syndrome of inadequate ADH-secretion, Schwartz-Bartter-syndrome) with hyponatremia and water retention. Hypokalemia was reported in one single case.
- in rare cases inflammation of the skin and mucous membrane : dermatitis and papular rash
- in rare cases hypersensitivity reactions, in isolated cases progressing to shock
- in rare cases blurred vision and episodes of dizziness.
- in uncommon cases : peripheral neuropathy, stomatitis, fatigue and malaise (unknown)
- in uncommon cases : cardiotoxicity was reported as congestive heart failure, tachycardia, pulmonary edema. Fatal outcome has been reported
- in uncommon cases : hypotension leading to shock and fatal outcome has been reported
- in common cases : hepatotoxicity was reported as increases in liver enzymes, i.e., serum alanine aminotransferase, serum aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase and lactate dehydrogenase, increased bilirubin, jaundice, hepatorenal syndrome
- in common cases : neutropenic fever, includes cases reported as granulocytopenic fever

An increase in liver enzymes and/or in the bilirubin level can also occur occasionally. Anorexia,diarrhea, constipation, phlebitis or pyrexia may more seldom be seen. Polyneuropathy, pneumonitis,impaired vision or an increased reaction to radiation were isolated seen. There have been isolatedreports of supraventricular or ventricular arrhythmias, ST-T segment changes and heart failureafter very high doses of ifosfamide and/or after pretreatment or concomitant treatment with anthracyclines.
In this context, it is again necessary to stress the need for regular electrolyte monitoring and special caution when treating patients with history of heart disease. As with cytotoxic therapy in general, especially with alkylating agents, treatment with ifosfamide involves the risk of secondary tumours as late sequelae.

Post-marketing Adverse Reactions
The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

INFECTIONS AND INFESTATIONS:
The following manifestations have been associated with myelosuppression and immunosuppression caused by ifosfamide: increased risk for and severity of infections†, pneumonias†, sepsis and septic shock (including fatal outcomes), as well as reactivation of latent infections, including viral hepatitis†, *Pneumocystis jiroveci*†, herpes zoster, *Strongyloides*, progressive multifocal leukoencephalopathy†, and other viral and fungal infections.
†Severe immunosuppression has led to serious, sometimes fatal, infections.

NEOPLASMS, BENIGN AND MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS): As treatment-related secondary malignancy*, Acute leukemia* (Acute myeloid leukemia*, Acute promyelocytic leukemia*), Acute lymphocytic leukemia*, Myelodysplastic syndrome, Lymphoma (Non-Hodgkin's lymphoma), Sarcomas*, Renal cell carcinoma, Thyroid cancer

Progressions of underlying malignancies, including fatal outcomes, have been reported.
*Including fatal outcomes

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Hematotoxicity*, Myelosuppression manifested as Bone marrow failure, Agranulocytosis; Febrile bone marrow aplasia; Disseminated intravascular coagulation, Hemolytic uremic syndrome, Hemolytic anemia, Neonatal anemia, Methaemoglobinaemia
*Including fatal outcomes
IMMUNE SYSTEM DISORDERS: Angioedema*, Anaphylactic reaction, Immunosuppression, Urticaria, Hypersensitivity reaction *Including fatal outcomes

ENDOCRINE DISORDERS: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

METABOLISM AND NUTRITION DISORDERS: Tumor lysis syndrome, Metabolic acidosis, Hypokalemia, Hypocalcemia, Hypophosphatemia, Hyperglycemia, Polydipsia

PSYCHIATRIC DISORDERS: Panic attack, Catatonia, Mania, Paranoia, Delusion, Delirium, Bradyphrenia, Mutism, Mental status change, Echolalia, Logorrhea, Perseveration, Amnesia

NERVOUS SYSTEM DISORDERS: Convulsion*, Status epilepticus (convulsive and nonconvulsive), Reversible posterior leukoencephalopathy syndrome, Leukoencephalopathy, Extrapyramidal disorder, Asterixis, Movement disorder, Polyneuropathy, Dysesthesia, Hypoesthesia, Paresthesia, Neuralgia, Gait disturbance, Fecal incontinence, Dysarthria
*Including fatal outcomes

EYE DISORDERS: Visual impairment, Vision blurred, Conjunctivitis, Eye irritation

EAR AND LABYRINTH DISORDERS: Deafness, Hypoacusis, Vertigo, Tinnitus

CARDIAC DISORDERS: Cardiotoxicity*, Cardiac arrest*, Ventricular fibrillation*, Ventricular tachycardia*, Cardiogenic shock*, Myocardial infarction*, Cardiac failure*, Bundle branch block left, Bundle branch block right, Pericardial effusion, Myocardial hemorrhage, Angina pectoris, Left ventricular failure, Cardiomyopathy*, Congestive cardiomyopathy, Myocarditis*, Arrhythmia*, Pericarditis, Atrial fibrillation, Atrial flutter, Bradycardia, Supraventricular extrasystoles, Premature atrial contractions, Ventricular extrasystoles, Myocardial depression, Palpitations, Ejection fraction decreased*, Electrocardiogram ST-segment abnormal, Electrocardiogram T- wave inversion, Electrocardiogram QRS complex abnormal
*Including fatal outcomes

VASCULAR DISORDERS: Pulmonary embolism, Deep vein thrombosis, Capillary leak syndrome, Vasculitis, Hypertension, Flushing, Blood pressure decreased

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS: Respiratory failure*, Acute respiratory distress syndrome*, Pulmonary hypertension*, Interstitial lung disease* as manifested by Pulmonary fibrosis*, Alveolitis allergic, Interstitial pneumonitis, Pneumonitis*; Pulmonary edema*, Pleural effusion, Bronchospasm, Dyspnea, Hypoxia, Cough
*Including fatal outcomes

GASTROINTESTINAL DISORDERS: Cecitis, Colitis, Enterocolitis, Pancreatitis, Ileus, Gastrointestinal hemorrhage, Mucosal ulceration, Constipation, Abdominal pain, Salivary hypersecretion

HEPATOBILIARY DISORDERS: Hepatic failure*, Hepatitis fulminant*, Venoocclusive liver disease, Portal vein thrombosis, Cytolytic hepatitis, Cholestasis
*Including fatal outcomes

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Toxic epidermal necrolysis, Stevens-Johnson syndrome, Palmar-plantar erythrodysesthesia syndrome, Radiation recall dermatitis, Skin necrosis, Facial swelling, Petechiae, Macular rash, Rash, Pruritus, Erythema, Skin hyperpigmentation, Hyperhidrosis, Nail disorder

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS:
Rhabdomyolysis, Osteomalacia, Rickets, Growth retardation, Myalgia, Arthralgia, Pain in extremity, Muscle twitching

RENAL AND URINARY DISORDERS: Fanconi syndrome, Tubulointerstitial nephritis, Nephrogenic diabetes insipidus, Phosphaturia, Aminoaciduria, Polyuria, Enuresis, Feeling of residual urine
Fatal outcomes from acute and chronic renal failure have been documented.

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: Infertility, Ovarian failure, Premature menopause, Amenorrhea, Ovarian disorder, Ovulation disorder, Azoospermia, Oligospermia, Impairment of spermatogenesis, Blood estrogen decreased, Blood gonadotrophin increased

CONGENITAL, FAMILIAL AND GENETIC DISORDERS: Fetal growth retardation

GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS: Multiorgan failure*, General physical deterioration, Injection/Infusion site reactions including swelling, inflammation, pain, erythema, tenderness, pruritus; Chest pain, Edema, Mucosal inflammation, Pain, Pyrexia, Chills
*Including fatal outcomes

Class Reactions
The following adverse reactions have been reported with cyclophosphamide, another oxazaphosphorine cytotoxic agent:
Renal pelvis cancer, Ureteric cancer, Bladder cancer, Bladder necrosis, Bladder fibrosis, Bladder contracture, Hemorrhagic pyelitis, Hemorrhagic ureteritis, Ulcerative cystitis Intrauterine death, Fetal malformation, Fetal toxicity (including myelosuppression, gastroenteritis), Premature labor, Testicular atrophy, Oligomenorrhea

Overdose
Serious consequences of overdosage include manifestations of dose-dependent toxicities such as CNS toxicity, nephrotoxicity, myelosuppression, and mucositis.
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.

Effects on ability to drive and use machines:
HOLOXAN may affect a subject's ability to drive a motor vehicle or to operate machinery. This may occur either directly by induced encephalopathy or indirectly as a result of nausea and vomiting, especially when CNS-active drugs or alcohol are taken concomitantly.

Interactions with other drugs:
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.

- Myelotoxicity can be increased as a result of interaction with other cytostatics or radiation.
- Ifosfamide may intensify skin reactions due to irradiation.
- The prior or concurrent administration of nephrotoxic agents like cisplatin, aminoglycosides, acyclovir, carboplatin or amphotericin B may enhance the nephrotoxic effect of ifosfamide and consequently haematotoxic and neurotoxic (CNS) effects as well.
- Because of the immunosuppressive effect of ifosfamide, an impaired response to the respective vaccine may occur.
- Vaccination injury can be caused by live-virus vaccinations. The concurrent use of ifosfamide may increase the anticoagulant effect of warfarin and thus raise the risk of haemorrhages.
- In analogy with cyclophosphamide, the following interactions seem possible:
  - The myelo-suppressive action may be enhanced by the concurrent administration of allopurinol or hydrochlorothiazide.
  - The effect and the toxicity may be enhanced by the concurrent administration of chlorpromazin, triiodothyronine or aldehyde dehydrogenase inhibitors such as disulfiram.
  - The treatment may increase the hypoglycaemic actions of sulfonylureas.
  - Prior or concurrent treatment with phenobarbital, phenytoin or chloral hydrate involves the possibility of microsomal liver enzyme induction and thus a faster metabolism of ifosfamide.
  - The treatment may increase the muscle-relaxant effect of suxamethonium.
- 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)
- 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
- 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
- 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.

Dosage and administration:
The treatment should only be administered by an experienced oncologist. The dosage must be adapted to each patient individually. In single-drug therapy of adults, the most common treatment is based on fractionated doses. In the absence of individual prescriptions, the following recommendations may serve as a guideline.

In general HOLOXAN is given intravenously in divided doses of 1.2-2.4 g/m^2 body surface (up to 60 mg/kg of body weight) daily for 5 consecutive days (the duration of these infusions is about 30-120 minutes, depending on the volume).
Care should be taken to ensure that the ifosfamide concentration of the solution does not exceed 4 percent.
In combination-therapy with other cytostatics, the dose should be adapted to the type of therapeutic scheme.
Remarks:
Because of its urotoxicity, ifosfamide should as a matter of principle be used in combination with mesna. Other toxicities and the therapeutic effects of ifosfamide will not be influenced by mesna.
Should cystitis with micro- and macrohaematuria develop during therapy, the treatment should be discontinued until the patient has recovered.
Because the cytostatic effect of ifosfamide occurs only after activation in the liver, there is no danger of injuring the tissue in the case of paravenous injections.
Administration and duration of treatment:
The therapy cycles may be repeated every 3-4 weeks. The intervals will depend on the blood count and on the recovery from any adverse reactions or side-effects.
The administration of uroprotection with mesna (UROPROTECTOR, UROMITEXAN) as directed, should be maintained.
Regular blood counts, regular checks of renal function and regular urinalysis including urinary sediment are necessary.
Timely administration of antiemetics is indicated, whereby the additional influences on the CNS in combination with HOLOXAN should be taken into consideration.

Preparation of the solution:
The handling of HOLOXAN should always be in accordance with the safety precautions used for the handling of cytotoxic agents.
To prepare a 4% isotonic solution ready for injection, water for injection is added to the dry substance in the following amounts:

HOLOXAN	500 mg	1 g	2 g
Water for injection	13 ml	25 ml	50 ml

The substance dissolves readily if the vials are vigorously shaken for 0.5 to 1 min after addition of the water for injection. If the substance fails to dissolve immediately and completely, it is advisable to allow the solution to stand for a few minutes. The prepared solution can be kept for up to approx.
24 hours if stored at a temperature not exceeding +8°C (refrigerator). The HOLOXAN solution for short-term intravenous infusion (approx. 30-120 min) is prepared by diluting the above solution with 250 ml Ringer's solution or 5% glucose solution or physiological saline. For longer infusions over one to two hours, dilution is recommended with 500 ml Ringer's solution or 5% glucose solution or physiological saline.

Instructions for Use and Handling, and Disposal
The handling and preparation of ifosfamide should always be in accordance with current guidelines on safe handling of cytotoxic agents.
Skin reactions associated with accidental exposure to ifosfamide may occur. 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.

Special remark:
Because of its alkylating action, Ifosfamide is a mutagenic and also a potential carcinogenic substance. Contact with the skin and mucous membranes should therefore be avoided.

Stability note:
HOLOXAN should not be stored above 25°C!
HOLOXAN may 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).
Store drugs out of children's reach!

Presentation:
500 mg vials – Pack of 1 vial Reg. No.: DKI 1005000444A1
1 g vials – Pack of 1 vial Reg. No.: DKI 1005000444B1
2 g vials – Pack of 1 vial Reg. No.: DKI 1005000444C1

HOLOXAN is available on prescription only

HARUS DENGAN RESEP DOKTER

Manufactured by
Baxter Oncology GmbH
Kantstrasse 2
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Germany

Imported by
PT. Menarini Indria Laboratories,
Bekasi, Indonesia

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