Applicant/HCR:	Baxter Healthcare South Africa (Pty) Ltd
Product Name:	Holoxan 500 mg Injection, Holoxan 1g Injection & Holoxan 2 g Injection
	Intravenous injections containing 500 mg, 1 g or 2 g ifosfamide as dry substance

PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

HOLOXAN 500 mg Injection

HOLOXAN 1 g Injection

HOLOXAN 2 g Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HOLOXAN 500 mg Injection: Each vial contains 500 mg of ifosfamide as a dry substance for preparation for an injection.

HOLOXAN 1 g Injection: Each vial contains 1 g of ifosfamide as a dry substance for preparation for an injection.

HOLOXAN 2 g Injection: Each vial contains 2 g of ifosfamide as a dry substance for preparation for an injection.

3. PHARMACEUTICAL FORM

White, crystalline powder in clear glass vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oat cell bronchogenic carcinoma.

Ovarian carcinoma (especially cystadeno-carcinoma).

Mammary carcinoma.

Testicular tumours (seminoma, teratoma, teratocarcinoma, chorio-epithelioma).

Pancreatic carcinoma.

Hypernephroma.

Malignant lymphoma (non-Hodgkin's type).

Chondro-, osteo-, leio- and rhabdomyosarcoma.

Children and adolescents (see section 5.1, Paediatric population).

HOLOXAN is evidently ineffective in:

Fibro-, myxo- and spindle-cell sarcoma, carcinoma of the bladder, malignant melanoma and cerebral metastasis.

4.2 Posology and method of administration

Posology

HOLOXAN should be administered only by medical practitioners who are experienced in cancer chemotherapy.

Dosage must be individualised.

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.

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 section 4.6).

Before therapy, possible obstructions within the urinary tract should be excluded, any infections cleared up and disturbances of electrolyte balance corrected.

The optimal dosage is a total dose of 250 to 300 mg per kg per treatment: The normal dose administered on five consecutive days is 50 to 60 mg per kg i.v. Should a lower daily dosage or distribution of the total dose over a longer period be indicated, 20 to 30 mg per kg is injected i.v. for ten consecutive days.

In therapy-resistant cases, which do not respond to the lower dose (and only after the leucocyte count has recovered to 4 000), an injection of 80 mg per kg for two to three consecutive days should be administered.

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, Urothelial effects).

Duration of treatment

Treatment may be repeated after an interval of not less than three to four weeks. Duration of treatment and/or of the intervals depend on the therapeutic indication, the scheme of the combination therapy, the patient's general state of health, the laboratory parameters as well as on the recovery of the blood picture.

Note

The dosage recommendation mentioned above shall mainly apply in case of monotherapy with HOLOXAN. When used together with other cytostatic agents as combination chemotherapy, the dosage instructions of the appropriate therapy scheme must be observed. When used in combination with other chemotherapeutic substances of similar toxicity, dose

reduction and/or extension of the treatment-free intervals might become necessary.

Because of its urotoxicity, HOLOXAN should always be combined with Mesna. Other toxicities and the therapeutic effects of HOLOXAN are not affected by Mesna.

If cystitis with micro- and macrohaematuria occurs during treatment with HOLOXAN, therapy must be discontinued until the values have normalised.

Special dosage recommendations

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.

The dose may need to be adjusted in patients with renal impairment (see sections 4.3 and 4.4).

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

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.

The dose may need to be adjusted in patients with hepatic impairment (see section 4.4).

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 medicine therapy in this population. See section 4.4.

Children and adolescents (see section 5.1, Paediatric population)

A variety of dosage schedules and regimens of ifosfamide in combination with other antitumour 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 paediatric tumours range from 0,8 to 3 g/m^2/day for 2 – 5 days for a total dose of 4 – 12 g/m^2 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/m^2 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 hypophosphataemia and rickets has been reported rarely but should be taken into consideration.

Paediatric data from randomised controlled clinical studies are limited.

Recommendations concerning dose adjustment for patients with myelosuppression

Leucocyte count/µl	Thrombocyte count/µl	Dosage
> 4000	> 100000	100 % of the planned dose
4000 to 2500	100000 to 50000	50 % of the planned dose
< 2500	< 50000	Postponement until normalisation or individual decision

Preparation of the injectable solution

Attention must be paid to ensure that the ready-to-use HOLOXAN solution does not exceed a concentration of 4 %.

The injectable solution is prepared by dissolving:

500 mg HOLOXAN in 13 ml Water for Injections,

1000 mg HOLOXAN in 25 ml Water for Injections,

2000 mg HOLOXAN in 50 ml Water for Injections.

Water for Injections = double-distilled water.

The substance is easily soluble, provided the bottles are thoroughly shaken for a ½ to 1 minute after adding the solvent. If dissolution does not occur without any residue, it is advisable to

allow the solution to stand for a couple of minutes. Before parenteral administration, the substance must be completely dissolved. Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

In patients with sensitive veins or in cases where the vessels are already damaged, HOLOXAN can also be used by perfusion.

The solution of HOLOXAN injection can be kept for up to 24 hours in the refrigerator at 5 ºC.

For intravenous infusion (approx. 30 - 120 minutes) the prepared HOLOXAN solution is diluted in 250 ml of Ringer's solution or 5 % strength glucose solution or 0,9 % strength physiological saline solution. For longer administration over one to two hours it is recommended to dilute the solution with 500 ml of Ringer's solution or 5 % strength glucose solution or 0,9 % strength physiological saline solution. For continuous 24-hour infusion with high doses of HOLOXAN, the prepared HOLOXAN solution, e.g. 5 g/m^2 is diluted in 3 litres of 5 % strength glucose solution and/or 0,9 % strength physiological saline solution.

4.3 Contraindications

HOLOXAN is contraindicated in patients with:

- Known hypersensitivity to ifosfamide (see section 4.4).
- Severely depressed bone marrow function (especially in patients previously treated with cytotoxic agents or radiotherapy).
- Active infections.
- Severe renal impairment (see sections 4.2 and 4.4) and/or obstructions of the urine flow.
- Inflammation of the urinary bladder (cystitis).
- Pregnancy and lactation (see section 4.6).

Further conditions for exclusion of HOLOXAN-therapy are:

Advanced cerebral sclerosis.

Platelet values below 50 000 per mm^3.

Lack of willing co-operation of patient.

4.4 Special warnings and precaution for use

The handling and preparation of HOLOXAN should always be in accordance with current guidelines on safe handling of cytotoxic agents.

Skin reactions associated with accidental exposure to HOLOXAN may occur. In view of the possible absorption of ifosfamide through the skin and by inhalation, it is recommended to wear face masks and impervious gloves for protection when handling the HOLOXAN injection.

Avoid skin and mucosal contact. If HOLOXAN solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water.

Warnings

Myelosuppression, Immunosuppression, Infections

Treatment with HOLOXAN 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 HOLOXAN-associated myelosuppression has been reported.

HOLOXAN-induced myelosuppression can cause leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding events), and anaemia.

Administration of HOLOXAN 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).

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 HOLOXAN, 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 and/or leucopenia, antibiotics and/or fungal agents must be given empirically until infection has been cleared/improved.

Close haematologic monitoring is recommended. White blood cell (WBC) count, platelet (Pt) count and haemoglobin (Hb) levels should be obtained prior to each administration and at appropriate intervals after administration. Unless essential, HOLOXAN should not be given to patients with a WBC count below 2500 µl.

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

Central Nervous S*ystem *Toxicity, Neurotoxicity

Administration of HOLOXAN can cause Central Nervous System (CNS) toxicity and other neurotoxic effects.

Manifestations of CNS toxicity reported with HOLOXAN treatment include:

- Confusion
- Somnolence
- Coma
- Hallucinations
- Blurred vision
- Psychotic behaviour
- Extrapyramidal symptoms
- Urinary incontinence
- Seizures

There also have been reports of peripheral neuropathy associated with HOLOXAN use.

HOLOXAN neurotoxicity may manifest within a few hours to a few days after first administration and in most cases resolves within 48 to 72 hours of HOLOXAN 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 dose-dependent (see section 4.8).

Other risk factors that have been demonstrated or discussed in the literature include:

- Renal dysfunction, elevated serum creatinine (> 132,6 µmol/l)
- Low serum albumin
- Hepatic dysfunction
- Low bilirubin, low haemoglobin 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 tumour 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 pre-treatment with cisplatin (see section 4.5)

Neurotoxicity often manifests in patients without identifiable risk factors.

The risk of CNS toxicity and other neurotoxic effects of HOLOXAN necessitates careful monitoring of the patient.

If encephalopathy develops, treatment with HOLOXAN should be discontinued. The possibility to reintroduce HOLOXAN should be determined after careful assessment of the

benefits and risks for the individual patient.

The effectiveness of methylene blue for the treatment and prophylaxis of ifosfamide encephalopathy appears to be not well established and possibly inconsistent.

Due to the potential for additive effects, medicines acting on the CNS (such as anti-emetics, sedatives, narcotics or antihistamines) must be used with particular caution or, if necessary, be discontinued in the case of HOLOXAN-induced encephalopathy.

Renal and Urothelial Toxicity

HOLOXAN 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 HOLOXAN.

Disorders of renal function (glomerular and tubular) following HOLOXAN 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 HOLOXAN.

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 HOLOXAN treatment. Acute tubular necrosis, acute renal failure and chronic renal failure secondary to HOLOXAN therapy have been reported.

The risk of developing clinical manifestations of nephrotoxicity is increased with, for example:

- large cumulative doses of HOLOXAN.
- pre-existing renal impairment.
- prior or concurrent treatment with potentially nephrotoxic medicines (such as cisplatin) (see section 4.5).
- younger age in children (in particular for children up to approximately 5 years of age).
- reduced nephron reserve as in patients with renal tumours and those having

undergone renal radiation or unilateral nephrectomy.

The risks and expected benefits of HOLOXAN therapy should be carefully weighed when considering the use of HOLOXAN in patients with pre-existing renal impairment or reduced nephron reserve.

Urothelial Effects

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

Haemorrhagic cystitis requiring blood transfusion has been reported with HOLOXAN.

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

Haemorrhagic cystitis after a single dose of HOLOXAN has been reported.

Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions (see section 4.3, 4.4 and 4.5).

During or immediately after administration, adequate hydration with up to 3 litres of liquid/day should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity.

For prophylaxis of haemorrhagic cystitis, HOLOXAN should be used in combination with Mesna.

HOLOXAN 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 haemorrhagic cystitis.

A cystitis, which does not heal, may lead to bladder fibrosis or even bladder tumours. It is therefore necessary to initiate timely treatment for prophylaxis of cystitis or to treat intensively an existing cystitis. Should any bladder defects occur, treatment with HOLOXAN should be discontinued, until these have subsided.

In addition, it is advisable to prescribe a saluretic. Alkalisation of the urine e.g. with citrate complexes, should commence two days prior to the first HOLOXAN injection, and be continued until at least 24 hours after the last injection of HOLOXAN.

In high-risk patients (for example, those with previous bladder diseases, those who have undergone preliminary abdominal irradiation or those with bladder complaints) a preparation of the SH-containing medicines should be instilled into the bladder by an in-dwelling catheter every four hours. This treatment must be continued for 24 hours after the last injection of HOLOXAN.

Under treatment with HOLOXAN, special attention should be paid to sufficient hydration (up to 3 litres of liquid per day), regular emptying and draining of the bladder and the use of Mesna (see section 4.2). Especially in case of long-term treatment with HOLOXAN, sufficient diuresis and regular control of renal function will be required. In particular, this shall apply to children. In case of onset of nephropathy, irreversible kidney damage must be expected if treatment with HOLOXAN is continued. Careful appraisal of the risk-benefit ratio will be required

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;
- haemorrhagic cystitis (including severe forms with ulceration and necrosis);
- haematuria, which may be severe and recurrent; while haematuria 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 urethritis.

Cardiotoxicity, Use in Patients with Cardiac Disease

Fatal outcome of HOLOXAN-associated cardiotoxicity has been reported.

Manifestations of cardiotoxicity reported with HOLOXAN 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 (see section 4.5), and possibly, renal impairment.

Particular caution should be exercised when HOLOXAN is used in patients with risk factors

for cardiotoxicity and in patients with pre-existing cardiac disease.

There is a need for regular electrolyte controls.

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 HOLOXAN treatment.

Secondary Malignancies

As with all cytotoxic therapy, treatment with HOLOXAN 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 leukaemia's, is increased. Other malignancies reported after use of ifosfamide or regimens with HOLOXAN 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 HOLOXAN and also is a known complication with cyclophosphamide, 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 HOLOXAN. In addition, with cyclophosphamide, another oxazaphosphorine cytotoxic agent, oligomenorrhoea has been reported, see section 4.6.

Male Patients

Men treated with HOLOXAN may develop oligospermia or azoospermia, see section 4.6.

Anaphylactic / Anaphylactoid Reactions, Cross-sensitivity

Anaphylactic / anaphylactoid reactions have been reported in association with HOLOXAN.

Cross-sensitivity between oxazaphosphorine cytotoxic agents has been reported.

Impairment of Wound Healing

HOLOXAN may interfere with normal wound healing.

Precautions

Alopecia

Alopecia is a very common, dose-dependent effect of HOLOXAN administration.

Chemotherapy-induced alopecia may progress to baldness.

The hair can grow back, though it may be different in texture or colour.

Nausea and Vomiting

Administration of HOLOXAN may cause nausea and vomiting.

Current guidelines on the use of anti-emetics for prevention and amelioration of nausea and vomiting should be considered.

Alcohol consumption may increase chemotherapy-induced nausea and vomiting.

Stomatitis

Administration of HOLOXAN may cause stomatitis (oral mucositis).

Current guidelines on measures for prevention and amelioration of stomatitis should be considered. To reduce stomatitis attention should be paid to thorough oral hygiene.

Paravenous Administration

The cytotoxic effect of HOLOXAN 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 HOLOXAN, the infusion must be stopped immediately, the extravascular HOLOXAN 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 HOLOXAN 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 4.2).

Ifosfamide and its metabolites are dialyzable. In patients requiring dialysis, use of a consistent interval between HOLOXAN administration and dialysis should be considered (see section 4.2).

Use in Patients with Hepatic Impairment

Hepatic impairment, particularly if severe, may be associated with decreased activation of HOLOXAN. This may alter the effectiveness of HOLOXAN 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 4.2).

Use in Elderly Patients

HOLOXAN must be used cautiously in weak or elderly patients and in patients previously treated with radiation therapy.

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 medicine therapy in this population.

Investigations

The blood sugar level should be checked regularly in diabetic patients in order to adjust

antidiabetic therapy on time (see section 4.5).

4.5 Interaction with other medicines 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.

Potentiation of the myelotoxicity due to interaction with other cytostatics or irradiation must be borne in mind. HOLOXAN can intensify the dermal radiation reaction.

Patients being treated with HOLOXAN 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 HOLOXAN and, for example:

- ACE inhibitors: ACE inhibitors can cause leukopenia.
- Carboplatin
- Cisplatin
- Natalizumab

Increased cardiotoxicity may result from a combined effect of HOLOXAN and, for example:

- Anthracyclines
- Irradiation of the cardiac region

Increased pulmonary toxicity may result from a combined effect of HOLOXAN 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 HOLOXAN and, for example

- Cisplatin
- Aminoglycosides
- Acyclovir
- Amphotericin B
- Carboplatin

These medicines can potentiate the nephrotoxicity of HOLOXAN and consequently haematotoxicity and CNS-toxicity.

An increased risk of developing haemorrhagic cystitis may result from a combined effect of HOLOXAN and, for example:

- Busulfan
- Irradiation of the bladder

Additive CNS effects may result from a combined effect of HOLOXAN and, for example

- Anti-emetics
- Sedatives
- Narcotics
- Antihistamines

These medicines are to be used with particular caution in the case of HOLOXAN-induced encephalopathy, or, if possible discontinued.

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:

- Phenobarbital
- Phenytoin
- Benzodiazepines
- Primidone
- Carbamazepine
- Rifampicin
- Chloralhydrate
- Corticosteroids
- St. John's Wort

See also aprepitant below.

Findings from *in vitro* experiments indicate that bupropion is mainly metabolised via the micosomal enzyme cytochrome P450 IIB6 (CYP2B6). Therefore, caution must be exercised in case of concomitant administration of bupropion, as well as preparations that act on the isoenzyme CYP2B6 (such as orphenadrine, cyclophosphamide and ifosfamide).

Inhibitors of CYP 3A4: Reduced activation and metabolism of HOLOXAN may alter the effectiveness of HOLOXAN treatment. Inhibition of CYP 3A4 can also lead to increased formation of a HOLOXAN metabolite associated with CNS and nephrotoxicity. CYP 3A4

inhibitors include:

- Ketoconazole
- Fluconazole
- Itraconazole

See also aprepitant below.

Aprepitant: Reports suggest increased HOLOXAN 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 HOLOXAN was administered before docetaxel infusion.

Coumarin derivatives: Increased INR (international normalized ration) has been reported in patients receiving HOLOXAN and warfarin, which can lead to a stronger reduction of blood coagulation and an increased risk of haemorrhage.

Vaccines: The immunosuppressive effects of HOLOXAN 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 HOLOXAN therapy (see also interactions above).

Irinotecan: Formation of the active metabolite of irinotecan may be reduced when irinotecan is administered with HOLOXAN.

Alcohol: In some patients, alcohol may increase HOLOXAN-induced nausea and vomiting.

The following medicine interactions have been reported with cyclophosphamide. HOLOXAN may have similar interactions:

- Potentiation of myelosuppression on concomitant administration of allopurinol or hydrochlorothiazide.
- Intensified effect and toxicity of HOLOXAN on concomitant administration of chlorpromazine, triiodothyronine or aldehyde dehydrogenase inhibitors such as disulfiram.
- Potentiation of the blood glucose-lowering effect of sulphonylureas.
- Potentiation of the muscle-relaxant effect of suxamethonium.

Due to the possibility of a decreased activation and thus reduced efficacy of HOLOXAN by a substance (CYP isoenzyme inhibitor) included in grapefruit, grapefruit or grapefruit juice should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

Women should not become pregnant during treatment with HOLOXAN (see section 4.3).

The administration of HOLOXAN during organogenesis has been shown to have a fetotoxic effect in mice, rats and rabbits, and therefore may cause foetal damage when administered to pregnant women.

Foetal growth retardation and neonatal anaemia 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).

In a vital indication during the first trimester of pregnancy a medical consultation regarding abortion is absolutely necessary. After the first trimester of pregnancy, if therapy cannot be delayed 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 and the potential hazard for the fetus.

If HOLOXAN is used during pregnancy, or if the patient becomes pregnant while taking HOLOXAN or after treatment (see Genotoxicity) the patient should be apprised of the potential hazard to a fetus and should seek genetic consultation.

If treatment should be required in women with childbearing potential a reliable contraceptive method must be used during the therapy as well as for up to six months after the end of treatment.

Lactation

HOLOXAN may pass into the breastmilk. HOLOXAN toxicity may occur in a breastfed child. These toxicities include neutropenia, thrombocytopenia, low haemoglobin, and diarrhoea. Women must not breastfeed during treatment with HOLOXAN.

Fertility

HOLOXAN 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 HOLOXAN, duration of therapy, and state of gonadal function at the time of treatment. Sterility may be irreversible in some patients.

HOLOXAN may cause transient or permanent amenorrhea in women and oligospermia or azoospermia in men.

Female Patients

Women treated with HOLOXAN should be informed prior to treatment about the possibility to save and preserve their eggs.

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

Girls treated with HOLOXAN during prepubescence may develop secondary sexual characteristics normally and have regular menses.

Girls treated with HOLOXAN 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 to be treated with HOLOXAN should be informed about sperm preservation before treatment starts.

Sexual function and libido generally are unimpaired in these patients.

Boys treated with HOLOXAN 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 HOLOXAN have subsequently fathered children.

Genotoxicity

HOLOXAN is mutagenic and genotoxic in male and female germ cells. Therefore, women should not become pregnant and men should not father a child during therapy with HOLOXAN.

Women treated with HOLOXAN should take contraceptive measures for at least 1 year after discontinuation of ifosfamide therapy.

Men should not father a child for up to six months after 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Depending on individual sensitivity, the type of disease and the dosage, side effects of differing degrees may be encountered, for which adequate preliminary and secondary treatment is required.

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

Patients on HOLOXAN therapy may experience the following dose-dependent side effects:

(Please refer to the discussion section on these side effects following the tabular listing).

Primary SOC	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10000 to < 1/1000)**	**Very rare (< 1/10000), including isolated reports**	**Unknown (unable to calculate)**
Infections and infestations		Infections	Pneumonia Sepsis			
Neoplasms benign and malignant (incl. cysts and polyps)			Secondary tumours Urinary tract carcinoma Myelodysplastic syndrome Acute leukaemia			
Blood and lymphatic system disorders	Myelosuppression Leucopenia[1] (any) Leukopenia <1 x 10^3/µl Thrombocyto-paenia[2] (any) Anaemia[3]	Thrombocyto-paenia <50 x 10^3/µl			Haemolytic uraemic syndrome Disseminated intravascular coagulation	
Immune system disorders				Hypersensitivity reactions	Anaphylactic shock	
Endocrine disorders			Irreversible ovulation	SIADH (Syndrome of		

			disturbances	inadequate ADH secretion)		
Metabolism and nutrition disorders		Metabolic acidosis Anorexia		Hyponatraemia Dehydration Water retention Electrolyte imbalance	Hypokalaemia	
Psychiatric disorders			Hallucinations Depressive psychosis Disorientation Restlessness Confusion			
Nervous system disorders	Drowsiness Central nervous system toxicity[4,5]		Somnolence Forgetfulness Dizziness Peripheral neuropathy	Cerebellar syndrome	Coma Seizures Polyneuro-pathy	
Eye disorders				Blurred vision	Visual impairment	
Cardiac disorders			Dysrhythmia Ventricular dysrhythmia Supraventricular dysrhythmia Cardiac failure Cardiotoxicity[6]		Cardiac arrest Myocardial infarction	
Vascular disorders			Bleeding Hypotension[7]		Thrombo-embolism	
Respiratory disorders				Pulmonary disorder Cough Dyspnoea	Interstitial pneumonitis Interstitial pulmonary	

					fibrosis Respiratory failure Toxic allergic pulmonary oedema	
Gastro-intestinal disorders	Nausea Vomiting		Diarrhoea Constipation Stomatitis	Faecal incontinence	Acute pancreatitis	
Hepato-biliary disorders		Hepatotoxicity[8]	Liver function disturbances			
Skin and sub-cutaneous tissue disorders	Alopecia			Papular rash Dermatitis	Toxic skin reactions	
Musculo-skeletal and connective tissue disorders				Cramps	Rickets Osteomalacia Rhabdomyoly-sis	
Renal and urinary disorders	Haematuria with Mesna Haematuria without Mesna Microhaematuria without Mesna Haemorrhagic cystitis[9] Renal	Nephropathies Tubular dysfunction Macro-haematuria Microhaematuria with Mesna	Incontinence Dysuria Disturbed urinary frequency Bladder irritation	Glomerular dysfunctions Tubular acidosis	Fanconi syndrome	

	dysfunction[10] Renal structural damage[11]					
Repro-ductive system and breast disorders		Impairment of spermatogenesis	Amenorrhoea Reduced levels of female sex hormones	Azoospermia Persistent oligospermia		
Congenital, familial and genetic disorders				Aminoaciduria		
General disorders and admini-strative site conditions	.	Asthenic conditions Weakness Phlebitis[12] Neutropenic Fever[13]	Fatigue	Mucositis Injection site reactions	Death	Malaise
Investiga-tions			Elevation of the ST segment Increase in liver enzymes Increase in ALT Increase in AST Increase in gamma-GT Increase in ALP Increase in bilirubin	Phosphaturia		
Surgical and medical procedures					Intensified reaction on radiotherapy	

[1] The following adverse reaction terms have been reported for leukopenia: neutropenia, granulocytopenia, lymphopenia, and pancytopenia. For neutropenic fever, see below.

[2] Thrombocytopenia may also be complicated by bleeding. Bleeding with fatal outcome has been reported.

[3] Includes cases reported as anaemia and decrease in haemoglobin / haematocrit.

[4] Encephalopathy with coma and death has been reported.

[5] Central nervous system toxicity was reported to be manifested by the following signs and symptoms: Abnormal behaviour, Affect lability, Aggression, Agitation, Anxiety, Aphasia, Asthenia, Ataxia, Cerebellar syndrome, Cerebral function deficiency, Cognitive disorder, Coma, Confusional state, Convulsions, Cranial nerve dysfunction, Depressed state of consciousness, Depression, Disorientation, Dizziness, Electroencephalogram abnormal, Encephalopathy, Flat affect, Hallucinations, Headache, Ideation, Lethargy, Memory impairment, Mood change, Motor dysfunction, Muscle spasms, Myoclonus, Progressive loss of brainstem reflexes, Psychotic reaction, Restlessness, Somnolence, Tremor, Urinary incontinence.

[6] Cardiotoxicity was reported as congestive heart failure, tachycardia, pulmonary oedema. Fatal outcome has been reported.

[7] Hypotension leading to shock and fatal outcome has been reported.

[8] 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.

[9] Frequency of haemorrhagic cystitis is estimated based on the frequency of haematuria. Reported symptoms of haemorrhagic cystitis included dysuria and pollakiuria. See also Post Marketing Side effects.

[10] Renal dysfunction was reported to be manifested as: Renal failure (including acute renal failure, irreversible renal failure; fatal outcomes have been reported), Serum creatinine

increased, BUN increased, Creatinine clearance decreased, Metabolic acidosis, Anuria, Oliguria, Glycosuria, Hyponatremia, Uraemia, Creatinine clearance increased

[11] Renal structural damage was reported to be manifested as: Acute tubular necrosis, Renal parenchymal damage, Enzymuria, Cylindruria, Proteinuria.

[12] Includes cases reported as phlebitis and irritation of the venous walls.

[13] Frequency of neutropenic fever: Includes cases reported as granulocytopenic fever.

Post-Marketing

The following side effects were reported in literature and post-marketing events:

Infections and infestations:

Fever can occur in the context of neutropenia and may be accompanied by infections.

The following manifestations have been associated with myelosuppression and immunosuppression caused by HOLOXAN: 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, malignant and unspecified (including cysts and polyps):

Therapy with HOLOXAN may be followed by development of secondary cancers. Urinary tract carcinomas and myelodysplastic syndrome culminating in acute leukaemia have been reported amongst others.

Acute leukaemia* (acute myeloid leukaemia*, acute promyelocytic leukaemia*), acute

lymphocytic leukaemia*, lymphoma (non-Hodgkin's lymphoma), sarcomas*, renal cell carcinoma and thyroid cancer.

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

* Including fatal outcomes.

Blood and the lymphatic system disorders:

Haematotoxicity including fatal outcome, myelosuppression manifested as bone marrow failure, agranulocytosis, febrile bone marrow aplasia, thromboembolism, disseminated intravascular coagulation, haemolytic uraemic syndrome, haemolytic anaemia, neonatal anaemia and methaemoglobinaemia, have been reported.

Immune system disorders:

Hypersensitivity reactions have been reported. Clinical signs may be rash, fever, hypotension, angioedema, immunosuppression, urticaria etc. These reactions may progress to anaphylactic shock and fatal outcome.

Endocrine disorders:

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

Metabolism and nutrition disorders:

Moderate to severe forms of nausea and vomiting may lead to dehydration. Anorexia has been seen.

Tumour lysis syndrome, metabolic acidosis, hypokalaemia, hypocalcaemia,

hypophosphataemia, hyperglycaemia and polydipsia have also been reported.

Psychiatric disorders:

Panic attack, catatonia, mania, paranoia, delusion, delirium, bradyphrenia, mutism, mental status change, echolalia, logorrhoea, perseveration, amnesia, depressive psychoses, disorientation, restlessness, dizziness, confusion, hallucinations and–cerebellar syndrome have been reported.

Nervous system disorders:

Frequently encephalopathy may occur. It may develop within a few hours up to a few days after the treatment of HOLOXAN was initiated. The encephalopathy and associated symptoms are usually reversible and disappear spontaneously within a few days after the last administration of HOLOXAN. The frequently reported symptom of encephalopathy is drowsiness that may progress from somnolence. Progression to coma with fatal outcome has been reported. With a fractioned dose-regimen, encephalopathies are less frequent and less severe.

Polyneuropathy may occur.

Convulsion*, status epilepticus (convulsive and non-convulsive), extrapyramidal disorder, asterixis, movement disorder, dysesthesia, hypoesthesia, paresthesia, neuralgia, gait disturbance, incontinence (faecal and urinary) and dysarthria.

* Including fatal outcomes.

Eye disorders:

Transient blurred vision isolated cases of visual impairment, conjunctivitis and eye irritation

have been reported.

Ear and labyrinth disorders:

Deafness, hypoacusis, vertigo and 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 haemorrhage, 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 and electrocardiogram QRS complex abnormal.

* Including fatal outcomes.

Vascular disorders:

Pulmonary embolism, deep venous thrombosis, capillary leak syndrome, vasculitis, hypertension, flushing and 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 oedema*, pleural effusion, bronchospasm, cough, dyspnoea, hypoxia.

* Including fatal outcomes.

Gastrointestinal disorders:

Nausea and vomiting, diarrhoea, constipation, mucositis/stomatitis, cecitis, colitis, enterocolitis, ileus, pancreatitis, gastrointestinal haemorrhage, mucosal ulceration, abdominal pain and saliva hypersecretion have been seen.

Hepatobiliary disorders:

Liver function disturbances accompanied by increases in liver enzymes such as AST, ALT, gamma-GT, ALP and/or bilirubin may occur.

Hepatic failure*, hepatitis fulminant*, veno-occlusive liver disease, portal vein thrombosis, cytolytic hepatitis and cholestasis.

* Including fatal outcomes.

Skin and subcutaneous tissue disorders:

Alopecia, toxic epidermal necrolysis, Stevens-Johnson syndrome, palmar-plantar erythrodysesthesia syndrome, radiation recall syndrome, skin necrosis, facial swelling, petechiae, macular rash, rash, pruritus, erythema, skin hyperpigmentation, hyperhidrosis and nail disorder.

Musculoskeletal and connective tissue disorders:

Rhabdomyolysis, osteomalacia, rickets, growth retardation, myalgia, arthralgia, pain in extremity and muscle twitching.

Renal and urinary disorders:

Haematuria, Fanconi syndrome, tubulointerstitial nephritis, nephrogenic diabetes insipidus, phosphaturia, aminoaciduria, polyuria, enuresis and 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, amenorrhoea, ovarian disorder, ovulation disorder, blood oestrogen decreased and blood gonadotrophin increased.

Congenital, familial and genetic disorders:

Foetal growth retardation.

General disorders and administration site conditions:

Multiorgan failure*, general physical deterioration, injection/infusion site reactions including swelling, inflammation, pain, erythema, tenderness, pruritus, chest pain, oedema, mucosal inflammation, pain, pyrexia and chills.

* Including fatal outcomes.

Class Side effects

The following side effects have been reported with cyclophosphamide, another oxazaphosphorine cytotoxic agent:

Renal pelvis cancer, ureteric cancer, bladder cancer, bladder necrosis, bladder fibrosis, bladder contracture, haemorrhagic pyelitis, haemorrhagic urethritis, ulcerative cystitis, intrauterine death, foetal malformation, foetal toxicity (including myelosuppression, gastroenteritis), premature labour, testicular atrophy and oligomenorrhea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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.

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

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 dialysable. Therefore, rapid haemodialysis is indicated when treating any suicidal or accidental overdose or intoxication. In the case of overdose, myelosuppression, mostly leucocytopenia, is to be expected, among other reactions. The severity and duration of the myelosuppression depends on the extent of the overdose. Frequent checks of the blood count and monitoring of the patient are necessary. If neutropenia develops, infection prophylaxis must be given and infections must be treated adequately with antibiotics. If thrombocytopenia develops, thrombocyte replacement should

be ensured according to need.

Cystitis prophylaxis (uroprotector such as Mesna) is absolutely necessary in order to avoid severe haemorrhagic cystitis. Haemorrhagic cystitis may be treated by the instillation of substances containing the SH-group. The incidence of haemorrhagic cystitis has been reduced by bladder irrigation with acetyl cysteine. In uncontrollable haemorrhagic cystitis, it is recommended to instill 200 to 300 ml of a 5 % formalin solution into the bladder. The solution should be washed out after 15 minutes with 1 litre of distilled water.

5 PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 26 Cytostatic agents.

5.1 Pharmacodynamic properties

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

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

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

In the cell cycle the passage through the G2 phase is slowed down. The cytotoxic effect is

not specific to the phase of the cell cycle; however it is specific to the cell cycle.

Cross-resistance, mainly with structurally related cytostatic agents such as cyclophosphamide, but also with other alkylating agents, cannot be ruled out.

Paediatric population

Ewing's sarcoma

In a randomised 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 randomised 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 randomised 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-Hodgkin's lymphoma, Hodgkin's Disease, acute lymphoblastic leukaemia, neuroblastoma, Wilms tumour, and malignant CNS tumours. Favourable partial responses, complete responses and survival rates have been documented.

5.2 Pharmacokinetic properties

Absorption:

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

Distribution:

Ifosfamide and its metabolites distribute in the body among tissues and the organs, including the brain. The distribution volume comes to 0,5 - 0,8 l/kg. The plasma half-life of ifosfamide is between 4 and 7 hours. Unchanged ifosfamide may cross the blood-brain barrier. Ifosfamide is bound to about 20 % to plasma protein**.**

Metabolism:

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

Elimination:

Ifosfamide and its metabolites are mainly eliminated via the kidneys. Renal clearance is 6 - 22 ml/min.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

HOLOXAN contains the active ingredient ifosfamide only and no inactive ingredients.

6.2 Incompatibilities

Benzyl alcohol-containing solutions can reduce the stability of HOLOXAN.

6.3 Shelf life

48 months.

After dilution

The solution of HOLOXAN injection can be kept for up to 24 hours in the refrigerator at 5 °C.

6.4 Special precautions for storage

Injection vials must be stored at or below 25 °C.

Keep container in outer carton.

6.5 Nature and contents of container

Injection vials of 500 mg: Packs of 1 and 10.

Injection vials of 1 g: Packs of 1 and 10.

Injection vials of 2 g: Packs of 1 and 10.

6.6 Special precautions for disposal and other handling

The handling and preparation of HOLOXAN should always be in accordance with current guidelines on safe handling of cytotoxic agents.

Skin reactions associated with accidental exposure to HOLOXAN may occur. In view of the possible absorption of ifosfamide through the skin and by inhalation, it is recommended to wear face masks and impervious gloves for protection when handling the HOLOXAN injection.

Avoid skin and mucosal contact. If HOLOXAN solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Baxter Healthcare South Africa (Pty) Ltd

The Campus – Eden Gardens

57 Sloane & Cnr Main Rd

Bryanston

2021

8. REGISTRATION NUMBERS

HOLOXAN 500 mg Injection: K/26/32

HOLOXAN 1 g Injection: K/26/33

HOLOXAN 2 g Injection: K/26/34

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

HOLOXAN 500 mg Injection: 23 May 1978

HOLOXAN 1 g Injection: 30 May 1979

HOLOXAN 2 g Injection: 30 May 1979

10. DATE OF REVISION OF THE TEXT

24 November 2022

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