1 PRODUCT NAME

Holoxan 500mg powder for injection.

Holoxan 1000mg (1g) powder for injection.

Holoxan 2000mg (2g) powder for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ifosfamide 500mg, 1000mg or 2000mg.

3 PHARMACEUTICAL FORM

Powder for injection.

Holoxan (sterile ifosfamide) is supplied as single-dose vials of 500mg, 1000mg, or 2000mg for reconstitution and administration by intravenous injection/infusion.

Ifosfamide is a white crystalline powder that is soluble in water.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Holoxan is indicated in:

Bronchogenic carcinoma (including SCLC and NSCLC)

Testicular tumours of all histological variants

Soft tissue sarcomas (especially leiomyo-, rhabdomyo- and chondrosarcomas)

Osteosarcoma

Mammary carcinoma

Ovarian carcinoma

Endometrial carcinoma

Carcinoma of the uterine cervix

Hypernephroma

Pancreatic carcinoma

Malignant lymphomas.

4.2 Dose and method of administration

FOR INTRAVENOUS USE ONLY.

Ifosfamide should be administered only by physicians experienced with this medicine. Dosage must be individualized. Doses and duration of treatment and/or treatment intervals depend on the therapeutic indication, the scheme of a combination therapy, the patient's general state of health and organ function, and the results of laboratory monitoring. In combination with other agents of similar toxicity, a dose reduction or extension of the therapy-free intervals may be necessary.

Where indicated, use of haematopoiesis-stimulating agents (colony-stimulating factors and erythropoiesis-stimulating agents) may be considered to reduce the risk of myelosuppressive complications and/or help facilitate the delivery of the intended dosing.

A total dosage course of 10 - 12g/m^2 (250 - 300mg/kg) should be aimed at. As a rule 2000 - 2400mg/m^2 (50 - 60mg/kg) is given IV daily on 5 successive days. It is recommended that **Holoxan** should be given in the mornings.

If a lower daily dose or a distribution of the total dose over a longer period is indicated, **Holoxan** is given IV every 2nd day (days 1, 3, 5, 7 and 9) or on 10 successive days in a lower dose (800 – 1200mg/m^2, corresponding to 20 - 30mg/kg).

In cases which are refractory to treatment the administration of 3200mg/m^2 (corresponding to 80mg/kg) daily on 2 - 3 successive days may be considered.

The white cell count should not be less than 4 x 10^9/L or the platelet count less than 100 x 10^9/L before the start of each course.

A course should be repeated at the earliest after 3 - 4 weeks. Based on standard chemotherapy regimens, up to six cycles of **Holoxan** are administered depending on patient tolerability. The intervals depend on, among other things, the blood count and recovery from any adverse effects or reactions.

Holoxan may be administered by short IV. infusion. Care must be taken to ensure that the **Holoxan** solution does not exceed a 4% concentration.

However, a continuous 24-hour infusion with high-dose **Holoxan** (5g/m^2 in 3 litres of 5% dextrose-saline solution with mesna given simultaneously preceded by a preliminary mesna bolus injection and followed by a mesna infusion for further 8 - 12 hours) has been successfully used in sarcomas.

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.

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration. Before parenteral administration, the substance must be completely dissolved.

In order to prevent bladder toxicity, and for prophylaxis of haemorrhagic cystitis, **Holoxan** should always be given concurrently with the uroprotector **Uromitexan** (mesna). Although **Holoxan** has been administered to a small number of patients with compromised hepatic and/or renal function, studies to establish optimal dose schedules of **Holoxan** in such patients have not been conducted.

4.3 Contraindications

Holoxan is contraindicated in patients with:

- known hypersensitivity to ifosfamide
- severely impaired bone marrow function (especially in patients previously treated with cytotoxic agents or radiotherapy)
- inflammation of the urinary bladder (cystitis)
- impaired renal function and/or obstructions of the urine flow
- severe hepatic impairment
- acute infection
- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

In individual patients, risk factors for ifosfamide toxicities and their sequelae described here and in other sections may constitute contraindications. In such situations, individual assessment of risk and expected benefits is necessary. Adverse reactions, depending on their severity, may require dosage modification or discontinuation of treatment.

Holoxan should always be given concurrently with the uroprotector **Uromitexan** (mesna).

Holoxan is a potent cytotoxic medicine and should be used only by physicians experienced with cancer chemotherapeutic medicines.

Holoxan should be given cautiously to patients with impaired renal function and impaired hepatic function, as well to those with compromised bone marrow reserve, as indicated by leucopenia, granulocytopenia, extensive bone marrow metastases, prior radiation therapy or prior therapy with other cytotoxic agents. Moderate to severe myelosuppression can be expected in such patients.

As ifosfamide exerts an immunosuppressive action interruption or modification of dosage should be considered in those patients who develop bacterial, fungal or viral infections. Blood counts should be taken at regular intervals.

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

Urotoxic side effects, especially haemorrhagic cystitis, have been frequently associated with the use of **Holoxan**. Outflow disturbances in the efferent urinary tract, cystitis, infections and electrolyte imbalances must be excluded or rectified before start of therapy. During treatment, renal function, urinary status and urinary sediment must be checked regularly. It is recommended that a urinalysis should be performed prior to each dose of **Holoxan**. If haematuria (greater than 10 RBCs per high power field) is present, then subsequent administration should be withheld until complete resolution.

Administration of **Holoxan** should be given with vigorous oral or parenteral hydration, and with the uroprotective agent mesna (**Uromitexan**). The use of mesna has been demonstrated to reduce the incidence of urinary tract complications from 40% - 3.5%.

Extra care is required in unilaterally nephrectomised patients, who do not tolerate high doses of the medicine very well. **Holoxan** should not be given until three months after the nephrectomy.

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

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

Since use of ifosfamide is associated with myelosuppression, leucocyte, erythrocyte and platelet counts should be carried out prior to each administration and at appropriate intervals, if necessary daily. There is normally a reduction in the leucocyte count beginning on approximately day 5. The nadir, depending on dosage and baseline count, tends to be reached after 8 to 10 days. Recovery occurs after 10 to 14 days and is usually complete after 2 to 3 weeks. Unless essential, ifosfamide

should not be given to patients with a WBC count below $2.5x10^9$/L. In case of fever and/or leucopenia, the prophylactic use of antibiotics and/or antimycotics should be considered.

Neurologic manifestations consisting of somnolence, confusion, hallucinations and in some instances, coma, have been reported following **Holoxan** therapy. The risk of these toxic effects on the CNS necessitates careful monitoring of the patient. The occurrence of these symptoms requires discontinuation of **Holoxan** therapy. The symptoms have usually been reversible and supportive therapy should be maintained until their complete resolution. Recommencement of **Holoxan** should only be undertaken with caution and taking into consideration the clinical situation of the patient and the risk-benefit analysis.

Administration of ifosfamide can cause CNS toxicity including encephalopathy and other neurotoxic effects. There are some data to suggest that CNS toxicity is related to impaired renal function (creatinine > 1.5mg/dL), pre-treatment with nephrotoxic medicines (e.g. cisplatin), post-renal obstructions (e.g. pelvic tumours) and prior nephrectomy. Further risk factors for encephalopathy include a poor general state of health, old age, young age, obesity, female gender, individual predisposition, a history of alcohol abuse, decreased levels of serum albumin or serum bicarbonate, low bilirubin, low haemoglobin levels, decreased white blood cell count, acidosis, electrolyte imbalances, hyponatraemia 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 and hepatic dysfunction. 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. Patients with brain metastases and/or cerebral symptoms must be monitored on a regular basis.

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

Patients treated with ifosfamide should be closely monitored for symptoms of encephalopathies in particular if patients are at increased risk for encephalopathies.

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

To reduce stomatitis attention should be paid to thorough oral hygiene. Antiemetics must be administered prophylactically.

Close monitoring of patients with pre-existing hepatic impairment is recommended. Alcohol abuse may increase the risk of developing hepatic dysfunction.

The blood sugar level should be checked regularly in diabetic patients in order to adjust antidiabetic therapy on time (see also section 4.5).

Since ifosfamide may interfere with normal wound healing, therapy should not be initiated for at least 10 to 14 days after surgery.

Although ifosfamide is not a vesicant, in the case of extravasation, it is recommended to stop the infusion immediately, to aspirate the extravasate with the needle in place, and to irrigate with saline solution and to immobilize the extremity.

Use in Patients with Renal Impairment

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

Use in Elderly

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.

Paediatric Use

No data available.

Effects on Laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

The physician should be alert for possible combined medicines actions, desirable or undesirable, involving ifosfamide even though ifosfamide has been used successfully concurrently with other medicines, including other cytotoxic medicines.

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.

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

The nephrotoxic, haematotoxic and neurotoxic (CNS) effects associated with ifosfamide may be enhanced by prior or concomitant administration of nephrotoxic medicines, such as cisplatin, aminoglycosides, acyclovir or amphotericin B.

Holoxan therapy may exacerbate radiodermatitis.

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

Concurrent administration of anticoagulants such as warfarin, can result in a further decrease in clotting and an increased risk of bleeding.

Concurrent administration with antidiabetic agents such as sulfonylureas may enhance the hypoglycaemic effect.

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

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

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

The following interactions are theoretically possible: The therapeutic effect and the toxicity of ifosfamide may be enhanced by the concurrent administration of chlorpromazine, triiodothyreonine or aldehyde dehydrogenase inhibitors such as disulfiram. Potentiation of the muscle-relaxant effect of suxamethonium could occur.

4.6 Fertility, pregnancy and lactation

Fertility

Ifosfamide interferes with oogenesis and spermatogenesis. Amenorrhea, azoospermia, and sterility in both sexes have been reported. Patients, male or female, during the reproductive period of life should be advised of the mutagenic potential of ifosfamide. A reliable contraceptive method must be used by both male and female patients during therapy as well as for up to six months after the end of treatment for sexually active men and for 12 months after the end of treatment for sexually active women. Men to be treated with ifosfamide should be informed about sperm preservation before treatment starts.

Pregnancy (Category D)

Animal studies indicate that the medicine is capable of causing gene mutations and chromosomal damage *in vivo*. Embryotoxic and teratogenic effects have been observed in mice and rats at a dose of 5mg/kg injected IP on day 11 of pregnancy. It should not be used in pregnancy, particularly in early pregnancy, unless in the judgment of the physician the potential benefits outweigh the possible risks. Ifosfamide can cause foetal damage when administered to a pregnant woman. If ifosfamide is used during pregnancy, or if the patient becomes pregnant while taking this medicine, the patient should be informed of the potential hazard to the foetus.

Lactation

Ifosfamide is excreted in breast milk. Because of the potential for serious adverse events and the tumorigenicity shown for ifosfamide in animal studies, the continuation of breast feeding in women who are receiving ifosfamide should be discouraged strongly.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In 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.

In patients receiving **Holoxan** as a single agent, the dose-limiting toxicities are myelosuppression and urotoxicity.

Urinary

Haemorrhagic cystitis, manifested by the occurrence of haematuria, dysuria, urinary frequency and occasionally urinary incontinence or retention, develops frequently in patients treated with ifosfamide. The incidence, severity and persistence of ifosfamide-induced haemorrhagic cystitis increase as the dose of the medicine increases. In most instances, the haematuria resolves spontaneously upon cessation of therapy.

Disorders of renal function (glomerular and tubular) following ifosfamide administration are very common. Nephrotoxic effects such as increases in serum urea and/or serum creatinine, reduced creatinine clearance, proteinuria, enzymuria, clindruria, glycosuria, acidosis, aminoaciduria, phosphaturia, and/or electrolyte imbalance have been noted. Delay in the diagnosis and treatment of these nephrotoxic effects may lead to the full picture of Fanconi's syndrome. This may be particular risk in children; it can result in rickets, and in osteomalacia in adults. Ifosfamide-induced acidosis is commonly reported as metabolic acidosis.

Distal tubular dysfunction impairs the ability of the kidney to concentrate urine. Development of a syndrome resembling SIADH (syndrome of inappropriate antidiuretic hormone secretion) has been reported with ifosfamide. Tubular damage may become apparent during therapy, months or even years after cessation of treatment.

Glomerular or tubular dysfunction may resolve with time, remain stable, or progress over a period of months or years, even after completion of ifosfamide treatment. Acute tubular necrosis, acute renal failure, and chronic renal failure secondary to ifosfamide therapy have been reported, and fatal outcome from nephrotoxicity has been documented.

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

Granular casts in the urinary sediment have occurred mainly after high doses of ifosfamide. The cylindruria generally resolves spontaneously a few days after the last injection.

Renal parenchymal and tubular necrosis, which could lead to death, have been reported in rare instances. Episodes of renal tubular acidosis which progressed into chronic renal failure have been documented.

Decrease in creatinine clearance is usually reversible.

The urothelial toxicity, but not the renal toxicity of ifosfamide can be minimised by vigorous hydration and administering a uroprotective agent such as mesna (**Uromitexan**).

Haemorrhagic cystitis requiring blood transfusion has been reported with ifosfamide. 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 ifosfamide has been reported. Past or concomitant radiation of the bladder or busulfan treatment may increase the risk for haemorrhagic cystitis.

In very rare cases hypokalaemia is reported.

The risk of developing clinical manifestations of nephrotoxicity is increased with, for example – large cumulative doses of ifosfamide, pre-existing renal impairment, prior or concurrent treatment with potentially nephrotoxic agents, younger age in children (particularly in 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 ifosfamide therapy should be carefully weighed when considering the use of ifosfamide in patients with pre-existing renal impairment or reduced nephron reserve.

Haematopoietic

Leucopenia is an expected effect and ordinarily is used as a guide to therapy. Thrombocytopenia and anaemia have also been observed with ifosfamide therapy. Episodes of petechial bleeding due to severe thrombocytopenia have been reported. Myelosuppression was dose related and dose-limiting, and is increased with administration of a single high dose compared to fractionated administration. It consists mainly of leucopenia and, to a lesser extent, thrombocytopenia. In general, anaemia is a rare complication and does not develop until several treatment cycles have been given. A WBC count 3 x 10^9/L is expected in 50% of the patients treated with **Holoxan** single agent at doses of 1.2g/m^2 per day for five consecutive days. At this dose level, thrombocytopenia (platelets 100 x 10^9/L) occurs in about 20% of the patients. At higher dosages, leucopenia was almost universal, and at total dosages of 10 - 12g/m^2/cycle, one half of the patients have platelet counts less than 50 x 10^9/L. Treatment can usually be repeated at 3 - 4 week intervals. When **Holoxan** is used in combination with other myelosuppressive agents, adjustments in dosing may be necessary. Fever can occur in the context of neutropenia and may be accompanied by infection. In case of neutropenic fever, antibiotics and/or antimycotics must be given. Patients who experience severe myelosuppression are potentially at increased risk for infection that may progress into a life-threatening sepsis. Ifosfamide-induced myelosuppression can cause leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding events), and anaemia.

Severe myelosuppression must be expected particularly in patients pre-treated with and/or receiving concomitant chemotherapy/haemotoxic agents and/or radiation therapy. Concomitant use of other immunosuppressants may increase immunosuppression induced by ifosfamide.

Severe immunosuppression has led to serious, sometimes fatal, infections. Sepsis and septic shock also have been reported. Infections reported with ifosfamide include pneumonias, as well as other bacterial, fungal, viral, and parasitic infections. Latent infections can be reactivated. In patients treated with ifosfamide, reactivation has been reported for various viral infections. Infections must be treated appropriately.

There are certain complications, such as thromboembolism, DIC (disseminated intravascular coagulation), or haemolytic uraemic syndrome (HUS), that may be induced by the underlying

disease, but that might occur with an increased frequency under chemotherapy that includes ifosfamide.

Gastrointestinal

Nausea and vomiting occur in a large number of the patients who receive **Holoxan**. Moderate to severe forms occur in about 50% of patients and may lead to dehydration. They are usually controlled by standard antiemetic therapy. Alcohol consumption may increase chemotherapy-induced nausea and vomiting. Other gastrointestinal side effects include anorexia, diarrhoea, and in some cases, constipation; and rarely, mucositis/stomatitis have been seen. Current guidelines on measures for prevention and amelioration of stomatitis should be considered. In very rare cases acute pancreatitis may develop.

Hepatobiliary

Uncommonly, liver function disturbances accompanied by increases in liver enzymes such as SGOT, SGPT, gamma-GT, ALP and/or bilirubin may occur. Veno-occlusive liver disease has been reported with chemotherapy that included ifosfamide.

Integumentary

It is ordinarily advisable to inform patients in advance of possible alopecia, a frequent complication of ifosfamide therapy. Alopecia is a very common, dose-dependent effect of ifosfamide administration. Chemotherapy-induced alopecia may progress to baldness. Regrowth of hair can be expected although the new hair may be of different colour or texture. Non-specific dermatitis has been reported to occur with ifosfamide. Very rare cases of toxic skin reactions may develop.

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

CNS

Very commonly, encephalopathy may occur. It may develop within a few hours up to a few days after the treatment with ifosfamide was initiated. The encephalopathy and associated symptoms are usually reversible and disappear spontaneously within a few days after the last administration of ifosfamide. The most reported symptom of encephalopathy is drowsiness that can rarely progress from somnolence in very rare cases to coma. Other symptoms occurring uncommonly are forgetfulness, depressive psychoses, disorientation, blurred vision, restlessness, dizziness, confusion, hallucinations and rarely cerebellar syndrome and incontinence (faecal and urinary). Seizures of the tonic-clonic type have been reported occasionally. Isolated cases of generalised seizure and seizures resulting in coma have also been observed and in rare cases have proved fatal.

The incidence and extent of cerebral effects due to ifosfamide may be associated with the presence of pelvic tumour, a low serum albumin or impaired renal clearance.

Rarely, polyneuropathy may occur. There also have been reports of peripheral neuropathy associated with ifosfamide use.

An ifosfamide-induced CNS toxicity may become manifest within a few hours to a few days after first administration and in most cases, resolves within 48 to 72 hours of ifosfamide discontinuation. Symptoms may persist for longer periods of time. Occasionally, recovery has been incomplete. Fatal outcome of CNS toxicity has been reported. If CNS toxicity develops, administration of ifosfamide should be discontinued. The symptoms may include the following: confusion, somnolence, coma, hallucination, blurred vision, psychotic behavior, extrapyramidal symptoms, urinary incontinence, and seizures. Recurrence of CNS toxicity after several uneventful treatment courses has been reported. CNS toxicity seems to be dose-dependent. Risk factors for the development of ifosfamide

associated encephalopathy include hypoalbuminaemia, impaired renal function, poor performance status, pelvic disease (e.g. presence of tumour in lower abdomen, bulky abdominal disease), and previous or concomitant nephrotoxic treatments including cisplatin.

Cardiotoxicity

Uncommonly, arrhythmias such as ventricular and supraventricular arrhythmia, decreased QRS voltage, elevations of the ST segment or T-wave changes, atrial fibrillation, pulseless ventricular tachycardia and cardiac failure have been reported, especially following administration of extremely high doses of ifosfamide. In very rare cases arrhythmia may progress to fatal cardiac arrest. Toxic cardiomyopathy leading to heart failure with congestion and hypotension, pericardial effusion, fibrinous pericarditis and epicardial fibrosis have all been reported. In very rare cases myocardial infarction has been reported, which however cannot be clearly attributed to ifosfamide treatment.

The risk of developing cardiotoxic effects is dose-dependent. It is increased in patients with prior or concomitant treatment with other cardiotoxic agents or radiation of the cardiac region and, possibly, renal impairment. Particular caution should be exercised when ifosfamide is used in patients with risk factors for cardiotoxicity and in patients with pre-existing cardiac disease.

Respiratory

Uncommonly, pneumonia has been reported.

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

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

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

Immune system

In rare cases, hypersensitivity reactions have been reported. Common clinical signs are rash, fever, hypotension, etc. Very rarely allergic reactions may progress to anaphylactic shock. Cross-sensitivity between oxazaphosphorine cytotoxic agents has been reported.

Endocrine system

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

Musculoskeletal system

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

Reproductive system

Due to its mechanism of action, ifosfamide, as an alkylating agent, commonly causes impairment of spermatogenesis - rarely irreversible - resulting in azoospermia and/or persistent oligospermia. Uncommonly, reversible ovulation disturbances resulting in amenorrhoea and reduced levels of female sex hormones have been reported. The risk of permanent chemotherapy-induced amenorrhoea is increased in older women.

Ifosfamide interferes with oogenesis and spermatogenesis. Amenorrhoea, 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.

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

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.

Neoplasms

As generally with alkylating agents, therapy with ifosfamide also uncommonly involves a risk of development of secondary tumours or their precursors as late sequelae. Urinary tract carcinomas and myelodysplastic syndrome culminating in acute leukaemia have been reported amongst others. Other malignancies reported after use of ifosfamide or regimens with ifosfamide include lymphoma, thyroid cancer, and sarcomas. The secondary malignancy may develop several years after chemotherapy has been discontinued. Malignancy has also been reported after *in utero* exposure with cyclophosphamide, another oxazaphosphorine cytotoxic agent.

Ocular

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

Other

Adverse reactions in addition to those mentioned above have been noted with ifosfamide. They include infection with or without fever, diarrhoea, anorexia, haematemesis, and thrombophlebitis. Fever occurs very commonly under ifosfamide treatment in the context of neutropenia and associated with infections or in the context of hypersensitivity reactions sometimes with an unknown origin.

Asthenic conditions such as fatigue, weakness, malaise etc. are common complications in cancer patients. However, ifosfamide, like other cytostatic agents, may intensify such symptoms. Rarely, injection site reactions may occur.

Adverse effects: Incidence

Primary System Organ Class (SOC)	Very Common > 1/10	Common > 1/100 - < 1/10	Uncommon > 1/1000 - < 1/100	Rare > 1/10,000 - < 1/1000	Very Rare < 1/10,000 incl. isolated reports
Infections and infestations		Infections	Pneumonia Sepsis		
Neoplasm benign and malignant (including cysts and polyps)			Secondary tumours Urinary tract carcinoma Myelodysplastic syndrome Acute leukaemia		

Blood and lymphatic system disorders	Myelo-suppression Leukopenia Neutropenia	Thrombo-cytopenia		Anaemia	Haemolytic uremic syndrome Disseminated intravascular coagulation
Immune system disorders				Hypersensitivity reactions	Anaphylactic shock
Endocrine disorders			Irreversible ovulation disturbances	SIADH (Syndrome of inappropriate 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	Encephalopathy Drowsiness		Somnolence Forgetfulness Dizziness	Cerebellar syndrome	Coma Seizures Polyneuropathy
Eye Disorders				Blurred vision	Visual impairment
Cardiac disorder			Arrhythmia Ventricular arrhythmia Supraventricular arrhythmia Cardiac failure		Cardiac arrest Myocardial infarction
Vascular disorders			Bleeding	Hypotension	Thrombo-embolism
Respiratory disorders				Pulmonary disorder Cough Dyspnoea	Interstitial pneumonitis Interstitial pulmonary fibrosis Respiratory failure Toxic allergic pulmonary oedema
Gastrointestinal disorders	Nausea Vomiting		Diarrhoea Constipation	Stomatitis Faecal incontinence	Acute pancreatitis
Hepatobiliary disorders			Liver function disturbances		
Skin and subcutaneous tissue disorder	Alopecia			Rash Dermatitis	Toxic skin reactions

Musculoskeletal and connective tissue disorders				Cramps	Rickets Osteomalacia Rhabdomyo-lysis
Renal and urinary disorders	Haematuria Micro-haematuria	Haemorrhagic cystitis Nephropathies Tubular dysfunction Macro-haematuria	Incontinence Dysuria Disturbed urinary frequency Bladder irritation	Glomerular dysfunctions Tubular acidosis Proteinuria Acute renal failure Chronic renal failure Urinary incontinence	Fanconi syndrome
Reproductive system and breast disorders		Impairment of spermatogenesis	Amenorrhoea Reduced levels of female sex hormones	Azoospermia Persistent oligospermia	
General disorders and administration site conditions	Fever	Asthenic conditions Fatigue Weakness Malaise		Mucositis Injection site reactions	Death
Investigations			Elevation of the ST segment Increase in liver enzymes Increase in SGOT Increase in SGPT Increase in gamma-GT Increase in ALP Increase in bilirubin	Phosphaturia	
Injury poisoning and procedural complications					Intensified reaction on radiotherapy
Congenital familial and genetic disorders				Aminoaciduria	

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 (Including CYSTS AND POLYPS)

As treatment-related secondary malignancy*, Acute leukaemia* (Acute myeloid leukaemia*, Acute promyelocytic leukaemia*), Acute lymphocytic leukaemia*, 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

Haematotoxicity*, Myelosuppression manifested as Bone marrow failure, Agranulocytosis; Febrile bone marrow aplasia; Disseminated intravascular coagulation, Haemolytic uremic syndrome, Haemolytic anaemia, Neonatal anaemia, Methaemoglobinaemia.
*Including fatal outcomes.

IMMUNE SYSTEM DISORDERS

Angio-oedema*, Anaphylactic reaction, Immunosuppression, Urticaria, Hypersensitivity reaction.
*Including fatal outcomes.

ENDOCRINE DISORDERS

Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

METABOLISM AND NUTRITION DISORDERS

Tumour lysis syndrome, Metabolic acidosis, Hypokalaemia, Hypocalcaemia, Hypophosphatemia, Hyperglycaemia, Polydipsia.

PSYCHIATRIC DISORDERS

Panic attack, Catatonia, Mania, Paranoia, Delusion, Delirium, Bradyphrenia, Mutism, Mental status change, Echolalia, Logorrhoea, 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, Faecal 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 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, 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 oedema*, Pleural effusion, Bronchospasm, Dyspnoea, Hypoxia, Cough.
*Including fatal outcomes.

GASTROINTESTINAL DISORDERS

Cecitis, Colitis, Enterocolitis, Pancreatitis, Ileus, Gastrointestinal haemorrhage, 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, Amenorrhoea, Ovarian disorder, Ovulation disorder, Azoospermia, Oligospermia, Impairment of spermatogenesis, Blood oestrogen decreased, Blood gonadotrophin increased.

CONGENITAL, FAMILIAL AND GENETIC DISORDERS

Foetal growth retardation.

GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS

Multi-organ failure*, General physical deterioration, Injection/Infusion site reactions including swelling, inflammation, pain, erythema, tenderness, pruritus; Chest pain, Oedema, Mucosal inflammation, Pain, Pyrexia, Chills.
*Including fatal outcomes.

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 professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

No specific antidote for **Holoxan** is known. Management of overdose would include general supportive measures to sustain the patient through any period of toxicity that might occur. 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.

Ifosfamide as well as ifosfamide metabolites are dialyzable.

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

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group	Antineoplastic and Immunomodulating agents, Antineoplastic agents, Alkylating agents, Nitrogen mustard analogues
ATC code	L01AA06.

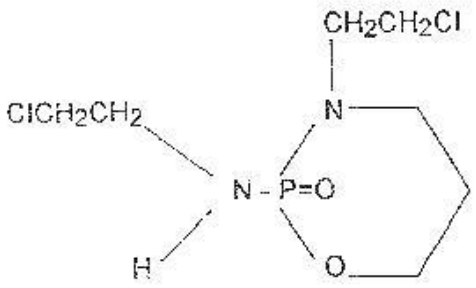
Ifosfamide is a chemotherapeutic agent related chemically to the nitrogen mustards and is a synthetic analogue of cyclophosphamide.

Pharmacology

Ifosfamide has been shown to require metabolic activation by microsomal liver enzymes to produce biologically active metabolites. Activation occurs by hydroxylation at the ring carbon atom 4 to form the unstable intermediate 4-hydroxyifosfamide. This metabolite rapidly degrades to the stable urinary metabolite 4-ketoifosfamide. Opening of the ring results in formation of the stable urinary metabolite, 4-carboxyifosfamide. These urinary metabolites have not been found to be cytotoxic. N, N-bis (2-chloroethyl)-phosphoric acid diamide (ifosphoramide) and acrolein are also found. Enzymatic oxidation of the chloroethyl side chains and subsequent dealkylation produces the major urinary metabolites, dechloroethyl ifosfamide and dechloroethyl cyclophosphamide. The dealkylated metabolites of ifosfamide have been shown to interact with DNA.

In vitro incubation of DNA with activated ifosfamide has produced phosphotriesters. The exposure of intact cell nuclei may also result in the formation of DNA-DNA crosslinks. DNA repair most likely occurs in G-1 and G-2 stage cells.

Ifosfamide is 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide.

Molecular formula	$C_7H_{15}Cl_2N_2O_2P$
Molecular weight	261.1
CAS Number	3778-73-2
Structural formula	

5.2 Pharmacokinetic properties

Ifosfamide exhibits dose-dependent pharmacokinetics in humans. At single doses of 3.8 - 5.0g/m^2, the plasma concentrations decay biphasically and the mean terminal elimination half-life is about 15 hours. At doses of 1.6 - 2.4g/m^2/day, the plasma decay is monoexponential and the terminal elimination half-life is about seven hours.

Two different dechloroethylated derivatives of ifosfamide, 4-carboxyifosfamide, thiodiacetic acid and cysteine conjugates of chloroacetic acid have been identified as the major urinary metabolites of ifosfamide in humans and only small amounts of 4-hydroxyifosfamide and acrolein are present. Small quantities (nmol/mL) of ifosfamide mustard and 4-hydroxyifosfamide are detectable in human plasma.

5.3 Preclinical safety data

Genotoxicity

The mutagenic potential of ifosfamide has been documented in bacterial systems *in vitro* and mammalian cells *in vivo*. *In vivo* ifosfamide has induced mutagenic effects in *Drosophila melanogaster* germ cells, and has induced recessive sex-linked lethal mutations in Drosophila.

Carcinogenicity

Ifosfamide, like other alkylating agents, has been reported to have oncogenic activity in animals. Thus, the possibility that it may have oncogenic potential in humans should be considered.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Holoxan is incompatible with benzyl-alcohol-preserved bacteriostatic water for injection.

Ifosfamide solutions are not compatible with cisplatin solutions.

6.3 Shelf life

5 Years (60 months).

24 hours after reconstitution.

6.4 Special precautions for storage

Store at or below 25°C.

See section 6.6 for storage following reconstitution.

6.5 Nature and contents of container

Glass vial with bromobutyl rubber stopper.

Pack sizes

500mg dry vials, single.

1000mg dry vials, single.

2000mg dry vials, single.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 **Holoxan** may occur. To minimise the risk of dermal exposure, always wear impervious gloves when handling vials and solutions continuing ifosfamide. 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.

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

Preparation

Injections are prepared for parenteral use by adding sterile water for injection to the vial and shaking to dissolve. Use the quantity of diluent shown below to reconstitute the product.

Dosage Strength	Quantity of Diluent	Final Vial Concentration
500mg	13mL	40mg/mL
1000mg	25mL	40mg/mL
2000mg	50mL	40mg/mL

Solutions of ifosfamide should not be stored in the glass vial, rather they should be diluted further to achieve concentrations of 3 to 4mg/mL in the following sterile fluids:

- Glucose Injection 5%
- Sodium Chloride Injection 0.9%
- Sodium Chloride and Glucose Injections, with concentrations ranging from 0 - 5% Glucose and 0 - 0.9% Sodium Chloride
- Lactated Ringer's Injection
- Sterile Water for Injection.

Solutions of ifosfamide when reconstituted and further diluted in the solutions nominated above may be prepared and, if necessary, stored for short periods under refrigeration and protected from light. However, in order to reduce microbiological hazards, it is recommended that reconstitution and/or further dilution be effected immediately prior to use, and infusion commenced as soon as practicable after preparation of the admixture.

Infusion should be completed within 24 hours of preparation of the admixture and any residue discarded.

Reconstituted solutions and further diluted solutions should be inspected visually before use. Any solutions which are discoloured, hazy or contain visible particulate matter should not be used.

Ifosfamide (3mg/mL) may be admixed with diluted **Uromitexan** (mesna) solutions 1.5 to 3.0mg/mL (0.15 to 0.3%). Admixtures of **Holoxan** 3.0mg/mL and **Uromitexan** 1.5 to 3.0mg/mL, when stored in PVC plastic bags and refrigerated have been shown to be chemically and physically stable for 24 hours when diluted in the following sterile solutions:

- Sodium Chloride Injection 0.9%
- Compound Sodium Lactate Injection
- Glucose Injection 5%
- Glucose 2.5% + Sodium Chloride 0.45% Injection

However, because of the risk of microbial contamination, it is recommended that admixtures be administered within 6 to 8 hours of preparation.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Holoxan *is distributed in New Zealand by:*

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

Holoxan *is distributed in Australia by:*

Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 9 March 1989.

10 DATE OF REVISION OF THE TEXT

30 January 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
1	Heading corrected.
4.4	Included information on use in patients with Renal Impairment, Hepatic Impairment, Elderly.
4.6	Information on contraceptive use included.
4.8	Added information on CNS toxicity. Adverse events table formatting changed (no change to text). url for adverse reaction reporting updated.

Based on Australian PI approved 13 September 2024; and CCSI 2023-0000493-O 14022024.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.