Baxter

Patient Information Leaflet
Please read carefully!

Baxter Oncology GmbH
Frankfurt am Main
Germany Allemagne Alemania

Holoxan®

Active substance: Ifosfamide

Composition:

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

as dry substance for preparing an injectable solution.

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

Special remark:

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

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

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

Use during pregnancy and lactation

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

Contraceptive measures

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

Side-effects:
Patients on Holoxan therapy may experience the following side-effects:

Myelosuppression:

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

Remark: Guidelines for dose reduction in myelosuppression

Leucocyte Count	Thrombocyte Count	
> 4000	> 100 000	100% of planned dose
4000 – 2500	100 000 – 50 000	50% of planned dose
< 2500	< 50 000	postponement until normalisation or individual decision

Urotoxicity and nephrotoxicity:

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

Remark:

Fractionated dosing, adequate hydration, maintenance of fluid balance and particularly concomitant treatment with mesna (Uromitexan®) can markedly reduce the frequency and severity of haemorraghic cystitis.
Disorders of glomerular renal function with an increase in serum creatinine, a decrease in creatinine-clearance and proteinuria can occasionally occur, or more frequently disorders of tubular renal function with hyperaminoaciduria, phosphaturia, acidosis or proteinuria. Severe nephropathies are rare. Possible risk factors for disorders of glomerular renal function are high doses of the drug and additional treatment with platinum containing drugs. Risk factors for disorders of tubular renal function are previous nephrectomy, additional treatment with platinum containing drugs or concomitant irradiation of the

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

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

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

Central nervous system:

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

Remarks:

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

Other adverse effects:

Nausea and vomiting are dose-dependent side-effects. Moderate to severe forms can be seen in about 50% of the cases. Another frequent side-effect is reversible alopecia which occurs in up to 100% of patients, depending on dosage and duration of treatment. Because of its alkylating mechanism of action, Holoxan can cause partly irreversible impairment of spermatogenesis with resulting azoospermia or persistent oligospermia, respectively less frequently irreversible ovulation disturbances with resulting amenorrhea and reduced levels of female sex hormones.

Additionally, there can occur:

- in isolated cases chronic interstitial pulmonary fibrosis. Toxic-allergic pulmonary oedema was reported in one single case.
- in isolated cases SIADH (syndrome of inadequate ADH-secretion, Schwartz-Bartter-syndrome) with hyponatremia and water retention. Hypokalemia was reported in one single case.
- in isolated cases acute pancreatitis

- in rare cases inflammation of the skin and mucous membrane
- in rare cases hypersensitivity reactions, in isolated cases with fever and progressing to shock
- in rare cases blurred vision and episodes of dizziness

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

Precautions:
The following measures and/or tests are indicated in order to limit or alleviate adverse reactions:
- Timely administration of antiemetics,
- Regular blood counts,
- Regular checks of renal function parameters,
- Regular check of urinalysis and urinary sediment.

In cases of hepatic or renal impairment before the start of therapy, the use of Holoxan has to be individually weighed for each patient. It is recommended that patients under Holoxan-therapy are monitored more frequently.
The blood sugar level should be checked regularly in diabetics in order to modify the antidiabetic therapy on time.
It is essential to ensure adequate diuresis.
Fever and/or severe leucopenia require prophylactic administration of antibiotics and/or antimycotics.
Attention should be paid to meticulous oral hygiene.
Effects on ability to drive and use machines:
Holoxan may affect a subject's ability to drive a motor vehicle or to operate machinery. This may occur either directly by induced encephalopathy or indirectly as a result of nausea and vomiting, especially when CNS-active drugs or alcohol are taken concomitantly.

Interactions with other drugs:
Myelotoxicity can be increased as a result of interaction with other cytostatics or radiation. Ifosfamide may intensify skin reactions due to irradiation.
The prior or concurrent administration of nephrotoxic agents like cisplatin, aminoglycosides, acyclovir or amphotericin B may enhance the nephrotoxic effect of ifosfamide and consequently haematotoxic and neurotoxic (CNS) effects as well.
Because of the immunosuppressive effect of ifosfamide, an impaired response to the respective vaccine may occur. Vaccination injury can be caused by live-virus vaccinations.
The concurrent use of ifosfamide may increase the anticoagulant effect of warfarin and thus raise the risk of haemorrhages.

In analogy with cyclophosphamide, the following interactions seem possible:
- The myelosuppressive action may be enhanced by the concurrent administration of allopurinol or hydrochlorothiazide.
- The effect and the toxicity may be enhanced by the concurrent administration of chlorpromazin, triiodothyronine or aldehyde dehydrogenase inhibitors such as disulfiram.
- The treatment may increase the hypoglycaemic actions of sulfonylureas.
- Prior or concurrent treatment with phenobarbital, phenytoin or chloral hydrate involves the possibility of microsomal liver enzyme induction and thus a faster metabolism of ifosfamide.
- The treatment may increase the muscle-relaxant effect of suxamethonium.

Dosage and administration:
The treatment should only be administered by an experienced oncologist. The dosage must be adapted to each patient individually. In single-drug therapy of adults, the most common treatment is based on fractionated doses. In the absence of individual prescriptions, the following recommendations may serve as a guideline.
In general, Holoxan is given intravenously in divided doses of 1.2–2.4 g/m^2 body surface (up to 60 mg/kg of body weight) daily for 5 consecutive days (the duration of these infusions is about 30–120 minutes, depending on the volume). Holoxan may also be given in a single high dose, usually as a 24-hours-prolonged infusion. The dosage is generally 5 g/m^2 body surface (125 mg/kg body weight) and should not exceed more than 8 g/m^2 body surface (200 mg/kg body weight) per cycle. A single high dose may cause higher haemato-, uro-, nephro- and CNS toxicity.
Care should be taken to ensure that the ifosfamide concentration of the solution does not exceed 4 percent.
In combination-therapy with other cytostatics, the dose should be adapted to the type of therapeutic scheme.
Remarks:
Because of its urotoxicity, ifosfamide should as a matter of principle be used in combination with mesna. Other toxicities and the therapeutic effects of ifosfamide will not be influenced by mesna. Should cystitis with micro- and macrohaematuria develop during therapy, the treatment should be discontinued until the patient has recovered.
Because the cytostatic effect of ifosfamide occurs only after activation in the liver, there is no danger of injuring the tissue in the case of paravenous injections.
Administration and duration of treatment:
The therapy cycles may be repeated every 3–4 weeks. The intervals will depend on the blood count and on the recovery from any adverse reactions or side-effects.
The administration of uroprotection with mesna (Uroprotector®, Uromitexan®) as directed, should be maintained.
Regular blood counts, regular checks of renal function and regular urinalysis including urinary sediment are necessary.
Timely administration of antiemetics is indicated, and the additional influences on the CNS in combination with Holoxan should be taken into consideration.

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

Holoxan	200 mg	500 mg	1 g	2 g
Water for injection	5 ml	13 ml	25 ml	50 ml

The substance dissolves readily if the vials are vigorously shaken for 0.5 to 1 min after addition of the water for injection. If the substance fails to dissolve immediately and completely, it is advisable to allow the solution to stand for a few minutes. The prepared solution can be kept for up to approx.

as a 24 hours prolonged infusion. The dosage is generally 3 g/m² body surface (120 mg/kg body weight) and should not exceed more than 8 g/m² body surface (200 mg/kg body weight) per cycle. A single high dose may cause higher haemato-, uro-, nephro- and CNS toxicity.
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Special remark:
Because of its alkylating action, ifosfamide is a mutagenic and also a potential carcinogenic substance. Contact with the skin and mucous membranes should therefore be avoided.

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

Store drugs out of children´s reach !

Name and permanent address of the manufacturer and the holder of the marketing authorization
Baxter Oncology GmbH
Daimlerstraße 40
60314 Frankfurt, Germany
Phone: +49 69-9686 60 00

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January 2002

Presentation:

200 mg vials – Packs of 10 vials
500 mg vials – Packs of 1 and 10 vials
1g vials – Packs of 1 and 10 vials
2g vials – Packs of 1 and 10 vials

Holoxan® is available on prescription only