**Baxter Oncology GmbH**
60314 Frankfurt
Germany

# Endoxan®

**Composition**

Endoxan® 200 mg

1 injection vial of Endoxan 200 mg contains:
213.8 mg cyclophosphamide monohydrate (equivalent to 200 mg anhydrous cyclophosphamide) as the active ingredient

Endoxan® 500 mg

1 injection vial of Endoxan 500 mg contains:
534.5 mg cyclophosphamide monohydrate (equivalent to 500 mg anhydrous cyclophosphamide) as the active ingredient

Endoxan® 1 g

1 injection vial of Endoxan 1 g contains:
1.069 g cyclophosphamide monohydrate (equivalent to 1 g anhydrous cyclophosphamide) as the active ingredient

Endoxan®

1 Endoxan sugar-coated tablet contains:
53.5 mg cyclophosphamide monohydrate (equivalent to 50 mg anhydrous cyclophosphamide) as the active ingredient
*List of excipients*
Calcium carbonate, calcium monohydrogen phosphate, carmellose sodium, gelatine, glycerol, lactose, maize starch, magnesium stearate, macrogol, montan glycol wax, polysorbate, polyvidone, saccharose, silicone dioxide, talcum, titanium dioxide.

**Pharmaceutical form**

Endoxan® 200 mg/500 mg/1 g, injection vials:
Powder for solution for i.v. injection

Endoxan®:
Sugar-coated tablet for oral use

**Indications**

Endoxan is used within a combination chemotherapy regimen or as monotherapy in

Leukaemias:
acute or chronic lymphocytic and myelogenous leukaemias

Malignant lymphomas:
Hodgkin's disease, non-Hodgkin's lymphomas, plasmacytoma

Metastasizing and non-metastasizing malignant solid tumours:
ovarian cancer, testicular cancer, breast cancer, small cell lung cancer, neuroblastoma, Ewing's sarcoma

Progressive "autoimmune diseases":
e.g. rheumatoid arthritis, psoriatic arthropathy, systemic lupus erythematosus, scleroderma, systemic vasculitides (e.g. with nephrotic syndrome), certain types of glomerulonephritis (e.g. with nephrotic syndrome), myasthenia gravis, autoimmune haemolytic anaemia, cold agglutinin diseases.

Immunosuppressive treatment ir organ transplantations

**Contraindications**

Endoxan should not be used in patients with

- known hypersensitivity to cyclophosphamide
- severely impaired bone-marrow function (particular in patients who have been pre-treated with cytotoxic agents and/or radiotherapy)
- inflammation of the bladder (cystitis)
- urinary outflow obstructions
- active infections
- for use during pregnancy and lactation see separate note

***Pregnancy and lactation***

Treatment with cyclophosphamide can cause genotype anomalies in men and women.
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.
Woman should not become pregnant during treatment. Should they still conceive during treatment, they should seek genetic consultation.
As cyclophosphamide is passing into the breast milk, mothers must not breast feed during treatment.
Men to be treated with Endoxan should be informed about sperm preservation before treatment.
The duration of contraception in men and women after the end of chemotherapy depends on the prognosis of the primary disease and on the intensity of the parents' desire for a child.

**Special warnings and special precautions for use**

Before starting treatment, it is necessary to exclude or correct any obstructions of the efferent urinary tract, cystitis, infections and electrolyte imbalances.
In general, Endoxan like all 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 or renal impairments, also require close observation.
Should a cystitis in connection with micro- or macrohaematuria appear during treatment with Endoxan, Endoxan therapy has to be interrupted until normalization.
Leukocyte controls must be conducted regularly during treatment: at intervals of 5-7 days when starting treatment and every 2 days if the counts drop below 3000/mm$^3$. Daily controls may be necessary under certain circumstances. In patients receiving long-term treatment, controls every two weeks are usually sufficient. If signs of myelosuppression become evident, it is recommended to check the red blood count and the platelet count (see 4.2). Urinary sediment should also be checked regularly for the presence of erythrocytes.

**Effects on ability to drive and use machines**

Due to the possibility of side effects when cyclophosphamide is administered, e.g. nausea, vomiting which may result in circulatory insufficiencies, the physician should individually decide on the patient's ability to participate in traffic or to operate machinery.

**Interaction with other medicaments and other**

**Interaction with other medicaments and other forms of interaction**

The blood glucose-lowering effect of sulfonyl ureas may be intensified, as well as the myelosuppressive action when allopurinol or hydrochlorothiazide is administered concomitantly.

Prior or concurrent treatment with phenobarbital, phenytoin, benzodiazepines or chloral hydrate involves the possibility of microsomal liver enzyme induction.

Since cyclophosphamide shows immunosuppressive effects, the patient can be expected to exhibit a diminished response to any vaccination; injection with activated vaccines may be accompanied by vaccine-induced infection.

If depolarizing muscle relaxants (e.g. succinylcholine halogenide) are applied concurrently, a prolonged apnoea may result from a reduced pseudocholinesterase concentration.

Concomitant administration of chloramphenicol leads to a prolonged half-life of cyclophosphamide and to a delayed metabolization.

Anthracyclines and pentostatin treatment may intensify the potential cardiotoxicity of cyclophosphamide. An intensification of the cardiotoxic effect may also occur after previous radiotherapy of the cardiac region.

Concomitant administration of indomethacin should be performed very carefully, since an acute water intoxication has been reported in a single case.

In general, patients receiving treatment with cyclophosphamide should abstain from drinking alcoholic beverages.

Because grapefruit contains a compound that may impair the activation of cyclophosphamide and thereby its efficacy, the patient must not eat any grapefruit or drink grapefruit juice.

**Posology and method of administration**

Endoxan should only be administered by experienced oncologists.

The dosage must be adapted to each patient individually.

Unless otherwise prescribed the following dosages are recommended:

Endoxan® 200 mg/500 mg/1 g, injection vials:

- for continuous treatment in adults and children 3 to 6 mg/kg body weight daily (equivalent to 120 to 240 mg/m$^2$ body surface)
- for intermittent treatment 10 to 15 mg/kg body weight (equivalent to 400 to 600 mg/m$^2$ body surface) at intervals of 2 to 5 days
- for high-dose intermittent treatment, e.g. 20 to 40 mg/kg body weight (equivalent to 800 to 1600 mg/m$^2$ body surface) and higher doses (e.g. for conditioning prior to bone-marrow transplantation) at intervals of 21 to 28 days.

**Preparation of the solution**

To prepare a solution for injection, the respective amount of physiological saline is added to the dry substance:

| **Endoxan vial** | **200 mg** | **500 mg** | **1 g** |
|---|---|---|---|
| Dry substance equivalent to | 213.8 mg | 534.5 mg | 1069.0 mg |
| Cyclophosphamide, anhydrous | 200 mg | 500 mg | 1 g |
| Physiological saline | 10 ml | 25 ml | 50 ml |

The substance dissolves readily if the vials are vigorously shaken after addition of the solvent. If the substance fails to dissolve immediately and completely, it is advisable to allow the vial to stand for a few minutes.

The solution is suitable for intravenous administration which preferably should be conducted as an infusion. For short-term intravenous infusion, the prepared Endoxan solution is added to Ringer's solution, saline or dextrose solution for a total volume of e.g. 500 ml.

The duration of infusion may range from 30 minutes to 2 hours, depending on the volume.

Endoxan®, sugar-coated tablets:

For continuous therapy 1-4 tablets (50-200 mg) daily; if necessary, more tablets may be taken.

The dose recommendations given mainly apply to the treatment with cyclophosphamide as a monotherapy. In combination with other cytostatics of similar toxicity, a dose reduction or extension of the therapy-free intervals may be necessary.

*Recommendations for dose reduction in patients with myelosuppression*

| **Leukocyte count [µl]** | **Platelet count [µl]** | **Dosage** |
|---|---|---|
| >4000 | >100 000 | 100 % of the planned dose |
| 4000 - 2500 | 100 000 - 50 000 | 50 % of the planned dose |
| <2500 | <50 000 | Adjustment until values normalize or specific decision is made |

*Recommendations for dose adjustment in patients with hepatic and renal insufficiency*

Severe hepatic- or renal insufficiency requires a dose reduction. A dose reduction of 25% for serum bilirubin from 3.1 to 5 mg/100 ml and of 50% for a glomerular filtration rate below 10 ml/minute is recommended. Cyclophosphamide is dialysable.

Endoxan® 200 mg/500 mg/1 g, injection vials

Duration of therapy and intervals will depend on the indication, the applied combination chemotherapy schedule, the patient's general state of health, the laboratory parameters and the recovery of blood cell counts.
Attention should be paid to adequate hydration as well as to the administration of the Uroprotector® Uromitexan®.

Endoxan®, sugar-coated tablets

Endoxan sugar-coated tablets should be administered in the morning. During or immediately after the administration adequate amounts of fluid should be ingested. It is important to ensure that the patient empties his/her bladder at regular intervals.
Duration of therapy and intervals will depend on the indication, the applied combination chemotherapy schedule, the patient's general state of health, the laboratory parameters and the recovery of blood cell counts.

**Instructions for use and handling**

The handling and preparation of Endoxan should always be in accordance with the safety precautions used for handling of cytotoxic agents.

**Overdose**

Since no specific antidote for cyclophosphamide is known, great caution is advised each time it is used. Cyclophosphamide can be dialysed. Therefore, rapid haemodialysis is indicated when treating any suicidal or accidental overdose or intoxication. A dialysis clearance of 78 ml/min was calculated from the concentration of non-metabolised cyclophosphamide in the dialysate (normal renal clearance is around 5 - 11 ml/min). A second working group reported a value of 194 ml/min. After 6 hours of dialysis, 72 % of the dose of cyclophosphamide administered was found in the dialysate. In the case of overdose, myelosuppression, mostly leukocytopenia, 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. It is essential that cystitis prophylaxis with Uromitexan® (mesna) be undertaken to avoid any urotoxic effects.

*Remark*

If a cyclophosphamide solution is inadvertently administered by paravenous injection, there is usually no danger of cytostatic tissue damage since such damage is not expected before cyclophosphamide has been bioactivated in the liver. If paravasation should occur, nevertheless stop the infusion immediately and aspirate the paravasate with the cannula in place, irrigate the area with saline solution and immobilize the extremity.

**Undesirable effects**

Patients on Endoxan therapy may experience the following dose-dependent side-effects which are reversible in most cases:

Blood and bone marrow

Depending on the dose given, different degrees of myelosuppression may occur, involving leukocytopenia, thrombocytopenia and anaemia. It can commonly be expected that leukocytopenia with and without fever and the risk of secondary (sometimes life-threatening) infections will occur, and thrombocytopenia associated with the higher risk of a bleeding event. The leukocyte and platelet nadirs are usually reached in week 1 and 2 of treatment. They usually recover within 3 to 4 weeks after the initiation of treatment. Anaemia will usually not develop until after several treatment cycles. More severe myelosuppression is to be expected in patients who have been pre-treated with chemo- and/or radiotherapy and in patients with renal impairment.
A combination treatment with other myelosuppressive agents may require dose adjustments. Please refer to the relevant tables on dose adjustment of cytotoxic drugs to the blood counts at the beginning of the cycle and the nadir-adjusted dosage of cytostatic agents.

Gastrointestinal tract

Gastrointestinal side effects, such as nausea and vomiting, are dose-dependent adverse reactions. Moderate to severe forms occur in around 50% of patients. Anorexia, diarrhoea, constipation and inflammatory conditions of the mucosa (mucositis), ranging from stomatitis to ulcerations, occur with a rarer frequency. There have been isolated reports of haemorrhagic colitis.

Kidney and efferent urinary tract

After their excretion in the urine, metabolites of cyclophosphamide cause changes in the efferent urinary tract and especially in the bladder. Haemorrhagic cystitis, microhaematuria and macrohaematuria are the most common dose-dependent complications of a therapy with Endoxan® and mandate interruption of treatment. Cystitis is initially abacterial, secondary bacterial colonisation may follow. There have been isolated reports of haemorrhagic cystitis resulting in death. Oedema of the bladder wall, suburethral bleeding, interstitial inflammations with fibrosis and a potential for sclerosis of the bladder wall have also been observed.
Renal lesions (in particular with a history of impaired renal function) are a rare side-effect after high doses.
Remark:
Treatment with Uromitexan® or strong hydration can markedly reduce the frequency and severity of these urotoxic side-effects.

Genital tract

By virtue of its alkylating mode of action, cyclophosphamide can be assumed to cause partially irreversible disturbances of spermatogenesis and the resulting azoospermia or persistent oligospermia. Ovulation disorders, that sometimes take an irreversible course, with the resulting amenorrhoea and lower levels of female sex hormones occur with a rarer frequency.

Liver

Rare cases of disturbances of hepatic function have been reported that are reflected by an increase in the corresponding laboratory test values (SGOT, SGPT, gamma-GT, alkaline phosphatase and bilirubin).
Veno-occlusive disease (VOD) is observed in approx. 15-50 % of the patients receiving high-dose cyclophosphamide in combination with busulfan or whole-body irradiation during allogenic bone marrow transplantation. By contrast, VOD is only rarely observed in patients with aplastic anaemia who are receiving high dose cyclophosphamide alone. The syndrome typically develops 1-3 weeks after the transplantation and is characterized by sudden weight gain, hepatomegaly, ascites and hyperbilirubinaemia. Hepatic encephalopathy may also develop.
Known risk factors predisposing a patient to the development of VOD are pre-existing disturbances of hepatic function, hepatotoxic drug therapy concurrently with high-dose (chemo)therapy and especially when the alkylating agent busulfan is an element of the conditioning therapy.

Cardiovascular and pulmonary systems:

In isolated cases, pneumonitis, interstitial pneumonia extending to chronic interstitial pulmonary fibrosis may develop. The occurrence of a secondary cardiomyopathy induced by cytostatic agents and manifesting as arrhythmias, EKG changes and LVEF (e.g. myocardial infarction) has been reported, especially following the administration of high doses of cyclophosphamide (120-240 mg/kg of body weight). Furthermore, there is evidence that the cardiotoxic effect of cyclophosphamide may be enhanced in patients who have received previous radiation treatment of the heart region and adjuvant treatment with anthracyclines or pentostatin. In this context, bear in mind that regular electrolyte controls are necessary and that special caution is advised in patients with pre-existing heart disease.

Secondary tumours

As with cytotoxic therapy in general, treatment with cyclophosphamide involves the risk of secondary tumours and their precursors as late sequelae. The risk of developing urinary tract cancer as well as myelodysplastic alterations partly progressing to acute leukaemias is increased. Animal studies prove that the risk of bladder cancer can be markedly reduced by an adequate administration of Uromitexan®.

Other adverse effects

Alopecia, a fu...

Other adverse effects

Alopecia, a frequent side-effect, is reversible in general. Cases of pigment changes of the palms, finger nails and the soles have also been reported.

In addition, the following side-effects were observed:

- SIADH (syndrome of inappropriate secretion of antidiuretic hormone, Schwartz-Bartter syndrome) with hyponatraemia and water retention
- Inflammation of the skin and mucosa
- Hypersensitivity reactions accompanied by fever, extending to shock in isolated cases
- Transient blurred vision and attacks of dizziness
- Acute pancreatitis may occur in isolated cases
- In very rare cases (< 0.01%) severe reactions e.g. Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported

Note:

There are certain complications, such as thromboembolism, DIC (disseminated intravascular coagulation), or haemolytic uraemic syndrome (HUS), that may also be induced by the underlying disease, but that might occur with an increased frequency under chemotherapy that includes Endoxan.

Attention should be paid to timely administration of antiemetics and to meticulous oral hygiene.

Regular blood counts are indicated during treatment: Intervals of 5 - 7 days at initial therapy, intervals of 2 days in case the leucocyte counts decreases to <3000 per $mm^3$, possibly daily. Checks every 2 weeks are generally sufficient in case of long-term therapy. The urinary sediment should be checked regularly on erythrocytes.

**Incompatibilities**

Benzyl alcohol containing solutions can reduce the stability of cyclophosphamide.

**Pharmacological properties**

***Pharmacodynamic properties***

Cyclophosphamide is a cytostatic from the group of oxazaphosphorines and is chemically related to nitrogen mustard. Cyclophosphamide is inactive in vitro and is activated by microsomal enzymes in the liver to 4-hydroxycyclophosphamide, which is in equilibrium with its tautomere aldophosphamide. The cytotoxic action of cyclophosphamide is based on an interaction between its alkylating metabolites and DNA. This alkylation results in breaks and linking of the DNA strands and DNA-protein cross-links. In the cell cycle, passage through the G2 phase is retarded. The cytotoxic action is not specific to the cell cycle phase, but is specific to the cell cycle.

Cross-resistance, particularly with structurally related cytostatics like ifosfamide as well as other alkylating agents, cannot be ruled out.

***Pharmacokinetic properties***

Cyclophosphamide is almost completely absorbed from the gastro-intestinal tract. In man, single intravenous injections of labelled cyclophosphamide are followed within 24 hours by a profound fall in the plasma concentrations of cyclophosphamide and its metabolites, though detectable levels may persist in the plasma for up to 72 hours.

Cyclophosphamide is inactive in vitro and is activated in vivo.

The mean serum half-life of cyclophosphamide is 7 hours for adults and 4 hours for children.

Cyclophosphamide and its metabolites are mainly excreted by the kidneys.

The blood levels after i.v. and oral doses being bioequivalent.

**Storage and Stability note**

Endoxan must not be stored above +25 °C.

The reconstituted solution should be used within 24 hours after preparation (do not store above +8° C).

Do not use Endoxan after the expiry date given on the package.

During transport or storage of Endoxan injection vials, temperature influences can lead to melting of the active ingredient cyclophosphamide. Vials containing melted substance can easily be visually differentiated from those containing the intact active ingredient: melted cyclophosphamide is a clear or yellowish viscous liquid (usually found as connected phase or in droplets in the affected vials). Do not use injection vials with melted content.

**Keep drugs out of children's reach!**

**Pack sizes**

| | |
|---|---|
| Vials of 200 mg | 1 and 10 |
| Vial of 500 mg | 1 |
| Vial of 1 g | 1 |

Sugar-coated tablets 50, 200, 500, 1.000

Hospital packs

Not all pack sizes may be marketed.

**Name and permanent address of the manufacturer and the holder of the marketing authorization**

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**Endoxan Tablets manufactured by**

Allmirall Prodesfarma S.L.
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