u/pendaftar

Baxter

Patient Information Leaflet
Please read carefully!

ENDOXAN

Cyclophosphamide

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.~~ μ

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.

BALAI POM
ACC
Kategori : VaMa/~~VaMi-B~~
Perubahan/Penambahan:
- ~~Administratif;~~
- ~~Indikasi, posologi;~~
- Informasi produk; PP, IO
- ~~Penandaan;~~
- ~~Mutu~~

Paraf/Tgl: μ 29/10-18

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~~ μ

Indications

For carcinomas, sarcomas.
- Leukaemia, lymphogranulomatosis, lymphosarcomas, retothelial sarcoma, multiple myeloma.
- Mammary carcinoma, ovarian carcinoma.

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.

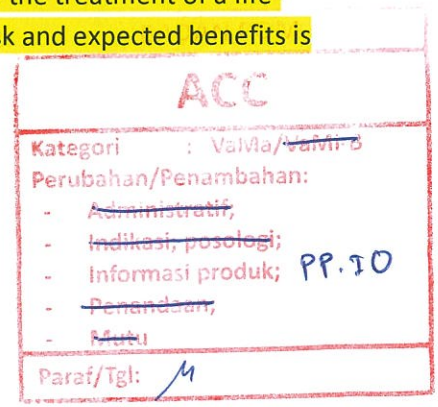
Pregnancy and lactation

Treatment with cyclophosphamide can cause genotype anomalies in men and woman.
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

The efferent urinary tract, cystitis, chronic hepatic or renal impairments, 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.

Risk factors for cyclophosphamide toxicities and their sequelae described here and in other sections may constitute contraindications if cyclophosphamide is not used for the treatment of a life-threatening condition. In such situations, individual assessment of risk and expected benefits is necessary.



WARNINGS

Myelosuppression, Immunosuppression, Infections

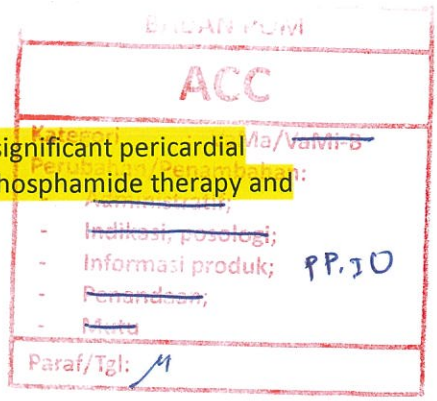
- Treatment with cyclophosphamide may cause myelosuppression and significant suppression of immune responses.
- Cyclophosphamide-induced myelosuppression can cause leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding events), and anemia.
- If signs of myelosuppression become evident, it is recommended to check the red blood count and the platelet count.
- Urinary sediment should also be checked regularly for the presence of erythrocytes
- Severe immunosuppression has led to serious, sometimes fatal, infections that include pneumonias, as well as other bacterial, fungal, viral, protozoal, and parasitic infections. Sepsis and septic shock have also been reported.
- Latent infections can be reactivated. Reactivation has been reported for various bacterial, fungal, viral, protozoal, and parasitic infections.
- Close hematological monitoring is required for all patients during treatment.

Urinary Tract and Renal Toxicity

- Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with cyclophosphamide therapy. Bladder ulceration/necrosis, fibrosis/contracture and secondary cancer may develop Cases of urotoxicity with fatal outcomes have been reported.
- Urotoxicity may mandate interruption of treatment.
- Cystectomy may become necessary due to fibrosis, bleeding, or secondary malignancy.
- Urotoxicity can occur with short-term and long-term use of cyclophosphamide. Hemorrhagic cystitis after single doses of cyclophosphamide has been reported.
- Past or concomitant radiation or busulfan treatment may increase the risk for cyclophosphamide-induced hemorrhagic cystitis.
- Cystitis is, in general, initially abacterial. Secondary bacterial colonization may follow.
- Adequate treatment with mesna and/or strong hydration to force diuresis can markedly reduce the frequency and severity of bladder toxicity. It is important to ensure that patients empty the bladder at regular intervals.
- Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity.
- Hematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist.
- Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions.
- Cyclophosphamide should be used with caution, if at all, in patients with active urinary tract infections.
- Cyclophosphamide has also been associated with nephrotoxicity, including renal tubular necrosis.
- Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone) have been reported in association with cyclophosphamide administration. Fatal outcomes have been reported.

Cardiotoxicity

- Myocarditis and myopericarditis, which may be accompanied by significant pericardial effusion and cardiac tamponade, have been reported with cyclophosphamide therapy and have led to severe, sometimes fatal congestive heart failure.



- Histopathologic examination has primarily shown hemorrhagic myocarditis. Hemopericardium has occurred secondary to hemorrhagic myocarditis and myocardial necrosis.
- Following exposure to treatment regimens that included cyclophosphamide, supraventricular arrhythmias (including atrial fibrillation and flutter) as well as ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported in patients with and without other signs of cardiotoxicity.
- The risk of cyclophosphamide cardiotoxicity may be increased for example, following high doses of cyclophosphamide, in patients with advanced age, and in patients with previous radiation treatment of the cardiac region and/or previous or concomitant treatment with other cardiotoxic agents.

Pulmonary Toxicity

- Pneumonitis and pulmonary fibrosis have been reported during and following treatment with cyclophosphamide. Pulmonary veno-occlusive disease and other forms of pulmonary toxicity have also been reported.
- Pulmonary toxicity leading to respiratory failure has been reported.
- While the incidence of cyclophosphamide-associated pulmonary toxicity is low, prognosis for affected patients is poor.
- Late onset of pneumonitis (greater than 6 months after start of cyclophosphamide) appears to be associated with a particularly high mortality. Pneumonitis may develop even years after treatment with cyclophosphamide.
- Acute pulmonary toxicity has been reported after a single cyclophosphamide dose.

Secondary Malignancies

- As with all cytotoxic therapy, treatment with cyclophosphamide involves the risk of secondary tumors and their precursors.
- In some cases, the second malignancy developed several years after cyclophosphamide treatment had been discontinued. Malignancy has also been reported after in utero exposure.
- The risk of urinary tract cancer as well as the risk of myelodysplastic alterations, partly progressing to acute leukemias, is increased. Othermalignancies reported after use of cyclophosphamide or regimens with cyclophosphamide include lymphoma, thyroid cancer, and sarcomas.
- The risk of bladder cancer can be markedly reduced by prevention of hemorrhagic cystitis.

Veno-occlusive Liver Disease

- Veno-occlusive liver disease (VOLD) including fata outcome has been reported in patients receiving cyclophosphamide.
- A cytoreductive regimen in preparation for bone marrow transplantation that consists of cyclophosphamide in combination with whole-body irradiation, busulfan, or other agents has been identified as a major risk factor for the development of VOLD. After cytoreductive therapy, the clinical syndrome typically develops 1 to 2 weeks after transplantation and is characterized by sudden weight gain, painful hepatomegaly, ascites, and hyperbilirubinemia/jaundice.
- However, VOLD has also been reported to develop gradually in patients receiving long-term low-dose immunosuppressive doses of cyclophosphamide.
- As a complication of VOLD, hepatorenal syndrome and multiorgan failure may develop.
- Risk factors predisposing a patient to the development of VOLD with high-dose cytoreductive therapy include :
  - preexisting disturbances of hepatic function

- previous radiation therapy of the abdomen, and a
- low performance score.

Genotoxicity

- Cyclophosphamide is genotoxic and mutagenic, both in somatic and in male and female germ cells. Therefore, women should not become pregnant and men should not father a child during therapy with cyclophosphamide.
- Men should not father a child for up to 6 months after the end of therapy.
- Animal data 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 cyclophosphamide 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.

Effects on Fertility

- Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes.
- Development of sterility appears to depend on the dose of cyclophosphamide, duration of therapy, and the state of gonadal function at the time of treatment.
- Cyclophosphamide-induced sterility may be irreversible in some patients.

Anaphylactic Reactions, Cross-sensitivity with Other Alkylating Agents

Anaphylactic reactions including those with fatal outcomes have been reported in association with cyclophosphamide.

Possible cross-sensitivity with other alkylating agents has been reported.

Impairment of Wound Healing

Cyclophosphamide may interfere with normal wound healing.

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.

Interaction with other medicaments and other forms of interaction

Planned coadministration or sequential administration of other substances or treatments that could increase the likelihood or severity of toxic effects (by means of pharmacodynamic or harmacokinetic 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 cyclophosphamide and agents that reduces its activation should be monitored for a potential reduction of therapeutic effectiveness and the need for dose adjustment.

Interactions Affecting the Pharmacokinetics of Cyclophosphamide and its Metabolites

- Reduced activation of cyclophosphamide may alter the effectiveness of cyclophosphamide treatment. Substances that delay activation of cyclophosphamide include
  - Aprepitant
  - Bupropion

- Busulfan: Cyclophosphamide clearance has been reported to be reduced and half-life prolonged in patients who receive high-dose cyclophosphamide less than 24 hours after high-dose busulfan.
- Ciprofloxacin: When given prior to the treatment with cyclophosphamide (used for conditioning prior to bone marrow transplantation), ciprofloxacin has been reported to result in a relapse of the underlying disease.
- Chloramphenicol
- Fluconazole
- Itraconazole
- Prasugrel
- Sulfonamides
- Thiotepa: A strong inhibition of cyclophosphamide bioactivation by thiotepa in high-dose chemotherapy regimens has been reported when thiotepa was administered 1 hour prior to cyclophosphamide.

- The blood glucose-lowering effect of sulfonyl ureas may be intensified, as well as the myelosuppressive action when allopurinol or hydrochlorothiazide is administered concomitantly.
- An increase of the concentration of cytotoxic metabolites may occur with
  - Allopurinol
  - Cimetidine

  Inducers of human hepatic and extrahepatic microsomal enzymes (e.g., cytochrome P450 enzymes): The potential for hepatic and extrahepatic microsomal enzyme induction must be considered in case of prior or concomitant treatment with substances known to induce an increased activity of such enzymes such as rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, and corticosteroids.
  - Protease inhibitors: Concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites. Use of protease inhibitor-based regimens was found to be associated with a higher incidence of infections and neutropenia in patients receiving cyclophosphamide, doxorubicin, and etoposide (CDE) than use of an NNRTI-based regimen.
- Ondansetron

  There have been reports of a pharmacokinetic interaction between ondansetron and high-dose cyclophosphamide resulting in decreased cyclophosphamide AUC.

Interactions Affecting the Pharmacokinetics and/or Actions of Other Drugs

- Bupropion

  Cyclophosphamide metabolism by CYP2B6 may inhibit bupropion metabolism.
- Coumarins

  Both increased and decreased warfarin effect have been reported in patients receiving warfarin and cyclophosphamide.
- Cyclosporine

  Lower serum concentrations of cyclosporine have been observed in patients receiving a combination of cyclophosphamide and cyclosporine than in patients receiving only cyclosporine. This interaction may result in an increased incidence of graft-versus-host disease.
- Depolarizing muscle relaxants

  Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity. Prolonged apnea may occur with concurrent depolarizing muscle relaxants (e.g., succinylcholine). If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

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 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.

- Digoxin, β-acetyldigoxin
  Cytotoxic treatment has been reported to impair intestinal absorption of digoxin and β-acetyldigoxin tablets.
- Vaccines
  The immunosuppressive effects of cyclophosphamide can be expected to reduce the response to vaccination. Use of live vaccines may lead to vaccine-induced infection.
- Verapamil
  Cytotoxic treatment has been reported to impair intestinal absorption of orally administered verapamil.

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/m2 body surface)
- for intermittent treatment 10 to 15 mg/kg body weight (equivalent to 400 to 600 mg/m2 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/m2 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 ml**	**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 and 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 patients are necessary. If neutropenia develops, infection prophylaxis must be given and infection must be treated adequately with antibiotics. If trombocytopenia develops, thrombocyte replacement should be ensured according to need. It is essential that cystitis prophylaxis with UROMITEXAN (mesna) be undertaken to avoid any urotoxic effect.
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:

<u>Blood and bone marrow:</u>
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.

<u>Gastrointestinal tract:</u>
Gastrointestinal side effect, 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 a bacterial, 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 value (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 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 reaction: 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 mm3, possibly daily. Checks every 2 weeks are generally sufficient in case of long-term therapy. The urinary sediment should be checked regularly on erythrocytes.

Incompatibilites
Benzyl alcohol containing solutions can reduce the stability of cyclophosphamide.

Pharmacological properties

Pharmacodynamic properties
Cyclophosphamide is 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, can not 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 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 +25ºC.
The reconstituted solution should be used within 24 hours after preparation (do not store above +8ºC).
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 injections vials with melted content.

Keep Drugs Out of Children's Reach!

Pack Sizes

Vials of 200 mg	Reg. No.: DKI 1105000644A1
Vial of 500 mg	Reg. No.: DKI 1105000644B1
Vial of 1 g	Reg. No.: DKI 1105000644C1

On Medical Prescription only
Harus dengan resep dokter

Manufactured by
Baxter Oncology GmbH
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Imported by
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