Baxter

Patient Information Leaflet -
Please read carefully!

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. A white crystalline powder contained in clear glass injection vials.
ENDOXAN:
Sugar-coated tablet for oral use.

Therapeutic 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 in 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

Endoxan should not be used in pregnancy and lactation (see pregnancy and lactation)

Pregnancy and lactation

- Cyclophosphamide crosses the placental barrier. Treatment with cyclophosphamide has a genotoxic effect and may cause fetal damage when administered to pregnant women.
- Malformations have been reported in children born to mothers treated with cyclophosphamide during the first trimester of pregnancy. However, there are also reports of children without malformations born to women exposed during the first trimester.
- Exposure to cyclophosphamide in utero may cause miscarriage, fetal growth retardation, and fetotoxic effects manifesting in the newborn, including leukopenia, anemia, pancytopenia, severe bone marrow hypoplasia, and gastroenteritis.
- Animal data suggest that an increased risk of failed pregnancy and malformations may persist after discontinuation of cyclophosphamide as long as oocytes/follicles exist that were exposed to cyclophosphamide during any of their maturation phases.
- If cyclophosphamide is used during pregnancy, or if the patient becomes pregnant while taking this drug or after treatment, the patient should be apprised of the potential hazard to a fetus.
- Cyclophosphamide is passed into the breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhea have been reported in children breast fed by women treated with cyclophosphamide. Women must not breastfeed during treatment with cyclophosphamide.

Special warnings and special precautions for use

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.
- 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.
- Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician.
- In case of neutropenic fever, antibiotics and/or antimycotics must be given.
- Cyclophosphamide should be used with caution, if at all, in patients with severe impairment of bone marrow function and in patients with severe immunosuppression.
- Unless essential, cyclophosphamide should not be administered to patients with a leukocyte count below 2500cells/microliter (cells/ mm3) and/or a platelet count below 50,000 cells/microliter (cells/mm3).
- Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop a serious infection.
- In principle, the fall in the peripheral blood cell and thrombocyte count and the time taken to recover may increase with increasing doses of cyclophosphamide.
- The nadirs of the reduction in leukocyte count and thrombocyte count are usually reached in weeks 1 and 2 of treatment. The bone marrow recovers relatively quickly, and the levels of peripheral blood cell counts normalize, as a rule, after approximately 20 days.
- Severe myelosuppression must be expected particularly in patients pretreated with and/or receiving concomitant chemotherapy and/or radiation therapy.
- Close hematological monitoring is required for all patients during treatment.
- Leukocyte counts must be obtained prior to each administration and regularly during treatment (at intervals of 5 to 7 days when starting treatment, and every 2 days if the counts drop below 3000 cells/microliter(cells/mm3)).
- Platelet count and hemoglobin value should be obtained prior to each administration and at appropriate intervals after administration.

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.
- It is usually necessary to discontinue cyclophosphamide therapy in instances of severe hemorrhagic cystitis.
- Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions. (See Section Contraindication)
- 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, Use in Patients with Cardiac Disease
- 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.
- Acute cardiac toxicity has been reported with a single dose of less than 20 mg/kg cyclophosphamide.
- 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. See Section Interaction with other medicaments and other forms of interaction.
- Particular caution is necessary in patients with risk factors for cardiotoxicity and in patients with pre-existing cardiac disease.

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. Other malignancies 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 (see Section Interaction with other medicamentsand other formsof interaction) 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. See also Section Pregnancy and Lactation.

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.

Female patients
- Amenorrhea, transient or permanent, associated with decreased estrogen and increased gonadotropin secretion develops in a significant proportion of women treated with cyclophosphamide.
- For older women, in particular, amenorrhea may be permanent.
- Oligomenorrhea has also been reported in association with cyclophosphamide treatment.
- Girls treated with cyclophosphamide during prepubescence generally develop secondary sexual characteristics normally and have regular menses.
- Girls treated with cyclophosphamide during prepubescence subsequently have conceived.
- Girls treated with cyclophosphamide who have retained ovarian function after completing treatment are at increased risk of developing premature menopause (cessation of menses before age of 40 years).

Male patients
- Men treated with cyclophosphamide may develop oligospermia or azoospermia, which are normally associated with increased gonadotropin but normal testosterone secretion.
- Sexual potency and libido generally are unimpaired in these patients.
- Boys treated with cyclophosphamide during prepubescence may develop secondary sexual characteristics normally, but may have oligospermia or azoospermia.
- Some degree of testicular atrophy may occur.
- Cyclophosphamide-induced azoospermia is reversible in some patients, though the reversibility may not occur for several years after cessation of therapy.
- Men temporarily rendered sterile by cyclophosphamide have subsequently fathered children.

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.

PRECAUTIONS
Alopecia
- Alopecia has been reported and may occur more commonly with increasing doses.
- Alopecia may progress to baldness.
- The hair can be expected to grow back after treatment with the drug or even during continued drug treatment, though it may be different in texture or color.

Nausea and Vomiting
- Administration of cyclophosphamide may cause nausea and vomiting.
- Current guidelines on the use of antiemetics for prevention and amelioration of nausea and vomiting should be considered.
- Alcohol consumption may increase cyclophosphamide-induced vomiting and nausea.

Stomatitis
- Administration of cyclophosphamide may cause stomatitis (oral mucositis).
- Current guidelines on measures for prevention and amelioration of stomatitis should be considered.

Paravenous Administration
- The cytostatic effect of cyclophosphamide occurs after its activation, which takes place mainly in the liver. Therefore, the risk of tissue injury from accidental paravenous administration is low.
- In case of accidental paravenous administration of cyclophosphamide, the infusion should be stopped immediately, the extravascular cyclophosphamide solution should be aspirated with the cannula in place, and other measures should be instituted as appropriate.

Use in Patients with Renal Impairment
- In patients with renal impairment, particularly in patients with severe renal impairment, decreased renal excretion may result in increased plasma levels of cyclophosphamide and its metabolites. This may result in increased toxicity and should be considered when determining the dosage in such patients.
- Cyclophosphamide and its metabolites are dialyzable, although there may be differences in clearance depending upon the dialysis system being used. In patients requiring dialysis, use of a consistent interval between cyclophosphamide administration and dialysis should be considered.

Use in Patients with Hepatic Impairment
- Severe hepatic impairment may be associated with decreased activation of cyclophosphamide. This may alter the effectiveness of cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected.

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.

Use in Adrenalectomized Patients
- Patients with adrenal insufficiency may require an increase in corticoid substitution dose when exposed to stress from toxicity due to cytostatics, including cyclophosphamide.

Effects on ability to drive and use machines

Patients undergoing treatment with cyclophosphamide may experience undesirable effects (including, e.g., dizziness, blurred vision, visual impairment) which could affect the ability to drive or use machines. The decision to drive or operate machinery should be made on an individual basis.

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 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 cyclophosphamide and agents that reduce 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.

• An increase of the concentration of cytotoxic metabolites may occur with
- Allopurinol
- Chloral hydrate
- Cimetidine
- Disulfiram
- Glyceraldehyde
- 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.

Pharmacodynamic Interactions and Interactions of Unknown Mechanism Affecting the Use of Cyclophosphamide
Combined or sequential use of cyclophosphamide and other agents with similar toxicities can cause combined (increased) toxic effects.
• Increased hematotoxicity and/or immunosuppression may result from a combined effect of cyclophosphamide and, for example
- ACE inhibitors: ACE inhibitors can cause leukopenia.
- Natalizumab
- Paclitaxel: Increased hematotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion.
- Thiazide diuretics
- Zidovudine

• Increased cardiotoxicity may result from a combined effect of cyclophosphamide and, for example
- Anthracyclines
- Cytarabine
- Pentostatin
- Radiation therapy of the cardiac region
- Trastuzumab

• Increased pulmonary toxicity may result from a combined effect of cyclophosphamide and, for example
- Amiodarone
- G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor): Reports suggest an increased risk of pulmonary toxicity in patients treated with cytotoxic chemotherapy that includes cyclophosphamide and G-CSF or GM- CSF.

• Increased nephrotoxicity may result from a combined effect of cyclophosphamide and, for example
- Amphotericin B
- Indomethacin: Acute water intoxication has been reported with concomitant use of indomethacin.

• Increase in other toxicities
- Azathioprine: Increased risk of hepatotoxicity (liver necrosis)
- Busulfan: Increased incidence of hepatic veno-occlusive disease and mucositis has been reported.
- Protease inhibitors: Increased incidence of mucositis.

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.
• 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.
Other interactions
• Alcohol
A reduced antitumor activity was observed in tumor-bearing animals during ethanol (alcohol) consumption and concomitant oral low-dose cyclophosphamide medication.
In some patients, alcohol may increase cyclophosphamide-induced vomiting and nausea.
• Etanercept
In patients with Wegener's granulomatosis, the addition of etanercept to standard treatment, including cyclophosphamide, was associated with a higher incidence of non-cutaneous solid malignancies.
• Metronidazole
Acute encephalopathy has been reported in a patient receiving cyclophosphamide and metronidazole. Causal association is unclear.
In an animal study, the combination of cyclophosphamide with metronidazole was associated with increased cyclophosphamide toxicity.
• Tamoxifen
Concomitant use of tamoxifen and chemotherapy may increase the risk of thromboembolic complications.

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 mg**	**1 g**
Dry substance equivalent to Cyclophosphamide, anhydrous	213.8 mg	534.5 mg	1069.0 mg
	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
- Serious consequences of overdosage include manifestations of dose dependent toxicities such as myelosuppression, urotoxicity, cardiotoxicity (including cardiac failure), veno-occlusive hepatic disease, and stomatitis.
- Patients who received an overdose should be closely monitored for the development of toxicities, and hematotoxicity in particular.
- No specific antidote for cyclophosphamide is known.
- Cyclophosphamide and its metabolites are dialyzable. Therefore, rapid hemodialysis is indicated when treating any suicidal or accidental overdose or intoxication.
- Overdosage should be managed with supportive measures, including appropriate, state-of-the-art treatment for any concurrent infection, myelosuppression, or other toxicity, should it occur.
- Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with cyclophosphamide overdose.

Adverse Reactions
Adverse Reactions From Clinical Trials
The list of adverse reactions to cyclophosphamide in this document is based on postmarketing data (see below).
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 cyclophosphamide: increased risk for and severity of pneumonias (including fatal outcomes), other bacterial, fungal, viral, protozoal, parasitic infections; reactivation of latent infections, including viral hepatitis, tuberculosis, JC virus with progressive multifocal leukoencephalopathy (including fatal outcomes), *Pneumocystis jiroveci*, herpes zoster, *Strongyloides*, Sepsis and Septic shock (including fatal outcomes)
NEOPLASMS, BENIGN AND MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS): Acute leukemia (Acute myeloid leukemia, Acute promyelocytic leukemia), Myelodysplastic syndrome, Lymphoma (Non-Hodgkin's lymphoma), Sarcomas, Renal cell carcinoma, Renal pelvis cancer, Bladder cancer, Ureteric cancer, Thyroid cancer, Treatment related secondary malignancy, Carcinogenic effect in offspring. Additionally, progression of underlying malignancies, including fatal outcomes, have been reported.
BLOOD AND LYMPHATIC SYSTEM DISORDERS: Myelosuppression manifested as Bone marrow failure, Pancytopenia, Neutropenia, Agranulocytosis, Granulocytopenia, Thrombocytopenia (complicated by bleeding), Leukopenia, Anemia; Febrile neutropenia, Lymphopenia, Disseminated intravascular coagulation, Hemolytic uremic syndrome (with thrombotic microangiopathy), Hemoglobin decreased.
IMMUNE SYSTEM DISORDERS: Immunosuppression, Anaphylactic shock, Anaphylactic/Anaphylactoid reaction (including fatal outcomes), Hypersensitivity reaction.
ENDOCRINE DISORDERS: Water intoxication, Syndrome of inappropriate antidiuretic hormone secretion
METABOLISM AND NUTRITION DISORDERS: Tumor lysis syndrome, Hyponatremia, Fluid retention, Anorexia, Blood glucose increased, Blood glucose decreased
PSYCHIATRIC DISORDERS: Confusional state
NERVOUS SYSTEM DISORDERS: Encephalopathy, Convulsion, Dizziness, Neurotoxicity has been reported and manifested as Reversible posterior leukoencephalopathy syndrome, Myelopathy, Peripheral neuropathy, Polyneuropathy, Neuralgia, Dysesthesia, Hypoesthesia, Paresthesia, Tremor, Dysgeusia, Hypogeusia, Parosmia
EYE DISORDERS: Visual impairment, Vision blurred, Conjunctivitis, Lacrimation increased
EAR AND LABYRINTH DISORDERS: Deafness, Hearing impaired, Tinnitus
CARDIAC DISORDERS: Cardiac arrest, Ventricular fibrillation, Ventricular tachycardia, Cardiogenic shock, Pericardial effusion (progressing to cardiac tamponade), Myocardial hemorrhage, Myocardial infarction, Cardiac failure congestive, Cardiac failure (including fatal outcomes), Left ventricular failure, Left ventricular dysfunction, Cardiomyopathy, Myocarditis, Pericarditis, Carditis, Atrial fibrillation, Supraventricular arrhythmia, Ventricular arrhythmia, Bradycardia, Tachycardia, Palpitations, Electrocardiogram QT prolonged, Ejection fraction decreased
VASCULAR DISORDERS: Pulmonary embolism, Venous thrombosis, Vasculitis, Peripheral ischemia, Hypertension, Hypotension, Flushing, Hot flush, Blood pressure decreased
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS: Pulmonary veno-occlusive disease, Acute respiratory distress syndrome, Interstitial lung disease as manifested by Pulmonary fibrosis, Respiratory failure (including fatal outcomes), Obliterative bronchiolitis, Organizing pneumonia, Alveolitis allergic, Pneumonitis; Respiratory distress, Pulmonary hypertension, Pulmonary edema, Pleural effusion, Bronchospasm, Dyspnea, Hypoxia, Cough, Nasal congestion, Nasal discomfort, Oropharyngeal pain, Rhinorrhea, Sneezing
GASTROINTESTINAL DISORDERS: Enterocolitis hemorrhagic, Gastrointestinal hemorrhage, Acute pancreatitis, Colitis, Enteritis, Cecitis, Mucosal ulceration, Stomatitis, Diarrhea, Vomiting, Constipation, Nausea, Abdominal pain, Abdominal discomfort, Parotid gland inflammation
HEPATOBILIARY DISORDERS: Veno-occlusive liver disease, Cholestatic hepatitis, Cytolytic hepatitis, Hepatitis, Cholestasis; Hepatotoxicity with Hepatic failure, Hepatic encephalopathy, Ascites, Hepatomegaly, Jaundice, Blood bilirubin increased, Hepatic function abnormal, Hepatic enzymes increased (Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Palmar-plantar erythrodysesthesia syndrome, Radiation recall dermatitis, Toxic skin eruption, Urticaria, Dermatitis, Rash, Blister, Pruritus, Erythema, Skin discoloration, Nail discoloration, Nail disorder, Alopecia, Facial Swelling, Hyperhidrosis
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS:
Rhabdomyolysis, Scleroderma, Muscle spasms, Myalgia, Arthralgia
RENAL AND URINARY DISORDERS: Renal failure, Renal tubular necrosis, Renal tubular disorder, Renal impairment, Nephropathy toxic, Hemorrhagic cystitis, Hemorrhagic ureteritis, Bladder necrosis, Cystitis ulcerative, Bladder fibrosis, Bladder contracture, Hematuria, Nephrogenic diabetes insipidus, Cystitis, Atypical urinary bladder epithelial cells, Blood creatinine increased, Blood urea nitrogen increased
PREGNANCY, PUERPERIUM, AND PERINATAL CONDITIONS: Premature labor
REPRODUCTIVE SYSTEM AND BREAST DISORDERS: Infertility, Ovarian failure, Ovarian disorder, Ovulation disorder, Amenorrhea, Oligomenorrhea, Testicular atrophy, Azoospermia, Oligospermia, Blood estrogen decreased, Blood gonadotrophin increased
CONGENITAL, FAMILIAL AND GENETIC DISORDERS: Intra-uterine death, Fetal malformation, Fetal growth retardation, Fetal toxicity (including myelosuppression, gastroenteritis)
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS: Multiorgan failure, General physical deterioration, Influenza-like illness, Injection/infusion site reactions (thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema), Pyrexia, Edema, Chest pain, Mucosal inflammation, Asthenia, Pain, Chills, Fatigue, Malaise, Headache.
INVESTIGATIONS: Blood lactate dehydrogenase increased, C-reactive protein increased

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, 1.000Hospital packs
Not all pack sizes may be marketed.

Name and permanent address of the manufacturer
And the holder of the marketing authorization
Baxter Oncology GmbH
Kantstrasse 2
D-33790 Halle, Germany

ENDOXAN Tablets manufactured by
Prasfarma S.L., C/Sant Joan 11 -15,
08560 Manlleu/Barcelona,
España for
Baxter Oncology GmbH
Kantstrasse 2
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