Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Endoxan 500 mg injection

Endoxan 1 gram injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Endoxan 500 mg

1 vial contains: 534.5 mg cyclophosphamide 1 H_2O (equivalent to 500 mg cyclophosphamide without H_2O)

Endoxan 1 g

1 vial contains: 1069.0 mg cyclophosphamide 1 H_2O (equivalent to 1000.0 mg cyclophosphamide without H_2O)

3. PHARMACEUTICAL FORM

Endoxan / 500 mg / 1 g in vials: white powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Malignant diseases:

Cyclophosphamide, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to cyclophosphamide treatment:

1. Malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Hodgkin's disease, lymphocytic lymphoma (nodular or diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma.
2. Multiple myeloma.
3. Leukemias: Chronic lymphocytic leukemia, chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis), acute myelogenous and monocytic leukemia, acute lymphoblastic (stem-cell) leukemia in children.
4. Mycosis fungoides (advanced disease).
5. Neuroblastoma (disseminated disease).
6. Adenocarcinoma of the ovary.
7. Retinoblastoma.
8. Carcinoma of the breast.

Nonmalignant Diseases:

Biopsy proven Minimal Change nephrotic syndrome in children whose disease fails to respond adequately to another treatment.

Severe cases of systemic Lupus Erythematoses which did not respond to other treatment, especially with nephritis.

Notes on conditioning prior to allogeneic bone marrow transplantation:

Indication for bone marrow transplantation and thus for preceding conditioning therapy with Endoxan depends on a complex constellation of factors and must be decided on an individual basis. Significant factors include disease stage, prognosis (risk group), nature and success of previous treatments of the underlying disease, the patient's age and general condition as well as availability of a suitable bone marrow donor.

Special note:

If cystitis with micro- or macrohematuria occurs on treatment with Endoxan, the treatment should be discontinued until this condition normalizes.

4.2 Posology and method of administration

Treatment of lupus nephritis with Endoxan should only be performed by physicians who have specific experience with the diseases and with Endoxan.

Posology

Endoxan should only be administered by physicians experienced with this drug

The dosage must be adapted to each patient individually. The following dose recommendations 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.

Attention should be paid to adequate hydration as well as to the administration of the Uroprotector and Uromitexan.

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

Unless otherwise prescribed the following dosages are recommended:

Endoxan 500 mg / 1 g

- 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.

Patients with hepatic impairment

Severe hepatic impairment may be associated with decreased activation of cyclophosphamide. This may alter the effectiveness of Endoxan treatment and should be considered when selecting the dose and interpreting the response to the dose selected.

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. In the presence of renal impairment, dose reduction by 50% is a common recommendation for glomerular filtration rates below 10 mL per minute.

Cyclophosphamide and its metabolites are dialyzable, although there may be differences in clearance depending on the dialysis system being used. In patients requiring dialysis, the time between Endoxan administration and dialysis should be consistent (see section 4.4).

Recommendations for dose reduction in the presence of myelosuppression

WBC count [mL]	Platelet count [mL]	
> 4,000	> 100,000	100% of the proposed dose
4,000-2,500	100,000 to 50,000	50% of the proposed dose
< 2,500	< 50,000	Postponement until normalization or individual decision

Geriatric population

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.

Method of administration

Cyclophosphamide is inert until activated by enzymes in the liver. However, as with all cytotoxics, it is suggested that reconstitution should be performed by trained personnel, in a designated area.

Those handling the preparation should wear protective gloves. Care should be taken to avoid splashing material into the eyes. The material should not be handled by women who are pregnant or who are breast-feeding.

Intravenous administration

Intravenous administration preferably should be conducted as an infusion, usually given directly into the tubing of a fast running i.v. infusion with the patient supine. Care should be taken that extravasation does not take place, however, should it occur, no specific measures need be taken.

Duration of the infusion also should be appropriate for the volume and type of carrier fluid to be infused.

If injected directly, cyclophosphamide for parenteral administration should be reconstituted with physiological saline (0.9% sodium chloride).The pH of an aqueous solution is between 4 and 6.

Cyclophosphamide, reconstituted in water, is hypotonic and should not be injected directly. For infusion, cyclophosphamide should be reconstituted by adding sterile water and infused in the recommended intravenous solutions.

Before parenteral administration, the substance must be completely dissolved.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Notes on preparation and handling of the solution

To prepare a 2% isotonic solution, add the corresponding amount of physiological saline solution to the dry substance (25 mL to Endoxan 500 mg and 50 mL to Endoxan 1 g).

The substance dissolves readily when the vial is shaken vigorously after injecting the solvent. Allow the solution to stand for several minutes, if necessary.

For intravenous short infusion, add e.g. Ringer's solution, saline solution or glucose solution to the Endoxan solution to achieve a volume of 500 mL.

4.3 Contraindications

Endoxan should not be used in patients with:

- known hypersensitivity to cyclophosphamide, its metabolites or to any of the excipients listed in section 6.1;
- severe impairment of bone marrow function (myelosuppression, in particular in patients previously treated with antineoplastic agents and/or radiation therapy)
- urinary tract infection
- urinary obstruction
- acute infections
- acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy

See section 4.6 for information on use during pregnancy and lactation.

4.4 Special warnings and precautions for use

WARNINGS

Myelosuppression, immunosuppression, infections

- Treatment with Endoxan can cause myelosuppression and significant suppression of immune response.
- Cyclophosphamide-induced myelosuppression can cause leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding) and anemia.
- Severe immunosuppression has led to serious, sometimes fatal infections. Sepsis and septic shock have also been reported. Infections reported with cyclophosphamide include pneumonias as well as other bacterial, fungal, viral, protozoal and parasitic infections.
- Latent infections can be reactivated. Reactivation has been reported for various bacterial, fungal, viral, protozoal and parasitic infections.
- Infections must be treated appropriately.
- Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician.
- In the event of neutropenic fever, antibiotics and/or antifungals 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 2500 cells/microlitre (cells/ mm3 and/or a platelet count below 50,000 cells/microlitre (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 peripheral blood cell and platelet counts may decrease more quickly and the time taken to recover may increase with increasing doses of cyclophosphamide.
- The nadirs of the reduction in white cell count and platelet count are usually reached in weeks 1 and 2 of treatment. The bone marrow recovers relatively quickly and peripheral blood cell concentrations 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 radiotherapy.
- Close hematological monitoring is required for all patients during treatment.
  - Leukocyte counts must be obtained prior to each dose 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/mm^3)). For long-term treatment, monitoring at intervals of around 14 days is generally sufficient.
  - Platelet count and hemoglobin value should be obtained prior to each dose and at appropriate intervals after dosing.

Urinary tract and renal toxicity

- Hemorrhagic cystitis, pyelitis, ureteritis and hematuria have been reported with cyclophosphamide therapy. Bladder ulceration/necrosis, fibrosis/contracture and secondary malignancies may develop.
- Urotoxicity may mandate interruption of treatment.
- Cystectomy may become necessary due to fibrosis, bleeding, or secondary malignancy.
- Cases of urotoxicity with fatal outcomes have been reported.
- Urotoxicity can occur with short-term and long-term use of Endoxan. Hemorrhagic cystitis after single doses of cyclophosphamide has been reported.
- Past or concomitant radiation or busulfan treatment may increase the risk of cyclophosphamide-induced hemorrhagic cystitis.
- Cystitis is, in general, initially abacterial. Secondary bacterial colonization may follow.
- Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions (see section 4.3).
- Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity.
- 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.
- Hematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Should cystitis with micro- or macrohematuria develop on the treatment, the treatment should be discontinued until this has normalized.
- Cyclophosphamide has also been associated with nephrotoxicity, including tubular necrosis.
- Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate antidiuretic hormone secretion) 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 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 2 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 tachyarrhythmias) 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 of 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 4.5).
- 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 (more than 6 months after initiation of cyclophosphamide treatment) appears to be associated with 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 therapies, treatment with cyclophosphamide involves the risk of secondary tumors and their precursors as late sequelae.
- There is an increased risk of urinary tract cancer and myelodysplastic alterations, in some cases progressing to acute leukemias. Other malignancies reported after use of cyclophosphamide or treatment regimens with cyclophosphamide include lymphomas, thyroid cancers, and sarcomas.
- In some cases, the second malignancy developed several years after cyclophosphamide treatment had been discontinued. Malignancy has also been reported after in utero exposure.

Veno-occlusive liver disease

- Veno-occlusive liver disease (VOLD) has been reported in patients receiving cyclophosphamide.
- Cytoreductive therapy in preparation for bone marrow transplantation consisting 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 (see section 4.5). 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 immunosuppression with cyclophosphamide.
- As a complication of VOLD, hepatorenal syndrome and multiple organ failure may develop. There are reports of cyclophosphamide-associated VOLD with a fatal outcome.
- Risk factors predisposing a patient to the development of VOLD with high-dose cytoreductive therapy include**:**
  - preexisting disturbances of hepatic function;
  - previous radiation treatment of the abdomen and
  - low performance scores.

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 treatment with cyclophosphamide.
- Both women and men should wait at least 6 to 12 months after stopping Cyclophosphamide before attempting to conceive or father a child**.**
- Animal study 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 an effective method of contraception during this period of time (see section 4.6.).
- Fertility, see section 4.6

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 can affect 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 but may differ 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 relief 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 relief of stomatitis should be considered.

Paravenous injection

- 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 injection is low.
- In the event of accidental paravenous injection of cyclophosphamide, the infusion should be stopped immediately and the extravascular cyclophosphamide solution should be aspirated with the cannula in place. Other measures may need to be instituted as appropriate.

Use in adrenalectomized patients

Patients with adrenal insufficiency may require an increase in corticoid substitution dose when exposed to stress from toxicity due to cyclophosphamide or other cytostatics drugs.

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. See Section 4.2.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Planned co-administration or sequential administration of other substances or treatments that could increase the likelihood or severity of toxic effects (by means of pharmacodynamic or pharmacokinetic interactions) requires careful individual assessment of the expected benefit versus 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
- Chloramphenicol
- 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
- Fluconazole
- Itraconazole
- Prasugrel
- Sulfonamide
- Thiotepa: Marked inhibition of cyclophosphamide bioactivation by thiotepa in high-dose chemotherapy regimens has been reported when thiotepa was administered one 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
  - Clozapine
- 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 (hepatic necrosis)
  - Busulfan: Increased incidence of veno-occlusive liver disease and mucositis have been reported
  - Protease inhibitors: Increased incidence of mucositis

Other interactions

- Alcohol

Reduced antitumor activity was observed in tumor-bearing animals during ethanol (alcohol) consumption and concomitant low-dose oral cyclophosphamide medication.

In some patients, alcohol may increase cyclophosphamide-induced nausea and vomiting.

- 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.

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 co-administration of 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, beta-acetyldigoxin

Cytotoxic treatment has been reported to impair intestinal absorption of digoxin and beta-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-related infection.

- Verapamil

Cytotoxic treatment has been reported to impair intestinal absorption of orally administered verapamil.

4.6 Fertility, pregnancy and lactation

Pregnancy

Cyclophosphamide is contraindicated in pregnancy (see section 4.3). Cyclophosphamide crosses the placental barrier. Treatment with cyclophosphamide has a genotoxic effect and may cause foetal damage when administered to pregnant women. Both women and men should wait at least 6 to 12 months after stopping Cyclophosphamide before attempting to conceive or father a child.

- 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, foetal growth retardation, and foetotoxic effects manifesting in the newborn, including leukopenia, anaemia, 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. See Section 4.4, Genotoxicity.
- If cyclophosphamide is used during pregnancy, or if the patient becomes pregnant while taking this drug or after treatment (see Section 4.4, Genotoxicity), the patient should be apprised of the potential hazard to a foetus.

Breastfeeding

Cyclophosphamide is passed into the breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhoea have been reported in children breast fed by women treated with cyclophosphamide. Women must not breastfeed during treatment with cyclophosphamide.

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.

Sexually active women and men should use effective methods of contraception during these periods of time.

- Female patients

Amenorrhea, transient or permanent, associated with decreased oestrogen and increased gonadotrophin 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 gonadotrophin 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.

4.7 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.

4.8 Undesirable effects

The following adverse drug reactions are based on postmarketing data. They are listed in the table according to MedDRA system organ class and by frequency.

Side effect frequencies are based on the following categories:

Very common: (³ 1/10)
Common: (³ 1/100 to < 1/10)
Uncommon: (³ 1/1,000 to < 1/100)
Rare: (³ 1/10,000 to < 1/1,000)
Very rare: (< 1/10,000)
Unknown:

Unknown (adverse reactions reported in the post-marketing experience)

Adverse drug reactions

System organ class	Side effect	Frequency
Infections and infestations	Infections[1]	Common
	Pneumonias[2]	Uncommon
	Sepsis[1]	Uncommon
	Septic shock	Unknown
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Secondary tumors[4]	Rare
	Acute leukemia[3]	Rare
	Myelodysplastic syndrome	Rare
	Bladder cancer	Rare
	Tumor lysis syndrome	Unknown
Blood and lymphatic system disorders	Myelosuppression[6]	Very common
	Disseminated intravascular coagulation	Very rare
	Hemolytic uremic syndrome	Very common
	Lymphopenia	Unknown
Immune system disorders	Immunosuppression	Very common
	Hypersensitivity reactions	Uncommon
	Anaphylactic/anaphylactoid reaction[2]	Very rare
Endocrine disorders	Syndrome of inadequate ADH secretion (SIADH)	Rare
Metabolism and nutrition disorders	Anorexia	Uncommon
	Dehydration	Rare
	Hyponatremia	Very rare
	Fluid retention	Very rare
	Changes in blood glucose level (increase or decrease)	Unknown
Psychiatric diseases	Confusion	Very rare
Nervous system disorders	Dizziness	Rare
	Convulsion	Very rare
	Encephalopathy	Unknown
	Neurotoxicity[7]	Unknown
Eye disorders	Visual impairment	Rare
	Conjunctivitis	Very rare
	Eye edema	Very rare
	Lacrimation increased	Unknown
Ear and labyrinth disorders	Deafness	Unknown
	Tinnitus	Unknown
Cardiac disorders	Cardiomyopathy	Unknown
	Myocarditis	Unknown
	Cardiac failure (including isolated fatal cases)	Unknown
	Arrhythmias[8]	Unknown
	Myocardial infarction	Unknown
	Pericarditis	Unknown
	Cardiogenic shock	Unknown
	Pericardial effusion	Unknown
	Electrocardiogram QT interval prolonged	Unknown
	Ventricular fibrillation	Unknown
	Ventricular tachycardia	Unknown
Vascular disorders	Pulmonary embolism	Unknown
	Venous thrombosis	Unknown
	Vasculitis	Unknown
	Peripheral ischemia	Unknown
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Unknown
	Pulmonary edema	Unknown
	Pulmonary hypertension	Unknown
	Bronchospasm	Unknown
	Dyspnea	Unknown
	Hypoxia	Unknown
	Cough	Unknown
	Nasal congestion	Unknown
	Rhinorrhea	Unknown
	Pulmonary veno-occlusive disease	Unknown
	Interstitial Lung Diseases[9]	Unknown
Gastrointestinal disorders	Stomatitis	Very rare
	Diarrhea	Very rare
	Vomiting	Very rare
	Constipation	Very rare
	Nausea	Very rare
	Hemorrhagic enterocolitis	Very rare
	Acute pancreatitis	Very rare
	Mucosal ulceration	Very rare
	Gastrointestinal hemorrhage	Unknown
	Abdominal pain	Unknown
	Parotid gland inflammation	Unknown
	Colitis	Unknown
	Enteritis	Unknown
	Cecitis	Unknown
Hepatobiliary disorders	Hepatic function abnormal	Common
	Veno-occlusive disorder	Unknown
	Hepatitis	Unknown
	Cholestasis	Unknown
	Hepatotoxicity[10]	Unknown
Skin and subcutaneous tissue disorders	Alopecia	Very common
	Exanthema	Rare
	Dermatitis	Rare
	Discoloration of palms, fingernails and soles of the feet	Rare
	Stevens Johnson syndrome	Very rare
	Toxic epidermal necrolysis	Very rare
	Erythema multiforme	Unknown
	Radiation recall dermatitis	Unknown
	Radiation burn	Unknown
	Pruritus (including inflammatory itching)	Unknown
	Palmar-plantar erythrodysesthesia	Unknown
	Urticaria	Unknown
	Blistering	Unknown
	Facial swelling	Unknown
	Hyperhidrosis	Unknown
	Rash	Rare
	Erythema in irradiated area	Unknown
	Erythema	Unknown
Musculoskeletal and connective tissue disorders	Rhabdomyolysis	Unknown
	Scleroderma	Unknown
	Muscle spasms	Unknown
	Myalgia	Unknown
	Arthralgia	Unknown
Renal and urinary disorders	Cystitis	Very common
	Microhematuria	Very common
	Hemorrhagic cystitis (including isolated fatal cases)	Common
	Macrohematuria	Common
	Suburothelial bleeding	Very rare
	Edema of the bladder wall	Very rare
	Interstitial inflammation with fibrosis and sclerosis of the bladder	Very rare
	Renal failure	Very rare
	Blood creatinine increased	Very rare
	Renal Tubular necrosis	Unknown
	Renal tubular disorder	Unknown
	Toxic nephropathy	Unknown
	Hemorrhagic ureteritis	Unknown
	Ulcerative cystitis	Unknown
	Bladder contracture	Unknown
	Nephrogenic diabetes insipidus	Unknown
	Atypical bladder epithelial cells	Unknown
	Blood urea nitrogen increased	Unknown
Pregnancy, puerperium and perinatal conditions	Premature labor	Unknown
Reproductive system and breast disorders	Impairment of spermatogenesis	Common
	Ovulation disorder	Uncommon
	Amenorrhea[5]	Rare
	Azoospermia[5]	Rare
	Oligospermia[5]	Rare
	Infertility	Unknown
	Ovarian failure	Unknown
	Oligomenorrhea	Unknown
	Testicular atrophy	Unknown
	Blood estrogen reduced	Unknown
	Blood gonadotropin increased	Unknown
Congenital, familial and genetic disorders	Intrauterine death of the fetus	Unknown
	Fetal malformation	Unknown
	Fetal growth retardation	Unknown
	Fetal toxicity (including myelosuppression/ gastroenteritis)	Unknown
General disorders and administration site conditions	Fever	Very common
	Asthenia	Common
	Mucosal inflammation	Common
	Chest pain	Rare
	Headache	Very rare
	Multi-organ failure	Unknown
	Edema	Unknown
	Flu-like illness	Unknown
	General physical deterioration	Unknown
	Injection/infusion site reactions[11]	Unknown
Investigations	Blood lactate dehydrogenase increased	Unknown
	C-reactive protein increased	Unknown

1 including other bacterial, fungal, viral, protozoal, parasitic, reactivation of latent infections, including viral hepatitis, tuberculosis, JC virus with progressive multifocal leucoencephalopathy (including fatal outcomes), Pneumocystis jiroveci, herpes zoster, Strongyloides
2 including fatal outcomes
3 including acute myeloid leukemia and acute promyelocytic leukemia
4 in high-dose therapy: very common
5 persistent
6 manifested as Bone marrow failure, Pancytopenia, Neutropaenia, Agranulocytosis, Gra nulocytopenia,Thrombocytopaenia (complicated by bleeding), Leukopenia, Anaemia
7 manifested as reversible posterior leukoencephalopathy syndrome, myelopathy, peripheral neuropathy, polyneuropathy,neuralgia, dysesthesia, hypoesthesia, paresthesia, tremor, dysgeusia, hypogeusia,parosmia.
8 manifested as Atrial fibrillation,Supraventricular arrhythmia ,Ventricular arrhythmia, Bradycardia, Tachycardia,Palpitation
9 manifested by pulmonary fibrosis, obliterative bronchiolitis, organizing pneumonia, alveolitis allergic, pneumonitis
10 Hepatic failure, Hepatic encephalopathy, Ascites, Hepatomegaly, Jaundice, Blood bilirubin increased, Hepatic enzymes increased (ASAT, ALAT, ALP, gamma-GT)
11 manifested by thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il.

4.9 Overdose

- Serious consequences of overdosage include manifestations of dose-dependent toxicities such as myelosuppression, urotoxicity, cardiotoxicity (including cardiac failure), veno-occlusive liver disease, and stomatitis (see section 4.4).
- Patients who receive an overdose should be closely monitored for the development of toxicities, hematotoxicity in particular.
- No specific antidote for Endoxan is known.
- Cyclophosphamide and its metabolites are dialyzable. Consider haemodialysis in cases of severe overdose presenting early, particularly in patients with renal impairment.
- Overdosage should be managed with supportive measures, including appropriate, state-of-the-art treatment for any concurrent infections, myelosuppression or other toxicities.
- Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects of cyclophosphamide overdose (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: alkylating agents, nitrogen mustard analogs

ATC code: L01AA01

Cyclophosphamide is an antineoplastic agent from the oxazaphosphorine class. It is chemically related to nitrogen mustard.

Cyclophosphamide is inactive in vitro and is activated in vivo primarily in the liver by microsomal enzymes to 4-hydroxycyclophosphamide, which exists in equilibrium with its tautomer aldophosphamide. These tautomers undergo partly spontaneous, partly enzymatic conversion to inactive and active metabolites (in particular phosphoramide mustard and acrolein).

The cytotoxic effect of cyclophosphamide is based on an interaction of its alkylating metabolites with the DNA. The alkylation results in strand breaks and crosslinking of the DNA strands and DNA protein crosslinks. The passage through the G2 phase is slowed down in the cell cycle. The cytotoxic effect is not specific to cell cycle phase, rather to cell cycle. Acrolein does not have any antineoplastic activity, but is responsible for the urotoxic side effects. An immunosuppressive effect of cyclophosphamide is also being discussed.

Cross-resistance, in particular with structurally related antineoplastic agents such as ifosfamide, but also with other alkylating agents, cannot be ruled out.

5.2 Pharmacokinetic properties

Cyclophosphamide is well absorbed following an oral dose with a mean half-life of 4-8 hours for both oral and parenteral administration.

It is an inactive pro drug with alkylating metabolites produced by hepatic metabolism, reaching peak levels 4-6 hours after an i.v. injection. Hepatic enzymes may be induced. The parent compound binds poorly to plasma protein but the active metabolites are significantly protein-bound. The drug is widely distributed and crosses the blood-brain barrier, the placental barrier and is found in ascites. The metabolites are excreted renally.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains no excipients.

6.2 Incompatibilities

The stability of cyclophosphamide can be limited in carrier solutions containing benzyl alcohol.

6.3 Shelf-life

Endoxan 500 mg and Endoxan 1 g: 3 years

The reconstituted solution should be used within 24 hours after preparation.

6.4 Special precautions for storage

Endoxan vials should be stored at room temperature and not over 25 °C.

Store in the original package.

Store the reconstituted solution in the refrigerator (at 2–8 °C). Do not store above 8 °C.

The active substance cyclophosphamide can melt due to influences of temperature during transport or storage of Endoxan powder for solution for injection.

Vials with melted substance are optically readily distinguishable from vials with intact active substance. Melted cyclophosphamide is a clear or yellowish liquid in a continuous phase or in drops in the affected vials. Vials with melted contents must not be used.

6.5 Nature and contents of container

Endoxan 500 mg / 1 g

Packs with 1 vial

6.6 Special precautions for disposal and other handling

The handling, preparation and disposal of cyclophosphamide should always be in accordance with current guidelines on safe handling of cytotoxic agents.

7. MARKETING AUTHORIZATION HOLDER

Baxter Oncology GmbH, Halle/Westfalen, Germany

8. LICENSE HOLDER

Megapharm Ltd., P.O.B. 519, Hod Hasharon, 4510501, Israel

9. Marketing Authorisation Number

Endoxan 500 mg	114-18-29659
Endoxan 1 g	114-19-29660

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in March 2016.

END SPC 052016 P.2