Applicant/HCR:	Baxter Healthcare South Africa (Pty) Ltd
Product Name:	Endoxan 50 mg Tablets
	Each tablet contains cyclophosphamide monohydrate equivalent to 50 mg anhydrous cyclophosphamide.

PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ENDOXAN 50 mg TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains cyclophosphamide monohydrate equivalent to 50 mg anhydrous cyclophosphamide.

Excipients with known effect

ENDOXAN tablets contain 24,6 mg lactose monohydrate in the tablet core and 51,11 mg sucrose in the tablet coating.

3. PHARMACEUTICAL FORM

Tablets.

White round biconvex sugar-coated tablets with a white core.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Malignant Diseases:

Oral ENDOXAN is used in combination chemotherapy regimens or as monotherapy in the following indications:

- Chronic lymphocytic leukaemia
- Non-Hodgkin's lymphomas, plasmacytoma
- Neuroblastoma

- Primary and metastatic breast cancer
- Severe active forms of lupus nephritis, Wegener's granulomatosis

4.2 Posology and method of administration

Posology

ENDOXAN should only be prescribed by medical practitioners experienced with this medicine.

The dosage must be adapted to each patient individually.

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 the blood cell counts.

Unless otherwise prescribed the following dosages are recommended:

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:

Leucocyte count (per μl)	**Platelet count (per μl)**	**Dosage**
> 4 000	> 100 000	100 % of the planned dose
4 000 – 2 500	100 000 – 50 000	50 % of the planned dose
< 2 500	< 50 000	Adjustment until values normalise 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. ENDOXAN and its metabolites are dialysable, although there may be differences in clearance, depending upon the dialysis system being used. In patients requiring dialysis, use of a consistent interval between ENDOXAN administration and dialysis should be considered (see section 4.4).

Elderly:

In elderly patients, monitoring for toxicities and the need for dose adjustment, often reduction, should reflect the higher frequency of decreased hepatic, renal, cardiac, or other organ function, and concomitant diseases or other medicine therapies in this population.

Method of administration

ENDOXAN 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.

The coating of the tablets prevents direct contact of persons handling the tablets with the active substance. To prevent inadvertent exposure of third persons to the active substance, the tablets should not be divided or crushed.

4.3 Contraindications

ENDOXAN should not be used in patients with:

- Known hypersensitivity to cyclophosphamide and/or any of its metabolites and/or excipients.

- Severely impaired bone-marrow function (particularly in patients who have been pre-treated with cytotoxic agents and/or radiotherapy).
- Inflammation of the bladder (cystitis).
- Urinary outflow obstructions.
- Active urinary tract infections.
- Pregnancy and lactation. For use during pregnancy and lactation refer to section 4.6.
- Use of live vaccines may lead to vaccine-induced infection.
- Acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy.
- ENDOXAN should not be used in the management of non-malignant disease, except for immunosuppression in life-threatening situations.

4.4 Special warnings and precautions for use

Anaphylactic reactions, cross-sensitivity with other alkylating agents

- Anaphylactic reactions including those with fatal outcomes have been reported in association with ENDOXAN.
- Possible cross-sensitivity with other alkylating agents has been reported.

Weakened or elderly patients

ENDOXAN should be used with care in weakened or elderly patients and in patients who have had previous radiotherapy.

Patients with a weakened immune system, e.g. those with diabetes mellitus, chronic hepatic or renal impairments, also require close observation.

Myelosuppression, immunosuppression, infections

- Treatment with ENDOXAN may cause myelosuppression, including leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding events), and anaemia.
- Treatment with ENDOXAN can cause severe immunosuppression, which may lead to serious and 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.
- ENDOXAN should not be used in patients with severe impairment of bone marrow function and in patients with severe immunosuppression (see section 4.3).
- Unless essential, ENDOXAN should not be administered to patients with a leukocyte count below 2500 cells/microliter (cells/mm^3) and/or a platelet count below 50000 cells/microliter (cells/mm^3).
- ENDOXAN 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 ENDOXAN.
- 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. Anaemia will usually not develop until after several treatment cycles
- Severe myelosuppression must be expected particularly in patients pre-treated with and/or receiving concomitant chemotherapy and/or radiation therapy 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

medicines to the blood counts at the beginning of the cycle and the nadir-adjusted dosage of cytostatic agents (see section 4.2).

- Close haematological 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 two days if the counts drop below 3000 cells/microliter (cells/mm^3)). Daily controls may be necessary under certain circumstances. In patients receiving long-term treatment, controls every two weeks are usually sufficient.
  - Platelet count and haemoglobin value should be obtained prior to each administration and at appropriate intervals after administration.

Urinary tract and renal toxicity

- After their excretion in the urine, metabolites of ENDOXAN cause changes in the efferent urinary tract and especially in the bladder, such as haemorrhagic cystitis, pyelitis, ureteritis, and haematuria. Bladder ulceration/necrosis, fibrosis/contracture and secondary bladder cancer 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. Haemorrhagic cystitis after single doses of cyclophosphamide has been reported.
- Past or concomitant radiation or busulfan treatment may increase the risk for cyclophosphamide-induced haemorrhagic cystitis.
- ENDOXAN induced cystitis is initially abacterial. Secondary bacterial infection may follow.
- Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions (see section 4.3).

- Urinary sediment should also be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity.
- Treatment with mesna or strong hydration can reduce the frequency and severity of these urotoxic side effects. It is important to ensure that patients empty the bladder at regular intervals.
- Haematuria may resolve in a few days after ENDOXAN treatment is stopped, but it may persist.
- It is usually necessary to discontinue ENDOXAN therapy in instances of severe haemorrhagic cystitis.
- ENDOXAN has also been associated with nephrotoxicity, including renal tubular necrosis.
- Hyponatraemia 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 ENDOXAN 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 ENDOXAN therapy and have led to severe, sometimes fatal congestive heart failure.
- Histopathologic examination has primarily shown haemorrhagic myocarditis. Haemopericardium has occurred secondary to haemorrhagic myocarditis and myocardial necrosis.
- Acute cardiac toxicity has been reported with a single dose of less than 20 mg/kg ENDOXAN.
- Following exposure to treatment regimens that included ENDOXAN, supraventricular dysrrhythmias (including atrial fibrillation and flutter) as well as ventricular dysrrhythmias (including severe QT prolongation associated with ventricular

tachydysrrhythmia) have been reported in patients with and without other signs of cardiotoxicity.

- The risk of ENDOXAN cardiotoxicity is increased 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 medicines (see section 4.5). In this context, bear in mind that regular electrolyte controls are necessary.
- Particular caution is necessary in patients with risk factors for cardiotoxicity and in patients with pre-existing cardiac disease.

Pulmonary toxicity

- Interstitial pneumonitis and pulmonary fibrosis have been reported during and following treatment with ENDOXAN. Pulmonary veno-occlusive disease and other forms of pulmonary toxicity have also been reported. Pulmonary toxicity leading to respiratory failure has been reported.
- Late onset of pneumonitis (greater than 6 months after start of ENDOXAN) appears to be associated with a particularly high mortality. Pneumonitis may develop even years after treatment with ENDOXAN.
- Acute pulmonary toxicity has been reported after a single ENDOXAN dose.

Secondary malignancies

- Treatment with ENDOXAN 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. Other malignancies reported after use of ENDOXAN or regimens with ENDOXAN include lymphoma, thyroid cancer, and sarcomas.

- In some cases, the second malignancy developed several years after cyclophosphamide treatment had been discontinued. Malignancy has also been reported in children after *in utero* exposure.
- The risk of bladder cancer may be reduced by prevention of haemorrhagic cystitis.

Veno-occlusive liver disease

- Veno-occlusive liver disease (VOLD) has been reported in patients receiving ENDOXAN.
- A cytoreductive regimen in preparation for bone marrow transplantation that consists of cyclophosphamide in combination with whole-body irradiation, busulfan, or other medicines has been identified (see section 4.5) as a major risk factor for the development of VOLD. After cytoreductive therapy, typically VOLD develops 1 to 2 weeks after transplantation and is characterised by sudden weight gain, painful hepatomegaly, ascites, and hyperbilirubinaemia/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 multi-organ failure may develop. Fatal outcome of cyclophosphamide-associated VOLD has been reported.
- Risk factors predisposing a patient to the development of VOLD with high-dose cytoreductive therapy include:
  – pre-existing disturbances of hepatic function,
  – previous radiation therapy of the abdomen, and
  - a low ECOG performance score.

Genotoxicity

ENDOXAN is genotoxic and mutagenic, both in somatic and in male and female germ cells (see Section 4.6).

Impairment of wound healing

- ENDOXAN may interfere with normal wound healing.

Alopecia

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

Nausea and vomiting

- Administration of ENDOXAN may cause nausea and vomiting.
- The use of antiemetics for prevention and amelioration of nausea and vomiting should be considered. Attention should be paid to timely administration of antiemetics and to meticulous oral hygiene.
- Alcohol consumption may increase ENDOXAN-induced vomiting and nausea.

Stomatitis

- Administration of ENDOXAN may cause stomatitis (oral mucositis).
- Measures for prevention and amelioration of stomatitis should be considered.

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 ENDOXAN 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 ENDOXAN treatment and should be considered when selecting the dose and interpreting response to the dose selected.

Use in adrenalectomised patients

Patients with adrenal insufficiency may require an increased dose of corticosteroid substitution when exposed to stress from toxicity due to cytostatics, including ENDOXAN.

Lactose and Sucrose

ENDOXAN tablets contain lactose monohydrate in the tablet core and sucrose in the tablet coating. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption, fructose intolerance or sucrose-isomaltase should not take ENDOXAN.

4.5 Interaction with other medicines and other forms of interaction

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: ENDOXAN 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 (e.g. Leukaemia).
- Chloramphenicol.
- Fluconazole.
- Itraconazole.
- Prasugrel.
- Sulfonamides.
- Thiotepa: A strong inhibition of ENDOXAN 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.
  - 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 rifampicin, phenobarbitone, carbamazepine, phenytoin, benzodiazepines, chloral hydrate, St. John's Wort and corticosteroids.
  - Protease inhibitors: Concomitant use of protease inhibitors, used in the treatment of HIV, such as atazanivir, indinivair, lopinavir, ritonavir, nelfinavir 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 ENDOXAN resulting in decreased cyclophosphamide AUC.

Pharmacodynamic interactions and interactions of unknown mechanism affecting the use of ENDOXAN

Combined or sequential use of ENDOXAN and other medicines with similar toxicities can cause combined (increased) toxic effects.

- Increased haematotoxicity and/or immunosuppression may result from a combined effect of ENDOXAN and, for example:
  - ACE inhibitors: ACE inhibitors can cause leukopenia.
  - Alternate agents which also affect the renin angiotension system such as ARBs and direct renin inhibitors have not been associated with leukopenia.
  - Natalizumab.
  - Paclitaxel: Increased haematotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion.
  - Zidovudine.

- Increased cardiotoxicity may result from a combined effect of ENDOXAN and:
  - Anthracyclines.
  - Cytarabine.
  - Pentostatin.
  - Radiation therapy of the cardiac region.
  - Trastuzumab.

- Increased pulmonary toxicity may result from a combined effect of ENDOXAN and:
  - 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 GMCSF.

- Increased nephrotoxicity may result from a combined effect of ENDOXAN and:
  - 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.

Other interactions:

- Alcohol

  A reduced antitumour activity was observed in tumour-bearing animals during ethanol (alcohol) consumption and concomitant oral low-dose cyclophosphamide medication.

  Alcohol may increase ENDOXAN-induced vomiting and nausea.

  Patients receiving treatment with ENDOXAN should abstain from drinking alcoholic beverages.

- Etanercept

  In patients with Wegener's granulomatosis, the addition of etanercept to standard treatment, including ENDOXAN, was associated with a higher incidence of non-cutaneous solid malignancies.

- Metronidazole

  Acute encephalopathy has been reported in a patient receiving ENDOXAN and metronidazole. Causal association is unclear. In an animal study, the combination of ENDOXAN with metronidazole was associated with increased ENDOXAN toxicity.

- Tamoxifen

  Concomitant use of tamoxifen and chemotherapy may increase the risk of thromboembolic complications.

Interactions affecting the pharmacokinetics and/or actions of other medicines

- Bupropion

  ENDOXAN metabolism by CYP2B6 may inhibit bupropion metabolism.

- Warfarin

  Both increased and decreased warfarin effect have been reported in patients receiving warfarin and cyclophosphamide. Patients receiving warfarin should have more frequent monitoring of INR.

- Ciclosporin

Lower serum concentrations of ciclosporin have been observed in patients receiving a combination of ENDOXAN and ciclosporin, than in patients receiving only ciclosporin. This interaction may result in an increased incidence of graft-versus-host disease.

- Depolarising muscle relaxants

  ENDOXAN treatment causes a marked and persistent inhibition of cholinesterase activity. Prolonged apnoea may occur with concurrent depolarising muscle relaxants (e.g. succinylcholine). If a patient has been treated with ENDOXAN within 10 days of general anaesthesia, the anaesthesiologist should be alerted.

- Digoxin

  Cytotoxic treatment has been reported to impair intestinal absorption of digoxin and β-acetyldigoxin tablets.

- Vaccines

  The immunosuppressive effects of ENDOXAN can be expected to reduce the response to vaccination. Use of live vaccines may lead to vaccine-induced infection (see Section 4.3).

- Verapamil

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

The blood glucose-lowering effect of sulfonylureas may be intensified.

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

4.6 Fertility, pregnancy and lactation

The use of ENDOXAN is contraindicated in Pregnancy and lactation. Treatment with ENDOXAN can cause congenital abnormalities in offsprings

Pregnancy

Cyclophosphamide crosses the placental barrier. Treatment with ENDOXAN may cause congenital abnormalities in their offspring when administered to pregnant women. Malformations have been reported in children born to mothers treated with ENDOXAN. Exposure to ENDOXAN *in utero* may cause miscarriage, foetal growth retardation, and fetotoxic effects manifesting in the new-born, including leukopenia, anaemia, pancytopenia, severe bone marrow hypoplasia and gastroenteritis.

Genotoxicity

- ENDOXAN 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 ENDOXAN.
- 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 fertilisation or pregnancy after discontinuation of ENDOXAN 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.

Women of Childbearing Potential

Women should not become pregnant during treatment. Should they still conceive during treatment, they should seek counselling (see Genotoxicity).

Breastfeeding

As ENDOXAN passes into breast milk, mothers must not breast feed their infants during treatment. Neutropenia, thrombocytopenia, low haemoglobin and diarrhoea have been reported in children breast fed by women treated with ENDOXAN.

Fertility

Effects on Fertility

- ENDOXAN interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes.
- Men to be treated with ENDOXAN should be informed about sperm preservation before treatment.
- The duration of contraception in men and women, on completion of chemotherapy, depends on the prognosis of the primary disease and the intensity of the parent's desire for a child.
- Development of sterility appears to depend on the dose of ENDOXAN, duration of therapy, and the state of gonadal function at the time of treatment.
- ENDOXAN-induced sterility may be irreversible.

Female patients

- Amenorrhoea, transient or permanent, associated with decreased oestrogen and increased gonadotropin secretion develops in a significant proportion of women treated with ENDOXAN.
- For older women, in particular, amenorrhoea may be permanent.
- Oligomenorrhoea has also been reported in association with ENDOXAN treatment.

- Girls treated with ENDOXAN who have retained ovarian function after completing treatment, are at increased risk of developing premature menopause (cessation of menses before age of 40 years).
- Animal data suggest that an increased risk of failed pregnancy and malformations may persist after discontinuation of ENDOXAN as long as oocytes/follicles exist that were exposed to cyclophosphamide during any of their maturation phases which may be after 12 months.

Male patients

- Men treated with ENDOXAN may develop oligospermia or azoospermia, which are usually associated with increased gonadotropin, but normal testosterone secretion.
- Boys treated with ENDOXAN during prepubescence may have oligospermia or azoospermia.
- Testicular atrophy may occur.
- ENDOXAN-induced azoospermia may be reversible, though the reversibility may not occur for several years after cessation of therapy.
- Men temporarily rendered sterile by ENDOXAN have subsequently fathered children.

In a vital indication during pregnancy a medical consultation regarding termination of pregnancy is absolutely necessary.

4.7 Effects on ability to drive and use machines

Patients undergoing treatment with ENDOXAN 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

Patients on ENDOXAN therapy may experience the following dose-dependent side effects.

Side effects are presented according to system organ class and the frequency is defined as very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10000, < 1/1000) or very rare (< 1/10000).

Primary SOC	**Very common ≥ 1/ 10**	**Common ≥ 1/ 100 - < 1/ 10**	**Uncommon ≥ 1/ 1 000 - < 1/ 100**	**Rare ≥ 1/ 10 000 - < 1/ 1 000**	**Very rare < 1/ 10 000, incl. isolated reports**
Infections and infestations		Infections	Pneumonia Sepsis		Septic shock
Neoplasm benign and malignant (incl. cysts and polyps)				Secondary tumours Bladder cancer Myelo-dysplastic alterations Urinary tract cancer Acute leukaemia	Tumour lysis syndrome
Blood and lymphatic system disorders	Myelo-suppression Leukopenia Neutropenia	Neutropenic fever	Thrombo-cytopenia Anaemia		Haemolytic uremic syndrome Disseminated

Primary SOC	**Very common ≥ 1/ 10**	**Common ≥ 1/ 100 - < 1/ 10**	**Uncommon ≥ 1/ 1 000 - < 1/ 100**	**Rare ≥ 1/ 10 000 - < 1/ 1 000**	**Very rare < 1/ 10 000, incl. isolated reports**
					intravascular coagulation
Immune system disorders	Immuno-suppression		Anaphylactoid reactions Hyper-sensitivity reactions		Anaphylactic shock
Endocrine disorders			Ovulation disorders Reduced levels of female sex hormones	Irreversible ovulation disturbances	SIADH (Syndrome of inadequate ADH secretion)
Metabolism and nutrition disorders			Anorexia	Dehydration	Water retention Hypo-natraemia
Psychiatric disorders					Confusion
Nervous system disorders				Dizziness	Convulsions Paraesthesia Taste impairment Hepatic encephalo-

Primary SOC	**Very common ≥ 1/ 10**	**Common ≥ 1/ 100 - < 1/ 10**	**Uncommon ≥ 1/ 1 000 - < 1/ 100**	**Rare ≥ 1/ 10 000 - < 1/ 1 000**	**Very rare < 1/ 10 000, incl. isolated reports**
					pathy
Eye disorders				Blurred vision	Visual impairment Conjunctivitis and eye oedema in conjunction with hyper-sensitivity
Cardiac disorders			Cardio-myopathy Cardiac failure Tachycardia QT prolongation which may result in ventricular tachycardia	Dysrrhythmia Ventricular dysrrhythmia Supra-ventricular dysrrhythmia	Atrial fibrillation Ventricular fibrillation Angina pectoris Myocardial infarction Cardiac arrest Myocarditis Pericarditis
Vascular disorders				Bleeding	Thrombo-embolism Changes in blood pressure
Respiratory					Broncho-

Primary SOC	**Very common ≥ 1/ 10**	**Common ≥ 1/ 100 - < 1/ 10**	**Uncommon ≥ 1/ 1 000 - < 1/ 100**	**Rare ≥ 1/ 10 000 - < 1/ 1 000**	**Very rare < 1/ 10 000, incl. isolated reports**
disorders					spasm Dyspnoea Cough Interstitial pneumonia Pneumonitis Chronic interstitial pulmonary fibrosis Toxic pulmonary oedema Pleural effusion Respiratory failure Acute respiratory distress syndrome (ARDS) Unspecific lung disorders Hypoxia

Primary SOC	**Very common ≥ 1/ 10**	**Common ≥ 1/ 100 - < 1/ 10**	**Uncommon ≥ 1/ 1 000 - < 1/ 100**	**Rare ≥ 1/ 10 000 - < 1/ 1 000**	**Very rare < 1/ 10 000, incl. isolated reports**
					Pulmonary hypertension
Gastro-intestinal disorders	Nausea Vomiting			Diarrhoea Stomatitis Constipation Abdominal pain	Ascites Ulceration Haemorrhagic colitis Acute pancreatitis
Hepatobiliary disorders				Liver function disorders Hepatitis	Veno-occlusive liver disease Hepatomegaly Jaundice Activation of virus hepatitis
Skin and sub-cutaneous tissue disorders	Alopecia		Baldness	Rash Dermatitis Inflammation of skin	Stevens Johnson Syndrome Epidermal necrolysis Severe skin reactions Discolouration of the palms, fingernails,

Primary SOC	**Very common ≥ 1/ 10**	**Common ≥ 1/ 100 - < 1/ 10**	**Uncommon ≥ 1/ 1 000 - < 1/ 100**	**Rare ≥ 1/ 10 000 - < 1/ 1 000**	**Very rare < 1/ 10 000, incl. isolated reports**
					soles Inflammatory itching Erythema in the irradiated field
Musculo-skeletal and connective tissue disorders					Rhabdo-myolysis Cramp
Renal and urinary disorders	Cystitis Haematuria	Haemorrhagic cystitis			Suburethral bleeding Oedema of the bladder wall Interstitial inflammation, fibrosis and sclerosis of bladder Renal failure Renal impairment
Reproductive system and			Impairment of spermato-	Persistent: Oligospermia	

Primary SOC	**Very common ≥ 1/ 10**	**Common ≥ 1/ 100 - < 1/ 10**	**Uncommon ≥ 1/ 1 000 - < 1/ 100**	**Rare ≥ 1/ 10 000 - < 1/ 1 000**	**Very rare < 1/ 10 000, incl. isolated reports**
breast disorders			genesis Amenorrhoea	Azoospermia	
General disorders and admin-istration site conditions	Fever	Chills Asthenic conditions Fatigue Weakness Malaise Mucositis		Chest pain	Headache Pain Multi-organ failure
Investiga-tions			ECG changes Decreased LVEF Increased LDH Increased C-reactive protein	Increase in liver enzymes Increase in: SGOT SGPT gamma-GT ALP Bilirubin	Weight gain Drop in blood pressure Increase in creatinine values
Injury poisoning and procedural compli-cations					Radiation recall dermatitis

Post-marketing reported side effects

The following adverse reactions have been reported in the post-marketing experience.

Primary SOC	**Side effect**
Infections and infestations	Increased risk for and severity of 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.
Neoplasm benign and malignant (incl. cysts and polyps)	Lymphoma (Non-Hodgkin's Lymphoma), sarcomas, renal cell carcinoma, renal pelvis cancer, thyroid cancer, carcinogenic effect in offspring. Additionally, progression of underlying malignancies, including fatal outcomes, have been reported.
Blood and lymphatic system disorders	Pancytopenia, agranulocytosis, granulocytopenia, lymphopenia, haemoglobin decreased.
Immune system disorders	Anaphylactic reaction (including fatal outcomes).
Endocrine disorders	Water intoxication.
Metabolism and nutrition disorders	Blood glucose increased, blood glucose decreased.
Nervous system disorders	Encephalopathy, neurotoxicity has been reported and manifested as reversible posterior leukoencephalopathy syndrome, myelopathy, peripheral neuropathy, polyneuropathy, neuralgia, dysaesthesia, hypoaesthesia, tremor, hypogeusia, parosmia.
Eye disorders	Lacrimation increased.

Primary SOC	**Side effect**
Ear and labyrinth disorders	Deafness, hearing impaired, tinnitus.
Cardiac disorders	Ventricular tachycardia, cardiogenic shock, pericardial effusion (progressing to cardiac tamponade), myocardial haemorrhage, cardiac failure congestive, left ventricular failure, left ventricular dysfunction, bradycardia, palpitations, ejection fraction decreased.
Vascular disorders	Pulmonary embolism, vasculitis, peripheral ischaemia, hypertension, hypotension, flushing, hot flush.
Respiratory disorders	Pulmonary veno-occlusive disease, obliterative bronchiolitis, organising pneumonia, alveolitis allergic, respiratory distress, nasal congestion, nasal discomfort, oropharyngeal pain, rhinorrhoea, sneezing.
Gastro-intestinal disorders	Enterocolitis haemorrhagic, gastrointestinal haemorrhage, colitis, enteritis, cecitis, abdominal discomfort, parotid gland inflammation.
Hepatobiliary disorders	Cholestatic hepatitis, cytolytic hepatitis, cholestasis; hepatotoxicity with hepatic failure, hepatic encephalopathy, blood bilirubin increased, hepatic enzymes increased (aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased).
Skin and sub-cutaneous tissue disorders	Erythema multiforme, palmar-plantar erythrodysesthesia syndrome, toxic skin eruption, urticaria, blister, pruritus, erythema, skin discoloration, nail discoloration, nail disorder, facial swelling, hyperhidrosis.
Musculo-skeletal and connective	Scleroderma, muscle spasms, myalgia, arthralgia.

Primary SOC	**Side effect**
tissue disorders	
Renal and urinary disorders	Renal tubular necrosis, renal tubular disorder, nephropathy toxic, haemorrhagic ureteritis, bladder necrosis, cystitis ulcerative, bladder contracture, nephrogenic diabetes insipidus, atypical urinary bladder epithelial cells, blood creatinine increased, blood urea nitrogen increased.
Pregnancy, puerperium and perinatal conditions	Premature labour.
Reproductive system and breast disorders	Infertility, ovarian failure, ovarian disorder, ovulation disorder, oligomenorrhoea, testicular atrophy, blood oestrogen decreased, blood gonadotropin increased.
Congenital, familial and genetic disorders	Intra-uterine death, foetal malformation, foetal growth retardation, foetal toxicity (including myelosuppression, gastroenteritis).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers

are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 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 (see Section 4.4)
- Patients who received an overdose should be closely monitored for the development of toxicities and haematotoxicity in particular
- No specific antidote for ENDOXAN is known.
- ENDOXAN and its metabolites are dialysable. 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 ENDOXAN 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 ENDOXAN administered was found in the dialysate.
- Overdosage should be managed with supportive measures should it occur. The severity and duration of the myelosuppression depends on the extent of the overdose. Frequent checks of the blood count and monitoring of the patient are necessary. If neutropenia develops, infection prophylaxis must be given and infections must be treated adequately with antibiotics. If thrombocytopenia develops, thrombocyte replacement should be ensured according to need.
- Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with ENDOXAN overdose.

5 PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 26 Cytostatic agents

5.1 Pharmacodynamic properties

Cyclophosphamide is a cytostatic from the group of oxazaphosphorines and is chemically related to nitrogen mustard. Cyclophosphamide is activated by microsomal enzymes in the liver to 4-hydroxycyclophosphamide.

The cytotoxic action of cyclophosphamide is based on an interaction between its alkylating metabolites and DNA. This alkylation results in breaks and linking of DNA strands and DNA-protein cross-links. The cytotoxic action is not specific to the cell cycle.

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

5.2 Pharmacokinetic properties

Absorption

Cyclophosphamide is almost completely absorbed from the gastrointestinal 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.

Distribution

Cyclophosphamide was detected in the cerebrospinal fluid and in breast milk. Cyclophosphamide and its metabolites pass through the placental barrier

Protein Binding

Cyclophosphamide itself does not undergo any significant protein binding. However, the plasma protein binding rate of its metabolites is approximately 50 %.

Biotransformation

Cyclophosphamide is inactive *in vitro* and is activated *in vivo*.

Patients with impaired liver function have a delayed biotransformation of cyclophosphamide. In cases with pathologically decreased cholinesterase activity, there is therefore an increase of the serum half-life.

Elimination

The mean half-life of cyclophosphamide in serum is approximately 7 hours in adults and approximately 4 hours in children. Cyclophosphamide and its metabolites are mainly excreted by the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients:

Tablet:

Calcium hydrogen phosphate dihydrate, gelatine, glycerol 85 %, lactose monohydrate, magnesium stearate, maize starch and talc.

Coating:

Calcium carbonate, carboxymethyl cellulose sodium, colloidal silicon dioxide, montan glycol wax, polyethylene glycol 35000, polysorbate 20, polyvidone 25, sucrose, talc and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

ENDOXAN must be stored at or below 25 °C.

Protect from moisture.

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

6.5 Nature and contents of container

Aluminium foil (20 μm) suitable for heat-sealing with PVC and PVDC-coated PVC-sheet (7 g/m^2 coating).

Transparent PVC/PVDC deep-drawing sheet (200 μm), PVC coated with PVDC 40 g/m^2.

Pack sizes: Blister packs of 50 or 100 tablets.

6.6 Special precautions for disposal and other handling

The handling of ENDOXAN should always be in accordance with the safety precautions used for handling of cytostatic agents.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Baxter Healthcare South Africa (Pty) Ltd

The Campus – Eden Gardens

57 Sloane Street & Cnr Main Rd

Bryanston

2021

Applicant/HCR:	Baxter Healthcare South Africa (Pty) Ltd
Product Name:	Endoxan 50 mg Tablets
	Each tablet contains cyclophosphamide monohydrate equivalent to 50 mg anhydrous cyclophosphamide.

8. REGISTRATION NUMBER

A38/26/0593

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 September 2005

10. DATE OF REVISION OF THE TEXT

14 October 2022