Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Endoxana Injection 1000 mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cyclophosphamide monohydrate equivalent to 1000 mg anhydrous cyclophosphamide.

When reconstituted as directed, the solution contains 20mg cyclophosphamide per ml.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

A white crystalline powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Endoxana is a cytotoxic drug for the treatment of malignant disease in adults. As a single agent, it has successfully produced an objective remission in a wide range of malignant conditions.Endoxana is also frequently used in combination with other cytotoxic drugs, radiotherapy or surgery.

4.2 Posology and method of administration

Endoxana Injection is for intravenous administration.

Endoxana should only be used by clinicians experienced in the use of cancer chemotherapy. Endoxana should only be administered where there are facilities for regular monitoring of clinical, biochemical and haematological parameters before, during, and after administration and under the direction of a specialist oncology service.

Posology

Dosage must be individualized. Doses and duration of treatment and/or treatment intervals depend on the therapeutic indication, the scheme of a combination therapy,

the patient's general state of health and organ function, and the results of laboratory monitoring (in particular, blood cell monitoring).

A guide to the dosage regimens used for most indications is given below.

This treatment should be continued until a clear remission or improvement is seen or be interrupted when the extent of leucopenia becomes unacceptable.

Conventional dose:
80 - 300mg/m^2 daily as a single i.v. dose or daily divided oral doses.
300 - 600mg/m^2 as a single i.v. dose weekly.

High dose:
600 - 1500mg/m^2 as a single i.v. dose or short infusion given at 10 - 20 day intervals. In combination with other cytostatics of similar toxicity, a dose reduction or extension of the therapy-free intervals may be necessary.

Use of colony-stimulating factors may be considered to reduce the risk of myelosuppressive complications and/or help facilitate the delivery of the intended dosing.

During or immediately after the administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity. Therefore, Endoxana should be administered in the morning. See Section 4.4.

To reduce the likelihood of adverse reactions that appear to be administration rate-dependent (e.g., facial swelling, headache, nasal congestion, scalp burning), Endoxana should be injected or infused very slowly.

Patients with Hepatic Impairment

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

Patients with Renal Impairment

Clinically relevant changes in cyclophosphamide pharmacology due to alterations in renal function have not been demonstrated, however for optimal administration of cyclophosphamide in patients with renal insufficiency, the severity of renal impairment has to be considered.

Endoxana 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 Endoxana administration and dialysis should be considered. See Section 4.4.

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.

Children

The Safety and effectiveness of Endoxana has not been established in children.

Method of Administration

Endoxana 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.

For intravenous use, the contents of the vial should be dissolved in physiological saline (0.9% w/v sodium chloride) prior to administration. The pH of an aqueous solution is between 4 and 6.

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.

Endoxana, reconstituted in water, is hypotonic and should not be injected directly. For infusion, Endoxana 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 particulatematter and discoloration prior to administration, whenever solution and container permit.

4.3 Contraindications

Cyclophosphamide is contra-indicated in patients with:

- hypersensitivity to cyclophosphamide or to any of its metabolites.
- acute infections,
- bone-marrow aplasia,
- urinary tract infection
- acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy
- Urinary outflow obstruction.

Endoxana should not be used in the management of non-malignant disease, except for immuno-suppression in life-threatening situations.

Endoxana is contra-indicated during pregnancy.

4.4 Special warnings and 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

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.

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 anaemia.

Severe immunosuppression has lead 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 case of neutropenic fever, anti-microbial therapy should be commenced as advised by the treating centre's Microbiology department guidelines.

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 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 2 days if the counts drop below 3000 cells/microlitre (cells/mm3).
- Platelet count and hemoglobin value should be obtained prior to each administration and at appropriate intervals after administration.

<u>Urinary Tract and Renal Toxicity</u>

Hemorrhagic cystitis, pyelitis, ureteritis, and haematuria have been reported with cyclophosphamide therapy. Bladder ulceration/necrosis, fibrosis/contracture and secondary cancer may develop.

Urotoxicity may mandate interruption of treatment.

Cases of urotoxicity with fatal outcomes have been reported.

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.

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 dieresis 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.

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

Although some instances of cardiac dysfunction have been reported following use of recommended doses of cyclophosphamide, no causal relationship has been established.

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. Haemopericardium has occurred secondary to hemorrhagic myocarditis and myocardial necrosis.

Acute cardiac toxicity has been reported with doses as low as 2.4g/m2 of cyclophosphamide to as high as 26g/m2, usually as a portion of an intensive anti-neoplastic multi-drug regimen or in conjunction with transplantation procedures of less than 2mg/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 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 (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 tumours and their precursors as late sequelae.

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.

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 bladder cancer can be markedly reduced by prevention of hemorrhagic cystitis.

Veno-occlusive Liver Disease

Veno-occlusive liver disease (VOLD) 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 4.5) 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. 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:

– 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.

It is recommended that both women and men should wait at least 6 to 12 months after stopping Cyclophosphamide before attempting to conceive or father a child. See section 4.6.

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.

Fertility, see section 4.6.

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 colour.

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. 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. See section 4.2.

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.

4.5 Interaction with other medicinal products and other forms of interactions

Planned coadministration or sequential administration of other substances or treatments with cyclophosphamide 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

o 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
– 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.

o 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.

o Ondansetron

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

<u>Pharmacodynamic Interactions and Interactions of Unknown Mechanism Affecting the Use of Cyclophosphamide</u>

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

o 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

o Increased cardiotoxicity may result from a combined effect of cyclophosphamide and, for example

– Anthracyclines
– Cytarabine
– Pentostatin
– Radiation therapy of the cardiac region
– Trastuzumab

o 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 GMCSF.

o 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.

o 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

o 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.

o 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.

o 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.

o Tamoxifen

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

Interactions Affecting the Pharmacokinetics and/or Actions of Other Drugs

o Bupropion

Cyclophosphamide metabolism by CYP2B6 may inhibit bupropion metabolism.

o Coumarins

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

o Cyclosporine

Lower serum concentrations of cyclosporine have been observed in patients receiving a combination of cyclophosphamide and cyclosporine than in patients receiving only cyclosporine.

o 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.

o Digoxin, β-acetyldigoxin

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

o 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.

o Verapamil

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Cyclophosphamide crosses the placental barrier. Treatment with cyclophosphamide has a genotoxic effect and may cause foetal damage when administered to pregnant women.

o 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.

o 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.

o 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.

o 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.

o 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.

o 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.

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.

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

In patients receiving ENDOXANA as a single agent, the dose-limiting toxicities are myelosuppression and urotoxicity. Adequate treatment with UROMITEXAN (INN: mesna) or strong hydration can markedly reduce the frequency and severity of bladder toxicity. Other side effects include alopecia, nausea, and vomiting.

The list of adverse reactions to cyclophosphamide in this document is presented in two parts :

4.8.1 Adverse Reactions From Clinical Trials

The list of adverse reactions to cyclophosphamide in this document is based on studies and clinical trials conducted with initial application and are listed by MedDRA System Organ Class (SOC).

System Organ Class (SOC)	Preferred MedDRA Terms
Neoplasms benign, malignant and unspecified (incl cycts and polyps)	Neoplasia Acute leukemia Bladder cancer
Blood and lymphatic system disorders	Reticuloendothelial system disorders Myelosuppression Leukopenia Macrocytosis Haemolytic uraemic syndrome Disseminated intravascular coagulation (DIC)
Endocrine disorders	SIADH
Metabolism and nutrition disorders	Blood glucose changes (increase or decrease) Flud retention Hyponatraemia Water intoxication
Cardiac disorders	Cardiotoxicity Tachycardia Intractable Cardiac failure Arrhythmias
Vascular disorders	Thromboembolism
Respiratory, thoracic and mediastinal disorders	Pneumonitis

System Organ Class (SOC)	Preferred MedDRA Terms
	Interstitial pneumonia Chronic interstitial pulmonary fibrosis[1]
Gastrointestinal disorders	Anorexia Nausea Vomiting Mucosal ulceration Pancreatitis
Hepatobiliary disorders	Hepatic function abnormal Jaundice Hepatic enzymes increased Veno-occlusive disease
Skin and subcutaneous tissue disorders	Alopecia Pigmentation
Renal and urinary disorders	Hematuria Haemorrhagic cystitis Bladder contracture Fibrosis
Reproductive system and breast disorders	Azoospermia Amenorrhoea

[1] including fatal outcomes

4.8.2 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): Myelodysplastic syndrome, Lymphoma (Non-Hodgkin's lymphoma),

Sarcomas, Renal cell carcinoma, Renal pelvis cancer, Ureteric cancer, Thyroid cancer, Treatment related secondary malignancy, Carcinogenic effect in offspring, Tumor lysis syndrome. 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), Anemia; Febrile neutropenia, Lymphopenia Hemoglobin decreased

IMMUNE SYSTEM DISORDERS: Immunosuppression, Anaphylactic shock, Anaphylactic/Anaphylactoid reaction (including fatal outcomes), Hypersensitivity reaction

METABOLISM AND NUTRITION DISORDERS:

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, Left ventricular failure, Left ventricular dysfunction, Cardiomyopathy, Myocarditis, Pericarditis, Carditis, Atrial fibrillation, Supraventricular arrhythmia, Ventricular arrhythmia, Bradycardia, 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, Respiratory failure (including fatal outcomes), Obliterative bronchiolitis, Organizing pneumonia, Alveolitis allergic 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, Colitis, Enteritis, Cecitis, Stomatitis, Diarrhea, Constipation, Abdominal pain, Abdominal discomfort, Parotid gland inflammation

HEPATOBILIARY DISORDERS: Cholestatic hepatitis, Cytolytic hepatitis, Hepatitis, Cholestasis; Hepatotoxicity with Hepatic failure, Hepatic encephalopathy, Ascites, Hepatomegaly, Blood bilirubin 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, 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 ureteritis, Bladder necrosis, Cystitis ulcerative, 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, Oligomenorrhea, Testicular atrophy, 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: Multi-organ 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
Reporting of suspected adverse reactions

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

Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance,
Earlsfort Terrace,
IRL - Dublin 2.
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@hpra.ie

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 cyclophosphamide 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 infection, myelosuppression, or other toxicity, should it occur.

Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with cyclophosphamide overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cyclophosphamide is an antineoplastic agent which has been demonstrated to have a cytostatic effect in many tumour types. The active metabolites of cyclophosphamide are alkylating agents which transfer alkyl groups to DNA during the process of cell division, thus preventing normal synthesis of DNA.

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.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to the information already stated in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Benzyl alcohol increases the degradation of cyclophosphamide.

6.3 Shelf life

Unopened: 3 years.

After reconstitution for intravenous administration:
Chemical and physical in-use stability has been demonstrated (in aqueous, sodium chloride, and glucose solutions) for 48 hours at 2 – 8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton.

After reconstitution store at 2-8°C and protect from light.

6.5 Nature and contents of container

75 ml type I or type III glass vials with butyl rubber closures and plastic and aluminium caps.

Pack size: 1 vial

Vials are packed with or without a protective plastic overwrap. Protective plastic overwrap does not come into contact with the medicinal product and provides additional transport protection, which increases the safety for the medical and pharmaceutical personnel.

6.6 Special precautions for disposal and other handling

For intravenous administration:
Prior to administration the contents of a vial should be dissolved in 50 ml Sodium Chloride 0.9% w/v by introducing the saline into the vial and shaking vigorously until the powder is completely dissolved. Reconstitution results in a clear solution with a pH of between 4 and 6.

For single use only:
Discard any remaining contents.

Endoxana Injection is compatible with the following infusion solutions:
sodium chloride solution, glucose solution, sodium chloride and glucose solution.

General instructions:
If vials are stored above the recommended temperature this can cause degradation of the active ingredient, identifiable by a yellow melted appearance to the vial contents. Vials containing melted material should not be used.

Cyclophosphamide is a cytotoxic agent. The handling and preparation of cyclophosphamide should always be in accordance with current guidelines on safe handling of cytotoxic agents. Protective gloves and appropriate equipment to protect against contact with eyes should be worn when handling the product. The material should not be handled by women who are pregnant or who are breast-feeding.

Adequate care and precautions should be taken in the disposal of empty vials and items (syringes, needles, etc) used in reconstitution and administration.

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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