SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cyclophosphamide Tablets 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Cyclophosphamide monohydrate equivalent to 50 mg anhydrous cyclophosphamide

3. PHARMACEUTICAL FORM

Coated Tablet.
White round biconvex sugar coated tablets with a white core.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Cyclophosphamide Tablets are for oral use.

Cyclophosphamide should only be used by clinicians experienced in the use of cancer chemotherapy. Cyclophosphamide 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).

The dosage regimen used for most indications is 100 – 300 mg daily as a single or divided dose.

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

In combination with other cytostatics of similar toxicity, a dose reduction or extension of the therapy-free intervals may be necessary.

Activation of cyclophosphamide requires hepatic metabolism; therefore, oral and intravenous administrations are preferred.

Use of hematopoiesis stimulating agents (colony-stimulating factors and erythropoiesis stimulating agents) 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, cyclophosphamide should be administered in the morning. See Section 4.4.

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.

Patients with Renal Impairment

In patients with renal impairment, particularly in patients with severe renal impairment, decreased renal excretion may result in increased plasma levels of cyclophosphamide and its metabolites. This may result in increased toxicity and should be considered when determining the dosage in such patients.

Cyclophosphamide and its metabolites are dialyzable, although there may be differences in clearance depending upon the dialysis system being used. In patients requiring dialysis, use of a consistent interval between cyclophosphamide administration and dialysis should be considered. 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

No specific information. Children have received Cyclophosphamide. No adverse reactions specific to this group have been reported.

Method of Administration

Cyclophosphamide Tablets should be swallowed with sufficient fluid without chewing. The tablets are coated and should not be divided before use.

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.

Cyclophosphamide should not be used in the management of non-malignant disease, except for immunosuppression in life-threatening situations.

Cyclophosphamide is contra-indicated during pregnancy. See section 4.4 and 4.6.

4.4 Special warnings and precautions for use

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, antibiotics and/or antimycotics must be given.

Cyclophosphamide should be used with caution, if at all, in patients with severe impairment of bone marrow function and in patients with severe immunosuppression.

Unless essential, cyclophosphamide should not be administered to patients with a leukocyte count below 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 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.

<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.

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 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.

Cyclophosphamide should be used with caution, if at all, in patients with active urinary tract infections.

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.

It is usually necessary to discontinue cyclophosphamide therapy in instances of severe hemorrhagic cystitis.

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.

<u>Cardiotoxicity, Use in Patients with Cardiac Disease</u>

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 a single dose 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.

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.

Both women and men should wait at least 6 to 12 months after stopping Cyclophosphamide before attempting to conceive or father a child.

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.

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 interaction

Planned coadministration or sequential administration of other substances or treatments that could increase the likelihood or severity of toxic effects (by means of pharmacodynamic or pharmacokinetic interactions) requires careful individual assessment of the expected benefit and the risks.

Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention. Patients being treated with cyclophosphamide and agents that reduce its activation should be monitored for a potential reduction of therapeutic effectiveness and the need for dose adjustment.

Interactions Affecting the Pharmacokinetics of Cyclophosphamide and its Metabolites

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

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

- An increase of the concentration of cytotoxic metabolites may occur with:

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

- Ondansetron

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

<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.

- 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 GMCSF.

- Increased nephrotoxicity may result from a combined effect of cyclophosphamide and, for example

  – Amphotericin B
  – Indomethacin: Acute water intoxication has been reported with concomitant use of indomethacin.

- Increase in other toxicities

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

<u>Other interactions</u>

- Alcohol

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

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

- Etanercept

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

- Metronidazole

Acute encephalopathy has been reported in a patient receiving cyclophosphamide and metronidazole. Causal association is unclear.

In an animal study, the combination of cyclophosphamide with metronidazole was associated with increased cyclophosphamide toxicity.

- Tamoxifen

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

Interactions Affecting the Pharmacokinetics and/or Actions of Other Drugs

- Bupropion

Cyclophosphamide metabolism by CYP2B6 may inhibit bupropion metabolism.

- Coumarins

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

- Cyclosporine

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

- Depolarizing muscle relaxants

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

- Digoxin, β-acetyldigoxin

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

- Vaccines

The immunosuppressive effects of cyclophosphamide can be expected to reduce the response to vaccination. Use of live vaccines may lead to vaccine-induced infection.

- Verapamil

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

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

ADR frequency is based upon the following scale: 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), Unknown (adverse reactions reported in the post-marketing experience)

System Organ Class	Preferred term	Frequency
Infections and infestations	Infections[1]	Common
	Pneumonia[2]	Uncommon
	Sepsis[1]	Uncommon
	Septic shock	Not Known
Neoplasms benign, malignant and unspecified (incl cycts and polyps)	Acute leukemia[3]	Rare
	Myelodysplastic syndrome	Rare
	Secondary tumours	Rare
	Bladder cancer	Rare
	Tumour lysis syndrome	Not known
Blood and lymphatic system disorders	Myelosuppression [4]	Very common
	Haemolytic uraemic syndrome	Very common
	Disseminated intravascular coagulation (DIC)	Very rare
	Lymphopenia	Not known
Immune system disorders	Immunosuppression	Very common
	Anaphylactic/Anaphylactoid reaction	Very rare
	Hypersensitivity reaction	Uncommon
Endocrine disorders	SIADH	Rare
Metabolism and nutrition disorders	Anorexia	Uncommon
	Dehydration	Rare
	Hyponatraemia	Very rare
	Fluid retention	Very rare
	Blood glucose changes (increase or decrease)	Not known
Psychiatric disorders	Confusion	Very rare
Nervous system disorders	Dizziness	Rare
	Convulsion	Very rare
	Neurotoxicity[5]	Unknown
	Encephalopathy	Unknown
Eye disorders	Conjunctivitis	Very Rare
	Eye Oedema	Very Rare
	Visual impairment	Rare
	Lacrimation increased	Not known
Ear and labyrinth disorders	Deafness	Not known
	Tinnitus	Not known
Cardiac disorders	Ventricular fibrillation	Not known
	Ventricular tachycardia	Not known
	Cardiogenic shock	Not known
	Pericardial effusion	Not known
	Myocardial infarction	Not known
	Cardiac failure	Not known
	Cardiomyopathy	Not known
	Myocarditis	Not known
	Pericarditis	Not known
	Electrocardiogram QT prolonged	Not known
	Arrhythmias[6]	Not known

System Organ Class	Preferred term	Frequency
Vascular disorders	Flushing	Uncommon
	Pulmonary embolism	Not known
	Venous thrombosis	Not known
	Vasculitis	Not known
	Peripheral ischaemia	Not known
Respiratory, thoracic and mediastinal disorders	Pulmonary veno-occlusive disease	Not known
	Acute respiratory distress syndrome (ARDS)	Not known
	Interstitial Lung Diseases[7]	Not known
	Pulmonary hypertension	Not known
	Pulmonary oedema	Not known
	Bronchospasm	Not known
	Dyspnea	Not known
	Hypoxia	Not known
	Cough	Not known
	Nasal congestion	Not known
	Rhinorrhea	Not known
	Oropharyngeal pain	Not known
Gastrointestinal disorders	Enterocolitis haemorrhagic	Very rare
	Acute pancreatitis	Very rare
	Mucosal ulceration	Very rare
	Stomatitis	Very rare
	Diarrhoea	Very rare
	Vomiting	Very rare
	Constipation	Very rare
	Nausea	Very rare
	Gastrointestinal Haemorrhage	Unknown
	Colitis	Unknown
	Enteritis	Unknown
	Cecitis	Unknown
	Abdominal pain	Unknown
	Parotid gland inflammation	Unknown
Hepatobiliary disorders	Hepatic function abnormal	Common
	Veno-occlusive disorder	Not known
	Hepatitis	Not known
	Cholestasis	Not known
	Hepatotoxicity[8]	Not known
Skin and subcutaneous tissue disorders	Alopecia	Very common
	Rash	Rare
	Dermatitis	Rare
	Discoloration of the palms, fingernails, soles	Rare
	Toxic epidermal necrolysis	Very rare
	Stevens Johnson syndrome	Very rare
	Erythema multiforme	Not known
	Palmar-plantar erythrodysaesthesia	Not known
	Radiation recall dermatitis	Not known
	Erythema in irradiated area	Not known
	Pruritus (including inflammatory itching)	Not known
	Erythema	Not known
	Urticaria	Not known
	Blisters	Not known
	Facial swelling	Not known
	Hyperhidrosis	Not known

System Organ Class	Preferred term	Frequency
Musculoskeletal and connective tissue disorders	Rhabdomyolysis	Not known
	Scleroderma	Not known
	Muscle spasms	Not known
	Myalgia	Not known
	Arthralgia	Not known
Renal and urinary disorders	Cystitis	Very common
	Microhematuria	Very common
	Haemorrhagic cystitis	Common
	Macrohematuria	Common
	Suburethral bleeding	Very rare
	Oedema of the bladder wall	Very rare
	Interstitial inflammation, fibrosis, and sclerosis of bladder	Very rare
	Renal failure	Very rare
	Blood creatinine increased	Very rare
	Renal tubular necrosis	Unknown
	Renal tubular disorder	Unknown
	Nephropathy toxic	Unknown
	Hemorrhagic ureteritis	Unknown
	Cystitis ulcerative	Unknown
	Bladder contracture	Unknown
	Nephrogenic diabetes insipidus	Unknown
	Atypical urinary bladder epithelial cells	Unknown
	Blood urea nitrogen increased	Unknown
Pregnancy, puerperium and perinatal conditions	Premature labour	Not known
Reproductive system and breast disorders	Impairment of spermatogenesis	Common
	Ovulation disorder	Uncommon
	Amenorrhoea[9]	Rare
	Azoospermia[9]	Rare
	Oligospermia[9]	Rare
	Infertility	Unknown
	Ovarian Failure	Unknown
	Oligomenorrhoea,	Unknown
	Testicular atrophy	Unknown
	Blood oestrogen decreased	Unknown
	Blood gonadotrophin increased	Unknown
Congenital, familial and genetic disorders	Intra-uterine death	Not known
	Fetal malformation	Not known
	Fetal growth retardation	Not known
	Fetal toxicity (including myelosuppression/gastroenteritis)	Not known
General disorders and administration site conditions	Fever	Very common
	Asthenia	Common
	Mucosal inflammation	Common
	Chest pain	Rare
	Headache	Very Rare
	Injection/infusion site reactions[10]	Not known
	Multiorgan failure	Not known
	Oedema	Not known
	Influenza-like illness	Not known
	General physical deterioration	Not known

System Organ Class	Preferred term	Frequency
Investigations	Blood lactate hydrogenase increased C-reactive protein increased	Not known Not known

[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, acute promyelocytic leukemia

[4] manifested as Bone marrow failure, Pancytopenia, Neutropaenia, Agranulocytosis, Granulocytopenia,Thrombocytopaenia (complicated by bleeding), Leukopenia, Anaemia

[5] manifested as reversible posterior leukoencephalopathy syndrome, myelopathy, peripheral neuropathy, polyneuropathy,neuralgia, dysesthesia, hypoesthesia, paresthesia, tremor, dysgeusia, hypogeusia,parosmia.

[6] manifested as Atrial fibrillation,Supraventricular arrhythmia ,Ventricular arrhythmia, Bradycardia, Tachycardia,Palpitation

[7] manifested by pulmonary fibrosis, obliterative bronchiolitis, organizing pneumonia, alveolitis allergic, pneumonitis

[8] Hepatic failure, Hepatic encephalopathy, Ascites, Hepatomegaly, Jaundice, Blood bilirubin increased, Hepatic enzymes increased (ASAT, ALAT, ALP, gamma-GT)

[9] persistent

[10] manifested by thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema.

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:

Malta
ADR reporting
Website: www.medicines authority.gov.mt/adrportal

UK
Yellow card scheme
Website: www.mhra.gov.uk/yellowcard

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.

Cyclophophamide and its metabolites are dialysable. 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 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 iv 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. Pre-clinical 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

Tablet:
Maize starch
Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Talc
Magnesium stearate
Gelatine
Glycerol (85%).

Coating:
Sucrose
Titanium dioxide
Calcium carbonate
Talc
Macgrogol 35000
Silica colloidal anhydrous
Povidone
Sodium carboxymethylcellulose
Polysorbate 20
Montan glycol wax.

6.2. Incompatibilities

Not applicable.

6.3. Shelf-Life

36 months.

6.4. Special Precautions for Storage

Do not store above 25°C.
Store in original container.

6.5. Nature and Contents of Container

10 tablets in a PVC/aluminium blister strip and 10 blister strips in a box

6.6 Special precautions for disposal

Cyclophosphamide is a cytotoxic agent. The handling of cyclophosphamide should always be in accordance with current guidelines on safe handling of cytotoxic agents.

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.

The tablets should not be handled by women who are pregnant or who are breast feeding.

7. MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd
Caxton Way
Thetford
Norfolk
IP24 3SE
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00116/0389

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

9 January 2004

10 DATE OF REVISION OF THE TEXT

09/12/2016