# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT
CYCLOXAN

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial of Cyclophosphamide Powder for Solution for Injection or Infusion 500 mg contains 534.50 mg cyclophosphamide monohydrate equivalent to 500 mg cyclophosphamide.
Strength after reconstitution: 20 mg cyclophosphamide (anhydrous)/ml solution (for reconstitution volumes, see 6.6.)

## 3. PHARMACEUTICAL FORM
White crystalline Powder for Solution for Injection or Infusion

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications
Cyclophosphamide may be used alone or in combination with other chemotherapeutic agents, depending on the indication. Cyclophosphamide is indicated in the treatment of:

- Chronic Lymphocytic Leukemia (CLL)
- Acute Lymphocytic Leukemia (ALL)
- As conditioning for a bone marrow transplantation, in the treatment of Acute Lymphoblastic Leukemia, Chronic Myelogenous Leukemia and Acute Myelogenous Leukemia, in combination with whole body irradiation or busulfan.
- Hodgkin's lymphoma, non-Hodgkin’s lymphoma and Multiple Myeloma.
- Metastatic ovarian, and breast, carcinoma,
- Adjuvant treatment of breast carcinoma
- Ewing's sarcoma
- Small cell lung cancer
- Advanced or metastatic neuroblastoma,
- Life-threatening autoimmune diseases: severe progressive forms of lupus nephritis and Wegener's granulomatosis.

### 4.2 Posology and Method of Administration
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 specialist oncology service.

**Posology**
Dosage must be individualised. 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).

In combination with other cytostatics of similar toxicity, a dose reduction or extension of the therapy-free intervals may be necessary.
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.
Prior, during and 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.
**It is within the responsibility of the physician to decide on the use of Cyclophosphamide according to the operative treatment guidelines.**
The doses below can be regarded as general guidelines:

***Hematologic and solid tumours***
**a. For daily treatment:**
3 – 6 mg/kg body weight (= 120 – 240 mg/m2 body surface area), injected intravenously
**b. For intermittent treatment:**
10 – 15 mg/kg body weight (= 400 – 600 mg/m2 body surface area), injected intravenously, with therapy-free intervals of 2 to 5 days.
**c. For high-dose- intermittent treatment:**
20 – 40 mg/kg body weight (= 800 – 1600 mg/m2 body surface area), injected intravenously, with therapy-free intervals of 21 to 28 days.

***As preparation for a bone marrow transplantation***
2 days 60 mg/kg or 4 days 50 mg/kg body weight injected intravenously.
If a busulfan-cyclophosphamide (Bu/Cy) regimen is applied, the first dose of cyclophosphamide must be administered at least 24 hours after the last dose of busulfan.

***Autoimmune diseases***
Per month 500 – 1000 mg/m2 body surface area.

**Patients with Hepatic Impairment**
Severe hepatic impairment may be associated with a decreased activation of cyclophosphamide. This may alter the effectiveness of the cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected.
The dose must be reduced in patients with severe hepatic impairment. A dose reduction of 25 % is recommended in patients with serum bilirubin concentrations of 3.1 – 5 mg/100 ml (= 0.053 – 0.086 mmol/l).

**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. A dose reduction of 50% for a glomerular filtration rate below 10 mL/minute is recommended.

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.

**Paediatric population**

Cyclophosphamide has been administered to children. The safety profile of cyclophosphamide in paediatric patients is similar to that of the adult population

**Dose modification due to myelosuppression**

A leukocyte and platelet count should be regularly performed during treatment with cyclophosphamide. It is recommended to adjust the dose, if required, if signs of myelosuppression become evident.

Please refer to the table below. Urinary sediment should also be checked regularly for the presence of erythrocytes.

| Leukocyte count/µl | Platelet count /µl | Dosage |
|---|---|---|
| > 4000 | > 100 000 | 100% of the planned dose |
| 2500 – 4000 | 50 000 – 100 000 | 50 % of the planned dose |
| < 2500 | < 50 000 | Omit until values normalise or decide individually |

In combination therapy further dose reductions may have to be considered.

***Method of administration***

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

**Precaution to be taken before manipulating or administering the product**

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.

The choice of solvent for reconstituting Cyclophosphamide containing cyclophosphamide depends on the route of administration to be used.

***Infusion:***

If the solution is to be used for IV infusion, Cyclophosphamide (containing cyclophosphamide) is reconstituted by adding sterile water for injection or 0.9% sterile sodium chloride solution.

Reconstituted Cyclophosphamide should be further diluted in 5% dextrose or 0.9% sodium

chloride solution prior to infusion.

***Direct injection:***
If the solution is to be used for direct injection, Cyclophosphamide (containing cyclophosphamide) is reconstituted by adding 0.9% sterile sodium chloride solution.
Please note that only Cyclophosphamide reconstituted in 0.9% sterile sodium chloride solution is suitable for bolus injection.
**Cyclophosphamide (containing cyclophosphamide) reconstituted in water is hypotonic and should not be injected directly.**
For detailed instruction on reconstitution please refer to section 6.6.

**Intravenous use**
Intravenous administration should preferably be conducted as an infusion.
To reduce the likelihood of adverse reactions that appear to be administration rate-dependent (e.g. facial swelling, headache, nasal congestion, scalp burning), cyclophosphamide should be injected or infused very slowly. Duration of the infusion (ranging from 30 minutes to 2 hours) should be appropriate for the volume and type of carrier fluid to be infused.
Before intravenous use, the substance must be completely dissolved.
Drug products for intravenous use must be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

## 4.3 Contraindications

Cyclophosphamide is contra-indicated in patients with:

- hypersensitivity to cyclophosphamide, any of its metabolites
- acute infections
- bone marrow aplasia or bone marrow depression prior to treatment
- urinary tract infection
- acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy
- urinary outflow obstruction
- breastfeeding (see section 4.6)

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

## 4.4 Special warnings and precaution 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 (anaemia, leukopenia,

neutropenia and thrombocytopenia) and significant suppression of immune responses, which may result in severe, sometimes fatal, infections, sepsis and septic shock. 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 occurring during treatment with cyclophosphamide, including neutropenic fever, 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 must be administered with the necessary caution (or not at all) in patients with severe *functional impairment* of *bone marrow* and patients with severe immunosuppression.
Close haematological monitoring is required for all patients during treatment. Haematological parameters must be checked prior to each administration and regularly during treatment. More frequent monitoring may be required if leukocyte counts drop below 3000 cells/microlitre (cells/$mm^3$). Dose adjustment due to myelosuppression is recommended (see section 4.2).
Unless essential, cyclophosphamide should not be administered to patients with a leukocyte count below 2500 cells/microlitre (cells/ $mm^3$) and/or a platelet count below 50,000 cells/microlitre (cells/$mm^3$).
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 normalise, as a rule, after approximately 20 days.
Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop a serious infection.
Severe myelosuppression must be expected particularly in patients pre-treated with and/or receiving concomitant chemotherapy and/or radiation therapy.

**Urinary Tract and Renal Toxicity**

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. Cystectomy may become necessary due to fibrosis, bleeding, or secondary malignancy. Past or concomitant radiation or busulfan treatment may increase the risk for cyclophosphamide-induced hemorrhagic cystitis. Cystitis is, in general, initially a bacterial. Secondary bacterial colonisation may follow.
Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions. See section 4.3. Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity. Adequate treatment with

mesna and/or strong hydration to force diuresis can markedly reduce the frequency and severity of bladder toxicity. It is important to ensure that patients empty the bladder at regular intervals. Haematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Severe hemorrhagic cystitis usually requires a discontinuation of the treatment with cyclophosphamide.
Cyclophosphamide has also been associated with nephrotoxicity, including renal tubular necrosis.
Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone) have been reported in association with cyclophosphamide administration. Fatal outcomes have been reported.

**Cardiotoxicity, Use in Patients with Cardiac Disease**

Myocarditis and myopericarditis, which may be accompanied by significant pericardial effusion and cardiac tamponade, have been reported with cyclophosphamide therapy and have led to severe, sometimes fatal congestive heart failure. Histopathologic examination has primarily shown hemorrhagic myocarditis. Haemopericardium has been reported secondary to hemorrhagic myocarditis and myocardial necrosis. Acute cardiac toxicity has been reported with single doses as low as 20 mg/kg of 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 as a result of treatment with cyclophosphamide may, for example, be increased 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.
Particular caution is required in patients with risk factors for cardiotoxicity and in patients with a 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 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 lymphomas, 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 hemorrhagic cystitis prophylaxis.

**Veno-occlusive Liver Disease**

Veno-occlusive liver disease (VOLD) has been reported in patients receiving cyclophosphamide, mainly in patients receiving a cytoreductive regimen in preparation for bone marrow transplantation in combination with whole-body irradiation, busulfan, or other agents. 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 include pre-existing disturbances of hepatic function, previous radiation therapy of the abdomen, and a low performance score. VOLD incidence has been reported to reduce, if a time interval of at least 24 hours is observed between the last administration of busulfan and the first administration of cyclophosphamide.

**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.
Women should not become pregnant during the treatment and for a period of 12 months following discontinuation of the therapy.
Men should not father a child during the treatment and for a period of 6 months following discontinuation of the therapy.
malformations. This effect should be considered in case of intended fertilisation 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**

Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Men treated with cyclophosphamide should be informed about sperm

preservation prior to treatment.

**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 anti-emetics 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. The area should subsequently be rinsed with physiological saline solution, and the arm or leg should rest.

**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.

**Use in Patients with Hepatic Impairment**
Severe hepatic impairment may be associated with a decreased effect of cyclophosphamide. This may negatively 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. Due to the porphyrogenic effect of Cycolphosphamide patients with acute porphyria should be treated with caution.

**Use in Adrenalectomised Patients**

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

**Use in Patients with Diabetes Mellitus**

Caution is also advised in is patients with diabetes mellitus, since cyclophosphamide may interact with insulin and other hypoglycaemic agents.

**Use in Patients who have recently undergone surgery**

In general, cytostatics (among which agents cyclophosphamide) should not be administered to patients who had a surgery less than 10 days ago.

**4.5 Interaction with other medicinal products and other forms of interaction**

Cyclophosphamide is inactive, but is metabolised in the liver, mainly by CYP2A6, 2B6, 2C9, 2C19 and 3A4, into two active metabolites.

Planned co-administration 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 negatively 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: decreased elimination of cyclophosphamide and prolonged half-life has been reported in patients who received high-dose cyclophosphamide less than 24 hours after high-dose busulfan. Increased incidence of hepatic veno-occlusive disease and mucositis has been reported with concomitant administration (see section 4.2 and 4.4).
- Ciprofloxacin: when administered prior to treatment with cyclophosphamide (used for conditioning prior to bone marrow transplant), ciprofloxacin may cause regression of the underlying disease.
- Chloramphenicol
- Azole-antimycotics (Fluconazole, Itraconazole): Azole-antimycotics are known to inhibit cytochrome P450 enzymes. Increased amounts of toxic degradation products of cyclophosphamide have been reported in combination with Itraconazole.
- CYP2B6 and CYP3A4 inhibitors (Nevirapin, Ritonavir): co-administration may reduce the efficacy of cyclophosphamide
- Prasugrel

- Sulfonamides, e.g. sulfadiazine, sulfamethoxazoel and sulfapyridine
- Thiotepa: a strong inhibition of cyclophosphamide bio activation by thiotepa in high-dose chemotherapy regimens has been reported when thiotepa was administered 1 hour prior to cyclophosphamide.
- Ondansetron: There have been reports of a pharmacokinetic interaction between ondansetron and high-dose cyclophosphamide resulting in decreased cyclophosphamide AUC.
- Grapefruit (fruit or juice), Rifampicin, St. Johns worth: Co-administration with CYP3A4 Inhibitors or Inducers can reduce the efficacy or increase the toxicity of cyclophosphamide.

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

- Allopurinol: an increase of bone marrow suppression was reported
- Azathioprine: increased risk of hepatotoxicity (liver necrosis)
- Chloral hydrate
- Cimetidine
- Disulfiram
- Glyceraldehyde
- 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. Increased incidence of mucositis is reported in combined therapy of cyclophosphamide (CDE) and saquinavir
- Inducers of human hepatic and extra hepatic microsomal enzymes (e.g., cytochrome P450 enzymes): The potential for hepatic and extra hepatic 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, benzodiazepines and corticosteroids.
- Dabrafenib

**Pharmacodynamic Interactions and Interactions of Unknown Mechanism Affecting the Use of Cyclophosphamide**

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

- Increased hematotoxicity and/or immunosuppression may result from a combined effect of cyclophosphamide and, for example
- ACE inhibitors: ACE inhibitors can cause leukopenia.
- Natalizumab
- Paclitaxel: Increased hematotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion.
- Thiazide diuretics (e.g. hydrochlorthiazide): An increase of bone marrow suppression was reported.

- Zidovudine
- Clozapine

- Increased cardiotoxicity may result from a combined effect of cyclophosphamide and, for example
  - Anthracyclines
  - Mitomycin
  - Cytarabine
  - Pentostatin
  - Radiation therapy of the cardiac region or a whole-body irradiation in combination with high doses of cyclophosphamide
  - 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.

**Other interactions**

- Alcohol

A reduced antitumor activity was observed in tumour-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 effects 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 (GVHD).

- Depolarising muscle relaxants

Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity. Prolonged apnoea may occur with concurrent depolarizing muscle relaxants (e.g. succinylcholine, suxamethonium) as a result of a decreased pseudocholinesterase level. If a patient has been treated with cyclophosphamide within 10 days of general anaesthesia, the anaesthesiologist should be alerted.

- Digoxin, β- acetyldigoxin

Impaired absorption of digoxin and β-acetyldigoxin tablets have been reported during a concomitant cytotoxic treatment

- 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

Impaired intestinal absorption of orally administered verapamil has been reported.

- Sulfonylurea derivatives

Blood sugar levels may drop, if cyclophosphamide and sulfonylurea derivatives are used concomitantly.

**4.6 Fertility, pregnancy and lactation**

**Women of childbearing potential**

Girls treated with cyclophosphamide during pre-pubescence generally develop secondary sexual characteristics normally and have regular menses.

Girls treated with cyclophosphamide during pre-pubescence 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).

**Contraception in males and females**

Women should not become pregnant during the treatment and for a period of 12 months following discontinuation of the therapy.

Men should not father a child during the treatment and for a period of 6 months following discontinuation of the therapy.

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

**Pregnancy**

There are very limited data from the use of cyclophosphamide in pregnant women. There are reports of serious multiple congenital aberrations after use during the first trimester.
Animal studies have shown teratogenicity and other reproduction toxicity.
Considering the data from human case reports, animal studies and the mechanism of action of cyclophosphamide, its use during pregnancy, in particular during the first trimester, is not recommended.
In each individual case the potential benefit of the treatment should be weighed against the potential risk for the foetus.

**Breastfeeding**

Cyclophosphamide is excreted into the breast milk and can cause neutropenia, thrombocytopenia, low haemoglobin, and diarrhoea in children. Cyclophosphamide is contraindicated during breastfeeding.

**Fertility**

Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. In women cyclophosphamide may cause transient or permanent amenorrhea, and in boys treated with cyclophosphamide during pre-pubescence, oligospermia or azoospermia. Men treated with cyclophosphamide may develop oligospermia or azoospermia. Prior to treatment of men with cyclophosphamide, they should be informed of the possibility to store and keep viable sperm collected before treatment.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

The frequency of adverse reactions reported in the table below are derived from clinical trials and from post marketing experience and are defined using the following convention: very common (≥1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (< 1/10,000) not known.

| Organ System Class (SOC) | Recommended Med DRA term | Frequency |
|---|---|---|
| Infections and infestations | Infections 1 Pneumonia2 | Common<br>Uncommon |
| | Sepsis1 | Uncommon |

| | | |
|---|---|---|
| Neoplasms, benign and malignant and unspecified (including cysts and polyps) | Acute leukaemia3<br>Myelodysplastic syndrome<br>Secondary malignancies<br>Bladder cancer<br>Ureteric cancer Tumour lysis syndrome<br>Non-Hodgkin's lymphoma<br>Sarcoma<br>Renal cell carcinoma Renal pelvis cancer<br>Thyroid cancer | Rare<br>Rare<br>Rare<br>Rare<br>Rare<br>Very rare<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known |
| Blood and lymphatic system disorders | Myelosuppression4<br>Leukopenia<br>Neutropenia Febrile neutropenia<br>Thrombocytopenia<br>Anaemia<br>Disseminated intravascular coagulation<br>Haemolytic uremic syndrome<br>Agranulocytosis<br>Lymphopenia<br>Haemoglobin decreased | Very common<br>Very common<br>Very common<br>Common<br>Uncommon<br>Uncommon<br>Very rare<br>Very rare<br>Not known<br>Not known<br>Not known |
| Immune system disorders | Immunosuppression<br>Anaphylactic/Anaphylactoid reaction<br>Hypersensitivity reaction Anaphylactic shock | Very common<br>Uncommon<br>Uncommon Very rare |
| Endocrine disorders | SIADH (syndrome of in appropriate antidiuretic hormone secretion) | Rare |
| Metabolism and nutrition disorders | Anorexia Dehydration<br>Hyponatremia<br>Blood glucose increased Blood glucose decreased | Uncommon<br>Rare<br>Very rare<br>Not known<br>Not known |
| Psychiatric disorders | Confusional state | Very rare |
| Nervous system disorders | Peripheral neuropathy<br>Polyneuropathy Neuralgia | Uncommon<br>Uncommon<br>Uncommon |
| | Convulsion Dizziness<br>Dysgeusia<br>Hypogeusia<br>Paresthesia<br>Neurotoxicity5<br>Reversible posterior leukoencephalopathy Syndrome[6]<br>Encephalopathy | Rare Rare<br>Very rare<br>Very rare<br>Very rare<br>Not known<br>Not known<br>Not known |
| Eye disorders | Blurred vision Visual impairment<br>Conjunctivitis<br>Eye oedema 7<br>Lacrimation increased | Rare Rare<br>Very rare<br>Very rare<br>Not known |

| | | |
|---|---|---|
| Ear and labyrinth disorders | Deafness<br>Tinnitus | Uncommon<br>Not known |
| Cardiac disorders | Cardiomyopathy<br>Myocarditis<br>Heart failure<br>Tachycardia<br>Ventricular arrhythmia<br>Supraventricular arrhythmia<br>Ventricular fibrillation<br>Angina<br>Myocardial infarction<br>Pericarditis<br>Atrial fibrillation<br>Ventricular tachycardia<br>Cardiogenic shock<br>Pericardial effusion<br>Bradycardia<br>Palpitations<br>Electrocardiogram QT prolonged | Uncommon<br>Uncommon<br>Uncommon<br>Uncommon<br>Rare<br>Rare Very<br>rare Very<br>rare Very<br>rare Very<br>rare Very<br>rare<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known |
| Vascular disorders | Flushing Haemorrhage<br>Thromboembolism<br>Hypertension<br>Hypotension Pulmonary<br>embolism Venous<br>thrombosis | Uncommon<br>Rare<br>Very rare<br>Very rare<br>Very rare<br>Not known<br>Not known |
| | Vasculitis<br>Peripheral ischemia | Not known<br>Not known |
| Respiratory, thoracic and mediastinal disorders 89 | Acute respiratory distress syndrome (ARDS)<br>Chronic pulmonary interstitial fibrosis<br>Pulmonary oedema<br>Bronchospasm<br>Dyspnoea<br>Hypoxia Cough<br>Nasal congestion<br>Oropharyngeal pain<br>Rhinorhea<br>Sneezing<br>Pulmonary veno-occlusive disease<br>Obliterative bronchiolitis<br>Alveolitis allergic<br>Pneumonitis<br>Pleural effusion | Very rare<br>Very rare<br>Very rare<br>Very rare<br>Very rare<br>Very rare<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known |

| | | |
|---|---|---|
| Gastrointestinal disorders | Mucosal inflammation | Common |
| | Enterocolitis haemorrhagic | Very rare |
| | Acute pancreatitis | Very rare |
| | Ascites | Very rare |
| | Stomatitis | Very rare |
| | Diarrhoea | Very rare |
| | Vomiting | Very rare |
| | Constipation | Very rare |
| | Nausea Abdominal | Very rare |
| | pain | Not known |
| | Parotid gland inflammation | Not known |
| | Gastrointestinal haemorrhage | Not known |
| | Cecitis | Not known |
| | Colitis | Not known |
| | Enteritis | Not known |
| Hepatobiliary disorders | Hepatic function abnormal | Common |
| | Hepatitis | Rare Very |
| | Veno-occlusive liver disease | rare Very |
| | Hepatomegaly | rare Very |
| | Jaundice | rare |
| | Cholestatic hepatitis | Not known |
| | Hepatotoxicity 10 | Not known |
| Skin and subcutaneous tissue disorders | Alopecia | Very common |
| | Rash | Rare |
| | Dermatitis | Rare |
| | Nail discolouration | Rare |
| | Skin discolouration | Rare |
| | Stevens-Johnson syndrome | Very rare |
| | Toxic epidermal necrolysis | Very rare |
| | Radiation erythaema | Very rare |
| | Pruritus (including itching due to inflammation) | Very rare |
| | Erythaema multiforme | Not known |
| | Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) | Not known |
| | Urticaria | Not known |
| | Erythaema Facial swelling | Not known |
| | Hyperhidrosis | Not known |
| Musculoskeletal and connective tissue disorders | Rhabdomyolysis | Very rare |
| | Cramps | Very rare |
| | Scleroderma | Not known |
| | Muscle spasms | Not known |
| | Myalgia | Not known |
| | Arthralgia | Not known |

| | | |
|---|---|---|
| Renal and urinary tract disorders | Cystitis Microhaematuria<br>Haemorrhagic cystitis<br>Macrohematuria Suburethral<br>haemorrhage Bladder wall<br>oedema<br>Bladder fibrosis and sclerosis Renal<br>impairment<br>Blood creatinine increased<br>Renal tubular necrosis Renal<br>tubular disorder Nephropathy<br>toxic Hemorrhagic ureteritis<br>Bladder contracture<br>Nephrogenic diabetes insipidus<br>Atypical urinary bladder epithelial cells | Very common<br>Very common<br>Common<br>Common Very<br>rare Very rare<br>Very rare Very<br>rare Very rare<br>Very rare<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known<br>Not known |
| | Blood urea nitrogen increased | Not known |
| Pregnancy, puerperium and perinatal conditions | Premature labour | Not known |
| Reproductive system and breast disorders | Impairment of spermatogenesis<br>Ovulation disorder (rarely irreversible)<br>Amenorrhea 13<br>Azoospermia/asperima 13<br>Oligospermia 13<br>Infertility Ovarian<br>Failure<br>Oligomenorrhoe<br>Testicular atrophy | Common<br>Uncommon<br>Rare<br>Rare<br>Rare<br>Not known<br>Not known<br>Not known<br>Not known |
| Congenital, familial and genetic disorders | Intra-uterine death<br>Foetal malformation<br>Foetal growth retardation Foetal<br>damage<br>Carcinogenic effect on offspring | Not known<br>Not known<br>Not known<br>Not known<br>Not known |
| General disorders and administrative site conditions | Fever Chills<br>Asthenia<br>Malaise<br>Chest pain<br>Headache<br>Multiorgan failure<br>Injection/infusion site reactions<br>(thrombosis, necrosis, phlebitis,<br>inflammation, pain, swelling, erythaema) | Very common<br>Common<br>Common<br>Common<br>Rare<br>Very rare<br>Very rare<br><br>Very rare |
| Investigations | Blood lactate dehydrogenase increased<br>C-reactive protein increased<br>ECG changes<br>Decreased LVEF<br>Weight gain<br>Lower levels of female sex hormones<br>Blood oestrogen level decreased<br>Blood gonadotropin level increased | Uncommon<br>Uncommon<br>Uncommon<br>Uncommon<br>Very rare<br>Uncommon<br>Not known<br>Not known |

1. An increased risk for and severity of pneumonias (including fatal outcomes), other bacterial, fungal, viral, protozoal, and 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).
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 myelopathy, peripheral neuropathy, polyneuropathy, neuralgia, dysesthesia, hypoesthesia, paresthesia, tremor, dysgeusia, hypogeusia, parosmia.
6. manifested as headache, altered mental functioning, seizures and abnormal vision from blurriness to vision loss
7. Observed in connection with an allergic reaction
8. Including fatal outcomes
9. While the incidence of cyclophosphamide-associated pulmonary toxicity is low, prognosis for affected patients is poor.
10. Hepatic failure, Hepatic encephalopathy, Ascites, Hepatomegaly, Jaundice, Blood bilirubin increased, Hepatic enzymes increased (ASAT, ALAT, ALP, gamma-GT)
11. May progress to baldness
12. Of the palms and heels
13. Persistent

Remark:

Certain complication such as thromboembolisms, disseminated intravascular coagulation, and haemolytic uremic syndrome may occur as a result of the underlying disorders, but the frequency of these complications may increase due to chemotherapy with Cyclophosphamide.

**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 the Pharmacy and Poisons Board- Pharmacovigilance Electronic Reporting System (PvERS); https://pv.pharmacyboardkenya.org.

### 4.9 Overdose

Serious consequences of over dosage include manifestations of dose dependent toxicities such as myelosuppression, urotoxicity, cardiotoxicity (including cardiac failure), veno occlusive hepatic disease, and stomatitis.

Patients who received an overdose should be closely monitored for the development of toxicities, and hematotoxicity in particular.

There is no specific antidote for an over dosage of cyclophosphamide.

Cyclophosphamide and its metabolites are dialyzable. Therefore, rapid haemodialysis is indicated when treating any suicidal or accidental overdose or intoxication.

Over dosage 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 can help to prevent or reduce urotoxic effects in case of cyclophosphamide over dosage.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

**Pharmacotherapeutic group:** Antineoplastic and Immunomodulating Agents; Antineoplastic agents. Alkylating agents. Nitrogen mustard analogues.

**ATC Code:** L01AA01

**Mechanism of action**

It remains to be shown whether the cytostatic effect is entirely dependent on the alkylation of DNA or other mechanisms such as inhibition of chromatin transformation processes or inhibition of DNA polymerases play a role. The metabolite acrolein has no antineoplastic activity, but is responsible for the adverse urotoxic effect.

The immunosuppressive effect of cyclophosphamide is based on the fact that cyclophosphamide has an inhibitory effect on B-cells, CD4 + T-cells and to a lesser extent on CD8 +-T-cells. In addition, it is assumed that cyclophosphamide has an inhibitory effect on the suppressor that regulate the IgG2 class of antibodies.

Cross-resistance, especially with structurally related cytotoxic agents, e.g. ifosfamide, as well as other alkylating agents, cannot be excluded.

### 5.2 Pharmacokinetic Properties

Cyclophosphamide is administered as an inactive prodrug that is activated in the liver.

**Absorption**

Cyclophosphamide is quickly and almost completely absorbed from parenteral sites.

**Distribution**

Less than 20% of cyclophosphamide is bound to plasma proteins. The protein binding of the metabolites of cyclophosphamide is higher but less than 70%. To what extent the active metabolites protein bound, is not known.

Cyclophosphamide is about in the cerebrospinal fluid and the mother's milk. Cyclophosphamide and metabolites can pass through the placenta.

**Metabolism**

Cyclophosphamide is activated in the liver to the active metabolites 4-hydroxy-cyclophosphamide and aldofosfamide (tautomeric form of 4-hydroxy-cyclophosphamide) through phase I metabolism by cytochrome P450 (CYP) enzymes. Different CYP isozymes contribute to the bioactivation of cyclophosphamide, including CYP2A6, 2B6, 2C9, 2C19 and 3A4, 2B6 in which the exhibits highest 4-hydroxylase activity. Detoxification is done mainly through glutathione-S-transferases (GSTA1, GSTP1) and alcohol dehydrogenase (ALDH1, ALDH3). Two to four hours after administration of cyclophosphamide, the plasma concentrations of the active metabolites are maximal, after which a rapid decrease of plasma concentrations takes place.

**Elimination**

The plasma half-life of cyclophosphamide is about 4 to 8 hours in adults and children. The plasma half-lives of the active metabolites are not known.
order kinetics. Compared with conventional cyclophosphamide therapy, there is an increase in inactive metabolites, indicating saturation of activating enzyme systems, but not of the stages of metabolism leading to inactive metabolites. During the course of high-dose cyclophosphamide therapy over several days, there is a decrease in the areas under the plasma concentration-time curve of the parent compound, probably due to auto-induction of microsomal metabolism activity.
Cyclophosphamide and its metabolites are primarily excreted by the kidneys.

**5.3 Preclinical safety data**

***Acute toxicity***

The acute toxicity of cyclophosphamide is relatively low. This was demonstrated in studies on mice, guinea pigs, rabbits and dogs.

***Chronic toxicity***

Chronic administration of toxic doses led to hepatic lesions manifested as fatty degeneration followed by necrosis. The intestinal mucosa was not affected. The threshold for hepatotoxic effects was 100 mg/kg in the rabbit and 10 mg/kg in the dog

***Mutagenicity and carcinogenicity***

The mutagenic effects of cyclophosphamide have been demonstrated in various *in-vitro* and *in-vivo tests*. Chromosome aberrations following administration of cyclophosphamide have also been observed in humans. The carcinogenic effects of cyclophosphamide have been demonstrated in animal studies on rats and mice.

***Teratogenicity***

The *teratogenic effects* of cyclophosphamide have been demonstrated in various animals (mice, rats, rabbits, rhesus monkeys and dogs). Cyclophosphamide can cause skeletal, tissue as well as other malformations.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of Excipients**

None

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf Life**

24 months

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C for the reconstituted solution and for the diluted solution.
From a microbiological point of view, the reconstituted and diluted solution should be used immediately, unless reconstitution has taken place in controlled and validated aseptic conditions. 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°C- 8°C.

**6.4 Special Precautions for Storage**

Do not store above 25°C.

For storage conditions after reconstitution of the medicinal product, see section 6.3

**6.5 Nature and Contents of Container**

Cyclophosphamide, Powder for Solution for Injection or Infusion, is available in the following pack sizes:

White Crystalline Powder in 50 mL clear moulded vial along with 20 mm fluorotec coated chlorobutyl rubber stopper and 20 mm Aluminium flip off seal-Red color button.

Not all pack sizes may be marketed.

Vials are packed with or without a protective plastic overwrap (Onco-Safe). "Onco-Safe" 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 each 100 mg of cyclophosphamide, 5 ml of solvent must be added for reconstitution.

The choice of diluent for reconstituting Cyclophosphamide containing cyclophosphamide depends on the route of administration to be used.

*Direct injection:*

If the solution is to be used for direct injection, Cyclophosphamide (containing cyclophosphamide) is reconstituted by adding 0.9% sterile sodium chloride solution.

*Infusion:*

If the solution is to be used for IV infusion, Cyclophosphamide (containing cyclophosphamide) is reconstituted by adding sterile water for injection or 0.9% sterile sodium chloride solution.

The following quantities of water for injections or sodium chloride 0.9 % are added to the vials containing Cyclophosphamide, Powder for Solution for Injection or Infusion

Vial of 1000 mg: 50 ml

Injecting the solvent into the vial for injection creates an abnormally high pressure, which disappears as soon as the second sterile needle has been inserted in the rubber stop of the vial for injection. The powder easily dissolves when the vial for injection is shaken vigorously to produce a clear solution. If the powder does not immediately dissolve, continue to shake the vial vigorously for up to several minutes until complete dissolution of the powder. The solution must be administered as soon as possible following its reconstitution.

After reconstitution the solution is clear and colourless to light yellow. Please check the vial before further use. Only clear solutions must be used.

Cyclophosphamide, Powder for Solution for Injection or Infusion reconstituted in water for injection has an osmolality of 92 mOsm/kg.

Cyclophosphamide, Powder for Solution for Injection or Infusion reconstituted in 0.9% sodium chloride has an osmolality of 353 mOsm/kg and a pH of 4.6

**<u>Intravenous use</u>**

Intravenous administration should preferably be conducted as an infusion.

*Infusion:*
Reconstituted Cyclophosphamide should be further diluted in 5% dextrose or 0.9% sodium chloride injection prior to infusion.
*Direct injection:*
Please note that only Cyclophosphamide reconstituted in 0.9% sterile sodium chloride solution is suitable for bolus injection.
**Cyclophosphamide (containing cyclophosphamide) reconstituted in water is hypotonic and should not be injected directly.**
The rules and regulations for handling cytostatics in general must be observed when reconstituting or handling Cyclophosphamide. Reconstitution must, to the extent possible, be performed in a *laminar air flow safety* cabinet. The person handling the product must wear a protective mask and protective *gloves*. In case of spills, the area must be thoroughly rinsed with water. If Cyclophosphamide, Powder for Solution for Injection or Infusion is stored (e.g. during transport) at the temperature exceeding the maximum temperature, cyclophosphamide may melt. Vials for injections containing melted cyclophosphamide can be visually recognised. Cyclophosphamide is a white powder. M*elted cyclophosphamide* is a *clear or* yellowish viscous liquid (usually found as droplets in the affected vials.). Vials for injections containing melted cyclophosphamide may no longer be used.

## 7. MARKETING AUTHORISING HOLDER
Zydus Healthcare Limited
CTS No. 460/6, I.B. Patel Road,
Village Pahadi, Goregaon East,
Mumbai - 400063, INDIA.

## 8. MARKETING AUTHORISATION NUMBER(S)
16803

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28th August 2026

## 10. DATE OF REVISION OF THE TEXT
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