# PRODUCT INFORMATION

**CYCLONEX tablets 50 mg**

## 1. NAME OF THE MEDICINE

**Active Ingredient**

Chemical Name: Cyclophosphamide (as monohydrate)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Cyclophosphamide monohydrate is a white to almost white, crystalline powder, which is soluble in water and freely soluble in alcohol. It has a melting point of about 51°C. A 2% solution has a pH of 4 to 6.

In addition, the tablets contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate and Opadry 21F240000 Pink.

## 3. PHARMACEUTICAL FORM

**Cyclophosphamide tablets 50 mg**

Brown to pinkish round convex film coated tablet.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

The proper use of cyclophosphamide requires accurate diagnosis, careful assessment of the anatomic extent of the disease, knowledge of the type and effects of any previous therapy and continued evaluation of the patient's general and haematological status. It is essential that adequate clinical and laboratory facilities be available for proper monitoring of patients during treatment with cyclophosphamide. The clinical course of the disease should be recorded in objective terms before treatment is begun and thereafter at regular intervals. Careful management of patients receiving cyclophosphamide will help achieve maximum benefit with minimum risk.

**Antineoplastic Properties**

Patients with neoplasms that might preferably be treated by surgical and/or irradiation procedures should ordinarily not be treated by chemotherapy alone. The following classification is a guide to the various neoplastic conditions in which benefit may be derived from chemotherapy with cyclophosphamide.

(a) Frequently responsive myeloproliferative and lymphoproliferative disorders: malignant lymphomas (stages III and IV, Peter's Staging System**); multiple myeloma; leukaemias; mycosis fungoides (advanced disease).

**Modified as the International Staging Classification for Hodgkin's Disease in "Report of the Committee on the Staging of Hodgkin's Disease". Cancer Res. 26, 1310, 1966.

*Stage I.* Disease limited to one anatomic region (Stage I) or two contiguous anatomic regions (Stage I) on the same side of the diaphragm.

*Stage II.* Disease in more than two anatomic regions or in two contiguous regions on the same side of the diaphragm.

*Stage III.* Disease on both sides of the diaphragm, but not extending beyond the involvement of the lymph nodes, spleen and/or tonsils.

*Stage IV.* Involvement of the bone marrow, lung parenchyma, pleura, liver, bone, skin, kidneys, gastrointestinal tract, or any tissue or organ in addition to lymph nodes, spleen or tonsils.

All stages are sub classified as A or B to indicate the absence or presence respectively of systemic symptoms.

(b) Frequently responsive solid malignancies: neuroblastoma (patients with disseminated disease); adenocarcinoma of the ovary; retinoblastoma.

(c) Infrequently responsive malignancies: carcinoma of the breast; malignant neoplasm of the lung.

### Immunosuppressive Properties

Cyclophosphamide has been used in the treatment of autoimmune diseases and immunopathies of unspecified type (i.e. Wegener's granulomatosis) when these diseases have been resistant to the conventional first and second line treatment and for the prevention of transplant rejection. Cyclophosphamide can be recommended for use in the treatment of non-malignancies only when in the opinion of the physician the benefits to the patient outweigh the risk of treatment with cyclophosphamide.

## 4.2 DOSAGE AND METHOD OF ADMINISTRATION

### Antineoplastic Therapy

Chemotherapy with cyclophosphamide, as with other drugs used in cancer chemotherapy, is potentially hazardous and fatal complications can occur. It is recommended that it be administered only by physicians aware of the associated risks. Therapy may be aimed at either induction or maintenance of remission.

*Induction Therapy*

The usual initial intravenous loading dose for patients with no haematological deficiency is 40 - 50 mg/kg. This total initial intravenous loading dose usually is given in divided doses over a period of two to five days. Patients with any previous treatment that may have compromised the functional capacity of the bone marrow such as x-ray or cytotoxic drugs and patients with tumour infiltration of the bone marrow, may require reduction of the initial loading dose by one third to one half.

A marked leucopoeniais usually associated with the above doses but recovery usually begins after 7 to 10 days. The white blood cell count should be monitored closely during induction therapy. If initial therapy is given orally, a dose of 1 - 5 mg/kg/day can be administered depending on tolerance by the patient.

*Maintenance Therapy*

It is frequently necessary to maintain chemotherapy in order to suppress or retard neoplastic growth. A variety of schedules have been used:

1. 1 - 5 mg/kg orally daily.

2. 10 - 15 mg/kg intravenous every 7 to 10 days.

3. 3 - 5 mg/kg intravenous twice weekly.

Unless the disease is unusually sensitive to cyclophosphamide it is advisable to give the largest maintenance dose that can be reasonably tolerated by the patient. The total leucocyte count is a good objective guide for regulating the maintenance dose. Ordinarily, a leucopoenia 3,000 to 4,000 cells/mL can be maintained without undue risk of serious infection or other complications.

### Immunosuppressive Therapy

Doses used have been in the order of 1 - 3 mg/kg orally depending upon response and toxicity.

### Impaired Renal Function

Since cyclophosphamide is excreted in the urine, dosage adjustment may be necessary in patients with impaired renal function (see Section 5.2 Pharmacokinetics, Excretion).

## 4.3 CONTRAINDICATIONS

Cyclophosphamide is contraindicated in:

- Patients who have demonstrated a previous hypersensitivity to it.

- The presence of active infections, which may lead to fatal complications as a result of immunosuppression induced by the cytotoxic treatment.

- Patients with evidence of cystitis, acute systemic or urinary infection, urinary outflow obstruction, drug or radiation induced haemorrhagic cystitis.

- Patients with severely depressed bone marrow function, particularly in patients who have been pre-treated with cytotoxic agents and/or radiotherapy.

- The first trimester of pregnancy.
- Cyclophosphamide therapy should not be commenced for 4 to 8 days after major surgery.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Although toxic effects are likely to be related (in frequency and severity) to dose and/or frequency of drug administration, toxicity can occur at all doses. Patients should be fully informed by the attending physician of the risk of toxicity before undergoing cyclophosphamide treatment.

Routine baseline assessment should include a complete blood cell count and hepatic and renal function tests.

The following protective recommendations are given due to the toxic nature of this substance:
- personnel should be trained in good technique for handling;
- pregnant staff should be excluded from working with this drug;
- all items used for administration or cleaning, including gloves, should be placed in high risk, waste disposal bags for high temperature incineration;
- accidental contact with the skin or eyes should be treated immediately by copious lavage with water or sodium bicarbonate solution; medical attention should be sought.

Cyclophosphamide should be given cautiously to patients with any of the following conditions:

1. Leucopoenia
2. Thrombocytopenia
3. Tumour cell infiltration of bone marrow
4. Previous X-ray therapy or radiotherapy
5. Previous therapy with other cytotoxic agents
6. Impaired hepatic function
7. Impaired renal function

Cyclophosphamide should be used with caution in compromised or elderly patients. Patients prone to infection, such as those with a weakened immune system and those with diabetes mellitus, should be closely observed.

Before starting treatment, it is necessary to exclude or correct any obstructions of the efferent urinary tract, cystitis, infections and electrolyte imbalances.

It is ordinarily advisable to inform patients in advance of possible alopecia, a frequent complication of cyclophosphamide therapy. Regrowth of hair can be expected, although occasionally the new hair

may be of different colour or texture. The skin and fingernails may become darker during therapy. Nonspecific dermatitis has been reported to occur with cyclophosphamide.

**Monitoring**

Cyclophosphamide may be safely used in routine therapy if simple precautions are taken to avoid irreversible damage to the bone marrow. Weekly clinical and haematological examinations should be made. Total and differential blood cell counts and estimation of haemoglobin levels are essential. Many patients develop leucopoenia and neutropenia during treatment. If the leucocyte count is less than 3,000/mm³, a count should be undertaken every second day. In some cases, a daily count may be necessary. The lymphocyte and neutrophil counts usually return to normal levels upon completion of drug therapy.

If myelosuppression is evident, red blood cell and platelet counts should be monitored.

Urinary sediment should be checked regularly for the presence of erythrocytes.

## Mutagenic Potential

Patients, male and female, capable of conception should be advised of the mutagenic potential of cyclophosphamide. Adequate methods of contraception appear desirable for such patients receiving cyclophosphamide.

## Oncogenic Potential and Secondary Neoplasia

Cyclophosphamide has been reported to have oncogenic activity in rats and mice. The possibility that it may have oncogenic potential in humans undergoing long term immunosuppressive therapy should be considered (see Section 4.8 Adverse Effects).

## Adrenalectomised Patients

Since cyclophosphamide has been reported to be more toxic in adrenalectomised dogs, adjustment of the doses of both replacement steroids and cyclophosphamide may be necessary for the adrenalectomised patient.

## **Haemorrhagic Cystitis** (see Section 4.8 Adverse Effects)

Sterile haemorrhagic cystitis is a severe adverse reaction that has been reported with cyclophosphamide therapy. To prevent this toxic effect patients should be instructed to increase their fluid intake for a period of 24 hrs before, during and at least 24 hrs after receiving cyclophosphamide therapy. Patients should void frequently for 24 hrs after receiving the drug. Frequent voiding helps prevent the development of cystitis, but when it occurs, it is necessary to interrupt cyclophosphamide therapy.

Urine should be examined regularly for the presence of red cells, which may precede haemorrhagic cystitis. Since this complication may be severe and fatal, the drug should be discontinued in patients who develop this complication. Haematuria usually resolves spontaneously within a few days after cyclophosphamide therapy is discontinued but may persist for several months. In severe cases replacement of blood loss may be required.

The application of electrocautery to telangiectatic areas of the bladder and diversion of urine flow have been successful methods used in treatment of protracted cases. Cryosurgery has also been used (**See also Special Warnings and Precautions for use, Secondary Neoplasia**). Nephrotoxicity including haemorrhage and clot formation in the renal pelvis have been reported.

### Secondary Infection

Since cyclophosphamide therapy has immunosuppressive activity that can potentially lead to serious or fatal infections, the patient should be carefully monitored for any sign/symptom of infection (such as fever, sore throat or unusual bleeding or bruising). Interruption or modification of dosage should be considered for patients who develop bacterial, fungal, protozoal, helminthic or viral infections. This is especially true for patients receiving or who have recently received concomitant steroid therapy since infections appear to be particularly dangerous under these circumstances.

### Haematopoietic System

The patient's haematological status must be carefully monitored throughout each cycle of treatment. Cyclophosphamide-induced leucopoenia/neutropenia are dose-related and can be used as a guide to adjusting the drug dosage. Full recovery from leucopoenia is usually achieved within 28 days from dosing.

### Heart Disorders

Cardiotoxicity has been rarely reported in patients receiving cyclophosphamide. Therefore, monitoring of the cardiac functions is recommended in patients with pre-existing cardiac disturbances or impairments. In addition, special attention is required when using cyclophosphamide in combination with other potentially cardiotoxic drugs (such as anthracyclines and fluorouracil).

### Secondary Tumours

Cytotoxic drugs have been reported associated with an increased risk of development of secondary tumours in humans. Some patients receiving cyclophosphamide have developed secondary malignancies, most frequently urinary bladder, myeloproliferative and lymphoproliferative malignancies. Secondary malignancies have occurred mainly in patients who have been treated with cyclophosphamide for primary haematological malignancies or primary non-malignant diseases in which immune processes are believed to be involved. In some cases, the secondary malignancy was not detected until several years after discontinuing cyclophosphamide therapy.

### **Hyperuricaemia** (see Section 4.5 Interactions with other medicines and other forms of interactions)

As a result of extensive purine catabolism that may follow rapid cell lysis, hyperuricaemia may occur in some patients receiving cyclophosphamide; this effect may be minimized by adequate hydration, alkalinisation of the urine and/or administration of allopurinol. Patients should be monitored for cyclophosphamide toxicity following the administration of allopurinol.

### General

Since cyclophosphamide is converted into its active metabolites primarily within the liver, the drug has to be administered with caution in combination with compounds that induce liver microsomal enzymes (such as barbiturates), such combinations may result in an increased pharmacological effect and increased toxicity of cyclophosphamide.

Cyclophosphamide treatment may be unsafe in patients with acute porphyria since the drug has been shown to be porphyrinogenic in animals.

Caution should be used when treating patients with diabetes mellitus, since cyclophosphamide can interact with insulin and other hypoglycaemic agents.

### Use in Hepatic Impairment

Risk factors for Veno-occlusive disease are prexisting hepatic function disturbance and treatment with hepatotoxic drugs concurrent with high dose chemotherapy, especially when busulfan is used.

### Use in Renal Impairment

Since cyclophosphamide is excreted in the urine, dosage adjustment may be necessary in patients with impaired renal function (see Section 4.2 Dosage and Method of Administration, Impaired Renal Function and Section 5.2 Pharmacokinetics, Excretion).

### Use in the Elderly

Cyclophosphamide should be used with caution in compromised or elderly patients. Patients prone to infection, such as those with a weakened immune system and those with diabetes mellitus, should be closely observed.

### Effects on Laboratory Tests

Studied effects on laboratory tests include

Positive direct antiglobulin (Coombs') test results

Rare cases of hepatic function disturbance include increased laboratory test values for SGPT, SGOT, gamma-GT, alkaline phosphates and bilirubin.

Skin tests for candida, mumps, trichophyton and tuberculin (which may give false-negative results) and the Papanicolaou test (which may give false-positive results).

## 4.5 INTERATIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Cyclophosphamide is often used in combination with other cytotoxic drugs or immunosuppressant agents having similar pharmacological effects. Under these circumstances additive toxicity may be

expected and dose adjustment may be required, especially with regard to bone marrow depression/fostering of infection, gastrointestinal, kidney and heart toxicity.

Mesna (sodium 2-mercaptoethanesulfonate) is a synthetic sulfhydryl compound that can chemically interact with urotoxic metabolites of cyclophosphamide (e.g. acrolein) thought to be principally responsible for drug-induced haematuria and haemorrhagic cystitis. The concomitant administration of mesna not only contributes to the detoxification from these metabolites but also exerts uroprotective activity.

Simultaneous treatment with cyclophosphamide and allopurinol or hydrochlorothiazide increases the risk for bone marrow depression. This is probably due to decreased clearance of active metabolites of cyclophosphamide.

The rate of metabolism and the leucopoenia activity of cyclophosphamide are reportedly increased by chronic administration of high doses of phenobarbitone.

The concomitant administration of corticosteroids, such as prednisone, may also inhibit the activation of cyclophosphamide; this effect has however been reported as temporary since after long-term treatment the rate of activation has been increased.

Barbiturates and other drugs which induce liver microsomal enzymes, such as phenytoin, benzodiazepines and chloral hydrate may result in an increased pharmacological effect and increased toxicity of cyclophosphamide because of increased conversion of the drug to active (alkylating) metabolites.

Conversely, the concurrent use of inhibitors of microsomal enzyme activity in the liver, such as chloramphenicol, sulphaphenazole, chloroquine, imipramine, phenothiazines, potassium iodide and vitamin A may decrease the effects of cyclophosphamide.

Possible interaction between cyclophosphamide and digoxin yielding to cardiac arrhythmias has been reported during combination chemotherapy in a patient with atrial fibrillation previously well controlled with digoxin.

Cyclophosphamide may potentiate anthracycline-induced cardiotoxicity. An increased cardiotoxic effect may occur after radiotherapy of the cardiac region.

Cyclophosphamide treatment, which causes a marked and persistent inhibition of cholinesterase activity, potentiates the effect of succinylcholine chloride. If a patient has been treated with cyclophosphamide within ten days of planned general anaesthesia, the anaesthesiologist should be alerted.

Cyclophosphamide leads to a potentiation of the action of suxamethonium and may lead to prolonged apnoea.

In one report, a patient with multiple myeloma treated with low dose intravenous cyclophosphamide developed acute life-threatening hyponatraemia after receiving concurrent oral indomethacin.

Cyclophosphamide also interacts with anticoagulants and insulin. When other oral hypoglycaemic agents are given with cyclophosphamide, the reduction in blood sugar levels may be potentiated.

Due to its immunosuppressive activity, patients may have a diminished response to any vaccination; administration of activated vaccines may be accompanied by a vaccine-induced infection.

In general, patients receiving cyclophosphamide should refrain from drinking alcohol.

Grapefruit contains a compound that may impair the activation of cyclophosphamide, thereby reducing efficacy. Patients should avoid grapefruit and grapefruit juice.

Laboratory values which can be altered by cyclophosphamide in addition to those mentioned above are the skin tests for candida, mumps, trichophyton and tuberculin (which may give false-negative results) and the Papanicolaou test (which may give false-positive results).

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

Cyclophosphamide interferes with oogenesis and spermatogenesis. The drug may cause sterility in both sexes, depending upon the dose of cyclophosphamide, the duration of the therapy and the state of gonadal function at the time of treatment. Long-term effects include azoospermia, oligospermia and ovarian failure. Libido and sexual capability are usually not affected. Azoospermia may be reversible but recovery is usually slow and often incomplete. Irregular menses and amenorrhoea associated with decreased oestrogen and increased gonadotropin secretion may be permanent in some patients.

**Use in pregnancy** - Pregnancy Category D

Cyclophosphamide crosses the placenta and can cause foetal toxicity when administered to pregnant women. The following abnormalities have been reported in infants born to women treated with the drug during pregnancy: missing fingers and/or toes, cardiac defects and hernias.

Cyclophosphamide should not be used in pregnancy, particularly in early pregnancy unless, in the judgement of the physician, the potential benefits outweigh the possible risks. Women of child-bearing potential should be advised to avoid becoming pregnant and use reliable contraceptive methods during and until about 3 months after discontinuation of the drug.

### Use in lactation

Cyclophosphamide is excreted in breast milk. Breast feeding should be terminated prior to institution of cyclophosphamide therapy.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to the possibility of side effects that might result in circulatory deficiencies e.g. nausea and vomiting, the physician should determine the individual patient's ability to drive or operate machinery.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

### General

Rare instances of anaphylactic reaction have been reported. One case of possible cross-sensitivity with other alkylating agents has been reported.

There are isolated reports of rhinitis, headache, acute pancreatitis and, very rarely (< 0.01%), severe reactions e.g. Stevens Johnson Syndrome and toxic epidermal necrolysis.

Other reactions associated with the use of cyclophosphamide include, dizziness, myxoedema, asthenia/fatigue, diaphoresis, decreased serum cholinesterase concentrations, hypoprothrombinemia, positive direct antiglobulin (Coombs') test results, haemolytic anaemia and recurrent transient blurred vision.

Certain complications which are induced by the underlying disease might occur with an increased frequency during cyclophosphamide therapy. These include thromboembolism, disseminated intravascular coagulation and haemolytic uraemic syndrome.

### Haematopoietic

One of the major (and dose-limiting) toxicities of cyclophosphamide is bone marrow suppression. Leucopoenia and neutropenia (granulocytopenia) are expected to occur following therapeutic doses of the drug and they may be severe. Leucopoenia may occur with or without fever, and carries the risk of secondary and potentially life-threatening infections. Maximum depression of the white cell/neutrophil count occurs between 7 and 14 days following a single large dose, with recovery usually seen in 3 to 4 weeks.

Thrombocytopenia, is less common, with low platelet counts occurring 10 - 15 days after administration of the drug and anaemia may occur. These effects are almost always reversible when therapy is interrupted and white cell count usually returns to pre-treatment levels by 3 weeks from a single large dose administration.

Secondary leukaemias have been reported in patients treated with cyclophosphamide-containing regimens.

More severe myelosuppression is to be expected in patients who have been pretreated with chemotherapy and/or radiotherapy, and in patients with renal impairment.

## Gastrointestinal

Anorexia, nausea (often delayed) and vomiting are common while under cyclophosphamide treatment particularly following large intravenous administration, however, individual susceptibility may vary.

Less frequently, abdominal discomfort or pain, diarrhoea, constipation, haemorrhagic colitis, and mucosal irritation may occur. Rarely, stomatitis, enterocolitis and haemorrhagic colitis have been reported.

## Genitourinary

High doses may result in sterile haemorrhagic cystitis due to metabolites in the urine, the cystitis may be severe and intractable, haemorrhage may occur. When this occurs, treatment should be interrupted (**See Special Warnings and Precautions for use**). The cystitis appears to result from chronic inflammation leading to fibrosis and telangiectasia of the bladder epithelium but secondary bacterial colonisation may follow.

Non-haemorrhagic cystitis and/or fibrosis, sometimes extensive, of the bladder have been reported and atypical epithelial cells may be found in urinary sediment. Cystitis can be minimised by administration of cyclophosphamide in the mornings and by giving ample fluids orally or by infusion to encourage frequent voiding of urine. Alkalinisation of the urine and the administration of diuretics have been recommended.

Haematuria usually resolves spontaneously within a few days if cyclophosphamide therapy is temporarily suspended, but symptoms have been reported to occur up to 6 months after drug discontinuation. It is necessary to discontinue cyclophosphamide therapy in instances of severe haemorrhagic cystitis.

Oedema of the bladder wall, suburethral bleeding, interstitial inflammation with fibrosis and a potential for sclerosis of the bladder wall have been observed.

Nephrotoxicity, including haemorrhagic ureteritis and renal tubular necrosis have also been reported in patients treated with cyclophosphamide. Such lesions usually resolve following cessation of therapy.

Renal lesions, particularly with a history of impaired renal function, are a rare side effect after high doses.

Gonadal suppression, resulting in amenorrhoea and lower levels of female sex hormones or azoospermia or persistent oligospermia, has been reported in a number of patients treated with cyclophosphamide and appears to be related to dosage, duration of therapy and the state of gonadal function at the time of treatment. Cyclophosphamide may cause sterility in both sexes. Long-term complications and toxicity involved with cyclophosphamide therapy include azoospermia or oligospermia and ovarian failure, teratogenic and oncogenic effects. Libido and sexual capability are usually not affected. Irregular menses and amenorrhoea associated with decreased oestrogen and increased gonadotropin secretion may be permanent in some patients.

Cyclophosphamide treatment has been reported to be associated with the development of bladder carcinoma.

## Hepatic

Hepatotoxicity, as evidenced by jaundice and hepatic dysfunction, has been reported.

Rare cases of hepatic function disturbance include increased laboratory test values for SGPT, SGOT, gamma-GT, alkaline phosphates and bilirubin.

Veno-occlusive disease (VOD) has been observed in 15 - 50% of patients receiving high dose cyclophosphamide in combination with busulfan or whole body irradiation during allogenic bone marrow transplantation.

VOD is only rarely observed in patients with aplastic anaemia who are receiving high dose cyclophosphamide alone. Typically, the syndrome develops 1 - 3 weeks after the transplantation and is characterised by sudden weight gain, hepatomegaly, ascites and hyperbilirubinaemia. Hepatoencephalopathy may also develop.

Risk factors for VOD are prexisting hepatic function disturbance and treatment with hepatotoxic drugs concurrent with high dose chemotherapy, especially when busulfan is used.

## Dermatological

Alopecia occurs in approximately 30% of patients within 3 weeks of normal dose regimes with cyclophosphamide and almost all patients who receive massive dose regimes. Regrowth of hair can be expected although occasionally the new hair may be of a different colour or texture.

Skin hyperpigmentation and nail changes (transverse ridging, retarded growth and/or pigmentation of fingernails) may also occur.

Facial flushing and skin rash have also been reported. An erythematous pruritic rash, similar to the palmar-plantar syndrome seen with other antineoplastics, but occurring on the dorsal surfaces of the hands and feet, has been reported.

Non-specific dermatitis has been reported to occur. There are isolated reports of local irritation at the infusion site.

## Respiratory

There have been isolated cases of pneumonitis and interstitial pneumonia extending to chronic interstitial pulmonary fibrosis. The onset of pulmonary toxicity may occur weeks to years after therapy.

## Cardiac Toxicity

Although a few instances of cardiac dysfunction have been reported following cyclophosphamide, no causal relationship has been established. Cardiotoxicity, manifesting as arrhythmias, ECG changes and LVEF (e.g. myocardial infarction) has been observed in some patients receiving high doses of cyclophosphamide ranging from 120 to 270 mg/kg administered over a period of a few days, usually as a part of an intensive antineoplastic multi-drug regimen or in conjunction with transplantation procedures. In a few instances with high doses of cyclophosphamide, severe and sometimes fatal congestive heart failure has occurred within a few days after the first cyclophosphamide dose. Histopathological examination has primarily shown haemorrhagic myocarditis. Deaths have also been reported from diffuse haemorrhagic myocardial necrosis and from a syndrome of acute myopericarditis.

Haemopericardium has occurred secondary to haemorrhagic myocarditis and myocardial necrosis. Pericarditis has been reported independent of haemopericardium.

The cardiotoxic effects of cyclophosphamide may be enhanced by previous radiation of the cardiac region, and adjuvant treatment with anthracyclines. Regular control of electrolytes and caution are advised in patients with pre-existing heart disease.

## Secondary Neoplasia

Secondary malignancies have developed in some patients treated with cyclophosphamide alone or in association with other anti-neoplastic drugs and/or modalities. These malignancies have more frequently been urinary bladder, myeloproliferative and lymphoproliferative malignancies. Secondary malignancies more frequently develop in cyclophosphamide-treated patients with primary myeloproliferative disease or lymphoproliferative malignancies of non-malignant disease in which immune processes are believed to be pathologically involved. In some cases, the secondary malignancy was detected up to several years after cyclophosphamide treatment was discontinued. The secondary urinary bladder malignancies have generally occurred in patients who previously developed haemorrhagic cystitis (See Special Warnings and Precautions for use, Haemorrhagic cystitis).

## Metabolic

Hyperuricaemia, as a component of the so-called ‘rapid tumour lysis syndrome’, may occur (especially in non-Hodgkin’s lymphoma and leukaemia patients). The effect can be minimised by adequate hydration, alkalinisation of the urine and/or administration of allopurinol.

A syndrome of inappropriate antidiuretic hormone secretion (SIADH) has also been reported.
Hyponatraemia associated with weight gain without oedema may result from impaired excretion of water; this event can be particularly severe in cyclophosphamide-treated patients given the common practice to increase fluid intake to prevent chemical cystitis and the formation of uric acid calculi.

## Reproductive System

Cyclophosphamide interferes with oogenesis and spermatogenesis. The drug may cause sterility in both sexes, depending upon the dose of cyclophosphamide, the duration of the therapy and the state

of gonadal function at the time of treatment. Long-term effects include azoospermia, oligospermia and ovarian failure. Libido and sexual capability are usually not affected. Azoospermia may be reversible but recovery is usually slow and often incomplete. Irregular menses and amenorrhoea associated with decreased oestrogen and increased gonadotropin secretion may be permanent in some patients.

### Wound Healing

Cyclophosphamide may interfere with normal wound healing.

### Inappropriate Water Retention

In high doses cyclophosphamide has been reported to cause inappropriate water retention, resulting in hyponatraemia, seizures and death. The effect is directly upon the renal tubule.

Reporting suspected adverse reactions after registration 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 at *http://www.tga.gov.au/reporting-problems*.

## 4.9 OVERDOSE

The most serious consequence of overdosage are mylosupression (particularly granulocytopenia), and haemorrhagic cystitis. Bleeding, possibly severe, may occur from the bladder and gastrointestinal tract.

Profound myelosuppression may require such measures as blood transfusions, antibiotic therapy, colony stimulating factors (G-CSF, GM-CSF) and reverse barrier nursing. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. In all cases, forced alkaline diuresis with copious fluid intake, using diuretics if necessary, should be employed. Patients should be observed for signs of water overload and monitored for electrolyte disturbances. Haemodialysis may be of benefit when traditional measures are ineffective.

Contact the Poisons Information Centre for advice on the management of an overdose by telephoning 131126 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

### Mechanism of action

Alkylating antineoplastic agent/cytostatic alkylating agent.

Cyclophosphamide itself is not an alkylating agent. Cyclophosphamide is converted by a series of reactions in the liver to its active form which interferes with the growth of susceptible neoplasms and to a certain extent, with normal tissue regeneration.

Cyclophosphamide has important immunosuppressive properties.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

Cyclophosphamide is absorbed from the gastrointestinal tract and from parenteral sites.

*Protein Binding:* Cyclophosphamide does not bind to human plasma proteins in appreciable amounts but on single intravenous doses of a 14C-labelled cyclophosphamide, it results in 14 $\pm$ 2.5% and 1.2 $\pm$ 5% of total radioactivity being bound to plasma proteins at plasma cyclophosphamide concentrations of 10 and 200 micromol/mL. Repeated doses increased the amount of radioactivity bound to plasma. Following five doses of 40 mg/kg about 56% of the plasma radioactivity was bound.

### Distribution

The tissue distribution of cyclophosphamide has been examined in cancer patients following intravenous administration. It was found that both unchanged drug and metabolites pass the blood brain barrier. Cerebral tissue contained radioactivity in a concentration range similar to that found in blood.

### Metabolism

Cyclophosphamide is metabolised in the body initially by the mixed function oxidase enzymes of the liver microsomes; several toxic metabolites have been identified.
Peak plasma concentrations of metabolites have been found to be almost proportional to the administered dose, but relatively wide individual variations have been reported. Peak plasma alkylating metabolite levels generally are reached at 2 or 3 hours after administration of the drug. The average plasma alkylating metabolite concentrations at 8 hours after intravenous administration of the drug was about 77% of the peak level in studies in 12 patients without prior drug exposure.

*Half Life:* Intravenously administered cyclophosphamide is reported to have a serum half-life of about 4 hours, however the drug and/or its metabolites may be detected in plasma for up to 72 hours.

### Excretion

In man, a generally higher proportion of the administered dose is excreted in the urine as metabolites. Of three alkylating metabolites found in urine, only one (nornitrogen mustard) has been definitely identified. Recovery of radioactivity after intravenously administered labelled cyclophosphamide ranged from 37% to 82% with 20% to 45% of that recovered attributable to the unchanged drug. The

total urinary excretion of unchanged cyclophosphamide ranged from 3% to 30% of the dose with most cases in the upper half of the range.

### 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**

Refer to Section 4.4 Special Warnings and Precautions for Use, Mutagenic Potential.

**Carcinogenicity**

Refer to Section 4.4 Special Warnings and Precautions for Use, Oncogenic Potential and Secondary Neoplasia and Secondary Tumours, and Section 4.8 Adverse Effects.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Refer to Section 2 – Qualitative and quantitative composition.

### 6.2 INCOMPATIBILITIES

See Section 4.5 – Interactions with other medicines and forms of interactions

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.
The ARTG number is 297901.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C, protect from light.

### 6.5 NATURE AND CONTENTS OF CONTAINER

The tablets are supplied in Al/Al blister packs, containing 50 tablets.

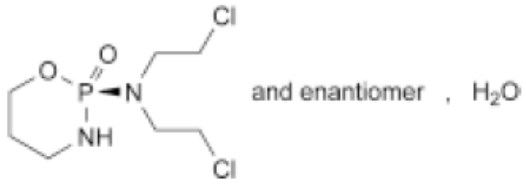
### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

### 6.7 PHYSICOCHEMICAL PROPERTIES

**Chemical structure**

Structural Formula:




Molecular Formula: $C_7H_{15}Cl_2N_2O_2.H_20$
Molecular Weight: 279.1

**CAS number**

CAS Registry Number: 6055-19-2

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4: Prescription Only Medicine

## 8 SPONSOR

Zenex Pharmaceuticals Pty Ltd
Level 6, 141 Flinders Lane
Melbourne, Victoria 3000

## 9 DATE OF FIRST APPROVAL

14 April 2003

## 10 DATE OF REVISION

14 March 2018

Summary table of changes

| Section changed | Summary of new information |
|---|---|
| All references to Trade Name and Sponsor. | Change to Trade Name |
| All | Changes to the formulation and packaging material<br>Change to new TGA format of product information document |