

New Zealand Data Sheet

1 PRODUCT NAME

CYCLONEX 50 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains cyclophosphamide monohydrate equivalent to 50 mg cyclophosphamide

Excipient(s) with known effect: sugars as lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet
Brown to pinkish round convex film coated tablet.

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 Dose and method of administration

Cyclonex 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.

Dose

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.

Special populations

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.

Use in 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

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

Method of administration

Cyclonex 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 contraindicated 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 led 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.

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.

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 diuresis 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.

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 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:

- pre-existing 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 medicines 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.

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
- 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

Other interactions

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

Amenorrhoea, 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, amenorrhoea may be permanent.

Oligomenorrhoea 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 ($\geq 1/10$); Common ($\geq 1/100 - < 1/10$), Uncommon ($\geq 1/1,000 - < 1/100$), Rare ($\geq 1/10,000 - < 1/1,000$), 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 cysts 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 Eye Oedema Visual impairment Lacrimation increased	Very Rare Very Rare Rare Not known
Ear and labyrinth disorders	Deafness Tinnitus	Not known Not known
Cardiac disorders	Ventricular fibrillation Ventricular tachycardia Cardiogenic shock Pericardial effusion Myocardial infarction Cardiac failure Cardiomyopathy Myocarditis Pericarditis Electrocardiogram QT prolonged Arrhythmias ⁶	Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known
Vascular disorders	Flushing Pulmonary embolism Venous thrombosis Vasculitis Peripheral ischaemia	Uncommon Not known Not known Not known Not known
Respiratory, thoracic and mediastinal disorders	Pulmonary veno-occlusive disease Acute respiratory distress syndrome (ARDS) Interstitial Lung Diseases ⁷ Pulmonary hypertension Pulmonary oedema Bronchospasm Dyspnea Hypoxia Cough Nasal congestion Rhinorrhea Oropharyngeal pain	Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known
Gastrointestinal disorders	Enterocolitis haemorrhagic Acute pancreatitis Mucosal ulceration Stomatitis Diarrhoea Vomiting Constipation Nausea Gastrointestinal Haemorrhage Colitis Enteritis Cecitis Abdominal pain Parotid gland inflammation	Very rare Very rare Very rare Very rare Very rare Very rare Very rare Very rare Unknown Unknown Unknown Unknown Unknown Unknown
Hepatobiliary disorders	Hepatic function abnormal Veno-occlusive disorder Hepatitis Cholestasis Hepatotoxicity ⁸	Common Not known Not known Not known Not known
Skin and subcutaneous tissue disorders	Alopecia Rash	Very common Rare

	Dermatitis Discoloration of the palms, fingernails, soles Toxic epidermal necrolysis Stevens Johnson syndrome Erythema multiforme Palmar-plantar erythrodysesthesia Radiation recall dermatitis Erythema in irradiated area Pruritus (including inflammatory itching) Erythema Urticaria Blisters Facial swelling Hyperhidrosis	Rare Rare Very rare Very rare Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known
Musculoskeletal and connective tissue disorders	Rhabdomyolysis Scleroderma Muscle spasms Myalgia Arthralgia	Not known Not known Not known Not known Not known
Renal and urinary disorders	Cystitis Microhematuria Haemorrhagic cystitis Macrohematuria Suburethral bleeding Oedema of the bladder wall Interstitial inflammation, fibrosis, and sclerosis of bladder Renal failure Blood creatinine increased Renal tubular necrosis Renal tubular disorder Nephropathy toxic Hemorrhagic ureteritis Cystitis ulcerative Bladder contracture Nephrogenic diabetes insipidus Atypical urinary bladder epithelial cells Blood urea nitrogen increased	Very common Common Common Very rare Very rare Very rare Very rare Very rare Very rare Very rare Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown
Pregnancy, puerperium and perinatal conditions	Premature labour	Not known
Reproductive system and breast disorders	Impairment of spermatogenesis Ovulation disorder Amenorrhoea ⁹ Azoospermia ⁹ Oligospermia ⁹ Infertility Ovarian Failure Oligomenorrhoea, Testicular atrophy Blood oestrogen decreased Blood gonadotrophin increased	Common Uncommon Rare Rare Rare Unknown Unknown Unknown Unknown Unknown Unknown Unknown
Congenital, familial and genetic disorders	Intra-uterine death Fetal malformation Fetal growth retardation	Not known Not known Not known Not known

	Fetal toxicity (including myelosuppression/gastroenteritis)	
General disorders and administration site conditions	Fever Asthenia Mucosal inflammation Chest pain Headache Injection/infusion site reactions ¹⁰ Multiorgan failure Oedema Influenza-like illness General physical deterioration	Very common Common Common Rare Very Rare Not known Not known Not known Not known Not known
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 leucoencephalopathy 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions

<https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Serious consequences of overdosage include manifestations of dose dependent toxicities such as myelosuppression, urotoxicity, cardiotoxicity (including cardiac failure), veno-occlusive hepatic disease, and stomatitis. See Section 4.4.

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

No specific antidote for cyclophosphamide is known.

Cyclophosphamide and its metabolites are 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, ATC code: L01AA01

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

Absorption

Cyclophosphamide is well absorbed following an oral dose with a mean half-life of 4-8 hours for both oral and parenteral administration.

Distribution

The drug is widely distributed and crosses the blood-brain barrier, the placental barrier and is found in ascites.

Biotransformation

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.

Elimination

The metabolites are excreted renally.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate and Opadry Pink 21F240000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Cyclonex tablets should be stored protected from light, in a dry place, at or below 25°C; the preparation will withstand brief exposure to temperatures up to 30°C, but should be protected from temperatures exceeding this value. Cyclonex tablets should be stored in closed containers.

6.5 Nature and contents of container

The tablets are supplied in Al/PA/AL/PVC blister packs of 50 tablets.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Boucher & Muir (NZ) Ltd t/a Mercury Pharma (NZ)
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

06 April 2021

10 DATE OF REVISION OF TEXT

23 March 2022

Summary table of changes

Section changed	Summary of new information
1	Dosage form updated
2	Qualitative and Quantitative composition made in line with product labels and excipient with known effect added
4.2,6.1 and 6.4	Minor editorial changes
6.5	Material of construction of immediate packaging added
8	Change in sponsor details