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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CYCLOCORD 500 mg

CYCLOCORD 1 g

Powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of **CYCLOCORD 500 mg** contains 534.5 mg cyclophosphamide monohydrate equivalent to 500 mg cyclophosphamide.

Each vial of **CYCLOCORD 1 g** contains 1069.0 mg cyclophosphamide monohydrate equivalent to 1000 mg cyclophosphamide.

Strength after reconstitution: 20 mg cyclophosphamide (anhydrous)/ml solution

Sugar-free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion

A white lyophilised powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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1. Active treatment of all neoplastic diseases of the reticulo-endothelial system e.g. lymphomas, lymphosarcomas, reticulo-sarcomas, Hodgkin's disease, chronic lymphatic leukaemias, multiple myelomas.
2. In combination with other cytostatics for various forms of carcinoma
3. Adjuvant therapy in surgery and/or radiotherapy for cancer
4. Palliation of inoperable malignancies
5. Progressive autoimmune diseases eg. systemic lupus erythematous, Wegener's granulomatosis

It is recommended that cancer surgery is conducted under protection of chemotherapy with **CYCLOCORD** to help prevent acute dissemination of malignant cells during surgery and thus to stop subsequent metastases.

4.2 Posology and method of administration

Posology

CYCLOCORD is to be administered by experienced oncologists only.

Duration of therapy and intervals will depend on the indication, the applied combination chemotherapy schedule, the patient's general state of health, the laboratory parameters and the recovery of blood cell counts. Attention should be paid to adequate hydration as well as to the administration of mesna, but be aware of mesna-related hypersensitivity.

The injection should be given intravenously, although intramuscular, intrapleural or intraperitoneal routes may also be used.

Dosage has to be adjusted to each patient individually. It has been found that the cytotoxic effect largely depends on an effective concentration of **CYCLOCORD** in the tissues. The highest tolerated dosage should therefore be given intravenously.

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The established maximum dosage is 50 mg per kg body mass; in exceptional cases higher single dosages have been given.

Tumour resistance to chemotherapy may develop from insufficient dosage.

1. Active treatment

The individually adjusted dose is given intravenously as rapidly as possible as a bolus. Regular leucocyte counts are necessary. If the leucocyte count does not drop below 2 000 per mm^3, a larger dose can be used. When the leucocytes have recovered, usually after ten to fourteen days, the next dose, if possible, even higher, is given. This form of treatment is continued until remission is clinically complete. Thereafter, massive dosage **CYCLOCORD** therapy should be discontinued and the patient's condition closely observed. In cases of recurrence a second full course of **CYCLOCORD** should be given without delay.

If the malignancy is resistant to **CYCLOCORD**, this will become apparent after three to six weeks treatment. In this event **CYCLOCORD** therapy should be discontinued.

2. In combination therapy

Smaller dosages, depending on the other medicines used.

3. Adjuvant therapy

In surgery: A single high dose (see "Active treatment") should be given ten to 14 days prior to surgery and a full course of **CYCLOCORD** after the operation.

In radiotherapy: Treatment should be given as outlined above, in consultation with the radiotherapist.

4. Palliative therapy (inoperable malignancies)

This should be conducted on the same principles as the active therapy but often a more moderate dosage might be indicated.

In cases of good response, surgical intervention may again become possible.

5. Maintenance therapy

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After an objective remission has been achieved, maintenance therapy should be instituted by prolonging the time interval between injections to two or even four weeks but without reducing the individual dosages. Also, during maintenance therapy, it is necessary to check the patient's leucocyte count at frequent intervals. In patients with bone-marrow lesions, a more moderate dosage regimen is indicated.

Recommendations for dose reduction in patients with myelosuppression

Leucocyte count (µl)	Platelet count (µl)	Dosage
> 4000	> 100 000	100 % of the planned dose
4000 – 2500	100 000 – 50 000	50 % of the planned dose
< 2500	< 50 000	Adjustment until values normalise or specific decision is made

Special populations

Use in patients with hepatic and renal insufficiency

Severe hepatic or renal insufficiency requires a dose reduction. A dose reduction of 25 % for serum bilirubin from 3,1 to 5 mg/100 ml and of 50 % for a glomerular filtration rate below 10 ml/minute is recommended.

CYCLOCORD is dialysable.

Method of administration

For intravenous injection or infusion.

For instructions on reconstitution and dilution of **CYCLOCORD** before administration, see section 6.6.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

4.3 Contraindications

- Hypersensitivity to cyclophosphamide or to any of the other ingredients listed in section 6.1
- Contra-indicated in the first trimester of pregnancy (see section 4.6)
- Lactation
- Severe bone marrow suppression
- Severely impaired bone-marrow function (particularly in patients who have been pre-treated with cytotoxic medicines and/or radiotherapy).
- Inflammation of the bladder (cystitis).
- Urinary outflow obstructions
- Infections

4.4 Special warnings and precautions for use

Anaphylactic Reactions, Interaction with Other Alkylating Medicines

Anaphylactic reactions including those with fatal outcomes have been reported in association with cyclophosphamide as in **CYCLOCORD**. Possible interaction with other alkylating medicines has been reported.

Myelosuppression, Immunosuppression, Infections

Treatment with cyclophosphamide as in **CYCLOCORD** 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 the use of

cyclophosphamide include pneumonias, as well as different 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 decision of the treating medical practitioner. In case of neutropenic fever, antibiotics and/or antimycotics must be prescribed.

Precaution should be applied when considering usefulness of concomitant use of cyclophosphamide 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 as in **CYCLOCORD** 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).

Intensity of 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 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 as in **CYCLOCORD** may not be recommended, or should be interrupted, or the dose reduced, in patients 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

Haemorrhagic cystitis, pyelitis, urethritis, 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. Haemorrhagic 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 development of cyclophosphamide-induced haemorrhagic cystitis. Cystitis is, in general, initially 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 any other signs of

uro/nephrotoxicity. Appropriate treatment with mesna and/or strong hydration with a forced diuresis can markedly reduce the frequency and severity of bladder toxicity. It is important to ensure that the patient empties the bladder at regular intervals. Haematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Severe haemorrhagic cystitis usually requires a discontinuation of the cyclophosphamide treatment.

Cyclophosphamide treatment has also been associated with nephrotoxicity, including renal tubular necrosis. Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) have been reported in association with cyclophosphamide administration. Fatal outcomes have been reported.

Cardiotoxicity, Use in Patients with Cardiac Disease

Myocarditis and myopericarditis accompanied by 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 haemorrhagic myocarditis. Haemopericardium has been developed secondary as a consequence of haemorrhagic 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 with different medicines that included cyclophosphamide, supraventricular dysrhythmias (including atrial fibrillation and flutter) as well as ventricular dysrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported in patients with and without other signs of cardiotoxicity.

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The risk of cyclophosphamide cardiotoxicity may be increased following high doses of cyclophosphamide in patients with advanced age or in patients with a previous exposure to radiation treatment of the cardiac region or concomitant treatment with other cardiotoxic agents (see section 4.5).

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 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. Although the incidence of cyclophosphamide-induced pulmonary toxicity is relatively low, prognosis for affected patients is poor. Late onset of pneumonitis (greater than 6 months after start of cyclophosphamide administration as in **CYCLOCORD**) appears to be associated with a particularly high mortality. Pneumonitis may develop even several years after treatment with cyclophosphamide. Acute pulmonary toxicity has been reported after a single cyclophosphamide dose.

Secondary Malignancies

Treatment with cyclophosphamide as in **CYCLOCORD** is associated with the risk of secondary tumours and their precursors as sequelae.

Increased risk of urinary tract cancer as well as the risk of acute leukaemia caused by Myelodysplastic alterations exist. Other malignancies reported after use of cyclophosphamide or regimens involving cyclophosphamide include lymphomas, thyroid cancer, and sarcomas. In some cases, the secondary 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 (VOLD)

Veno-occlusive liver disease has been reported in patients receiving cyclophosphamide as in **CYCLOCORD**. The most important factor in case of veno-occlusive disease appears to be cytoreductive therapy which is used in preparation for bone marrow transplantation and which includes the combination of cyclophosphamide with whole-body irradiation, busulfan, or other medicines (see section 4.5). After cytoreductive therapy, the clinical syndrome develops in 1 to 2 weeks after transplantation and is characterized by sudden weight gain, painful hepatomegaly, ascites, and hyperbilirubinemia/jaundice. However, gradual development of VOLD has also been reported in patients receiving long-term low-dose immunosuppressive doses of cyclophosphamide.
As a complication of VOLD, hepatorenal syndrome or multiorgan failure may develop.
Fatal outcome of cyclophosphamide-induced 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 (see section 4.2 and 4.5).

Genotoxicity

Cyclophosphamide as in **CYCLOCORD** 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 for a period of 6 months following discontinuation of the therapy.

Animal studies show that exposure of oocytes during follicular development phase may result in a decreased rate of implantations and alter viable pregnancies, and increase the risk of malformations. This effect should be considered when considering fertilisation or pregnancy after discontinuation of cyclophosphamide therapy. The duration of follicular development in humans is not known, but it may be longer than 12 months. Sexually active women and men should use effective methods of contraception during these periods of time (see section 4.6).

Fertility

Cyclophosphamide as in **CYCLOCORD** 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 (see section 4.6).

Impairment of Wound Healing

Cyclophosphamide as in **CYCLOCORD** may interfere with normal wound healing.

Alopecia

Alopecia has been reported, and its incidence increases with increasing doses. Alopecia may progress to baldness. The hair can be expected to grow back after treatment or even during continued drug treatment, though it may be different in texture or colour.

Nausea and vomiting

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Administration of cyclophosphamide as in **CYCLOCORD** 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 nausea and vomiting.

Stomatitis

Administration of cyclophosphamide as in **CYCLOCORD** may cause stomatitis (oral mucositis). Current guidelines on measures for prevention and amelioration of stomatitis should definitely be considered.

Paravenous Administration

The cytostatic effect of cyclophosphamide occurs only 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 locally with the cannula, 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 (see section 4.2).

Use in Patients with Hepatic Impairment

Severe hepatic impairment may inhibit the activation of cyclophosphamide. This may alter the effectiveness of **CYCLOCORD** treatment and should be considered when selecting the dose and estimating response to the medicine.

See section 4.2. Due to the porphyrogenic effect of cyclophosphamide patients with acute porphyria should be treated with caution.

Use in Adrenalectomised Patients

Patients with adrenal insufficiency may require an additional corticoid dose when exposed to stress from toxicity due to treatment with 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 medicines (also see section 4.5).

Use in Patients who have recently undergone surgery

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

4.5 Interaction with other medicines and other forms of interaction

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

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Planned co-administration or sequential administration of other medicines 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 expected risks and the benefit.

Patients receiving such combinations must be monitored closely to permit timely intervention if any symptoms of toxicity appear. Patients being treated with cyclophosphamide and medicines that reduce its activity should be monitored for a potential reduction of therapeutic effectiveness, and, if needed, the dose should be adjusted.

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: decreased clearance of cyclophosphamide and prolonged elimination half-life has been reported in patients who received high-dose cyclophosphamide less than 24 hours after administration of 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: regression of the underlying disease has been reported after administration of ciprofloxacin, when this medicine has been used before the administration of cyclophosphamide (for the correction of the condition prior to bone marrow transplantation)
    - ✓ 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 (Nevirapine, Ritonavir): co-administration may reduce the efficacy of cyclophosphamide
- ✓ Prasugrel
- ✓ Sulfonamides, e.g. sulfadiazine, sulfamethoxazole and sulfapyridine
- ✓ Thiotepa: a strong inhibition of cyclophosphamide bioactivation in case of chemotherapy including high-dose thiotepa, 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

- ✓ Inducers of human hepatic and extrahepatic microsomal enzymes (e.g., cytochrome P450 enzymes): The potential for possible increased activity must be considered in case of prior or planned concomitant treatment with medicines known to induce an activity of hepatic and extrahepatic microsomal enzymes such as rifampicin, phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines and corticosteroids
- ✓ Protease inhibitors: concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites. Use of protease inhibitor-involving treatment 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-involving treatment regimen. Increased incidence of mucositis is reported in combined therapy of cyclophosphamide (CDE) and saquinavir
- ✓ Dabrafenib

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

Concomitant or sequential use of cyclophosphamide and other medicines 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 may cause leukopenia
  - ✓ Natalizumab
  - ✓ Paclitaxel: increased haemotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion

- ✓ Thiazide diuretics (e.g. hydrochlorothiazide): 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 chemotherapy with cytotoxic medicines, including cyclophosphamide, and G-CSF or GM-CSF.
- Increased nephrotoxicity may result from a combined effect of cyclophosphamide and, for example
  - ✓ Amphotericin B
  - ✓ Indomethacin: acute water intoxication has been reported following concomitant use of indomethacin

Other interactions

- Alcohol: A reduced antitumor activity was observed in tumour-bearing animals during ethanol (alcohol) consumption and concomitant 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 concomitant cyclophosphamide and metronidazole. Causal association is unclear. In animal studies, the combination of cyclophosphamide with metronidazole was associated with increased cyclophosphamide toxicity
- Tamoxifen: Concomitant use of chemotherapy and tamoxifen may increase the risk of thromboembolic complications

Interactions Affecting the Pharmacokinetics and/or Actions of Other Medicines

- Bupropion: Cyclophosphamide metabolism by CYP2B6 may inhibit bupropion metabolism
- Warfarin: Both increased and decreased warfarin effects have been reported in patients receiving cyclophosphamide and warfarin.
- Ciclosporin: Lower serum concentrations of ciclosporin have been observed in patients receiving a combination of cyclophosphamide and ciclosporin than in patients receiving only ciclosporin. This interaction may stimulate the development 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 depolarising muscle relaxants

(e.g. succinylcholine, suxamethonium) as a result of a decreased pseudo cholinesterase level. If a patient has been treated with cyclophosphamide within 10 days of general anaesthesia, the anaesthesiologist should be alerted

- Digoxin, β-acetyldigoxin: Cytotoxic treatment is reported to impair absorption of digoxin and β-acetyldigoxin tablets
- Vaccines: Since cyclophosphamide has an immunosuppressive activity, reduced response to vaccines can be expected; vaccine-induced infection is possible when live virus vaccines are administered
- Verapamil: Cytotoxic treatment is reported to impair the intestinal absorption of orally administered verapamil
- Sulfonylurea derivatives: Blood sugar level may drop, if cyclophosphamide and sulfonylurea derivatives are used concomitantly

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women should not become pregnant during treatment. Should they still conceive during treatment, they should seek genetic consultation.

Contraception in males and females

Treatment with **CYCLOCORD** can cause genotype anomalies in men and women.

Pregnancy

In a vital indication during the first trimester of pregnancy a medical consultation regarding termination of pregnancy is absolutely necessary.

After the 1st trimester of pregnancy, if therapy cannot be delayed and the patient wishes to continue with her pregnancy, chemotherapy may be undertaken after informing the patient of the risk of teratogenic effects.

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Breast-feeding

As **CYCLOCORD** passes into breast milk, mothers must not breast-feed during treatment.

Fertility

Men to be treated with **CYCLOCORD** should be informed about sperm preservation before treatment.

4.7 Effects on ability to drive and use machines

Patients may experience undesirable effects during treatment with **CYCLOCORD** (including nausea, vomiting, dizziness, blurred vision, visual impairment) which could affect the ability to drive or use machines. The decision if the patient is allowed to drive or operate machinery should be made by the doctor on an individual basis.

4.8 Undesirable effects

Table 1: Undesirable effects as per System Organ Class

SYSTEM ORGAN CLASS	INCIDENCE	ADVERSE REACTION
Infections and infestations	Frequent	Infections[1]
	Less frequent	Pneumonia[2], sepsis[1]
Neoplasms, benign and malignant and unspecified	Less frequent	Acute leukemia[3], myelodysplastic syndrome, secondary malignancies, bladder cancer, ureteric cancer, tumour lysis syndrome

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(including cysts and polyps)	Frequency unknown	Non-Hodgkin's lymphoma, sarcoma, renal cell carcinoma, renal pelvis cancer, thyroid cancer
Blood and lymphatic system disorders	Frequent	Myelosuppression[4], leukopenia, neutropenia, febrile neutropenia
	Less frequent	Disseminated intravascular coagulation, haemolytic uremic syndrome
	Frequency unknown	Agranulocytosis, lymphopenia, haemoglobin decreased, thrombocytopenia, anaemia, leukocytopenia
Immune system disorders	Frequent	Immunosuppression
	Less frequent	Anaphylactic / Anaphylactoid reaction, hypersensitivity reaction, anaphylactic shock
Endocrine disorders	Less frequent	SIADH (syndrome of inappropriate antidiuretic hormone secretion)
Metabolism and nutrition disorders	Less frequent	Anorexia, dehydration, hyponatraemia
	Frequency unknown	Blood glucose increased, blood glucose decreased
Psychiatric disorders	Less frequent	Confusional state

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Nervous system disorders	Less frequent	Peripheral neuropathy, polyneuropathy, neuralgia, convulsion, dizziness, dysgeusia, hypogeusia, paraesthesia
	Frequency unknown	Neurotoxicity[5], Reversible posterior leuko encephalopathy syndrome[6], encephalopathy
Eye disorders	Less frequent	Blurred vision, visual impairment, conjunctivitis, eye oedema[7]
	Frequency unknown	Lacrimation increased
Ear and labyrinth disorders	Less frequent	Deafness
	Frequency unknown	Tinnitus
Cardiac disorders	Less frequent	Heart failure[8], cardiomyopathy, myocarditis, tachycardia, ventricular dysrhythmia, supraventricular dysrhythmia, ventricular fibrillation, angina, pericarditis, atrial fibrillation
	Frequency unknown	Ventricular tachycardia, cardiogenic shock, pericardial effusion, palpitations, bradycardia, electrocardiogram QT prolonged, myocardial infarction

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Vascular disorders	Less frequent	Flushing, haemorrhage, thromboembolism, hypertension, hypotension
	Frequency unknown	Pulmonary embolism, venous thrombosis, vasculitis, peripheral ischaemia
Respiratory, thoracic and mediastinal disorders[8,9]	Less frequent	Acute respiratory distress syndrome (ARDS), chronic pulmonary interstitial fibrosis, pulmonary oedema, bronchospasm, dyspnoea, hypoxia, cough
	Frequency unknown	Pulmonary veno-occlusive disease, alveolitis allergic, pneumonitis, nasal congestion, oropharyngeal pain, rhinorrhoea, sneezing, obliterative bronchiolitis, pleural effusion
Gastro-intestinal disorders	Frequent	Mucosal inflammation
	Less frequent	Haemorrhagic enterocolitis, acute pancreatitis, ascites, stomatitis, diarrhoea, vomiting, constipation, nausea

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	Frequency unknown	Gastrointestinal haemorrhage, cecitis, colitis, enteritis, abdominal pain, inflammation of parotid salivary glands
Hepato-biliary disorders	Frequent	Hepatic function abnormal
	Less frequent	Hepatitis, veno-occlusive liver disease, hepatomegaly, jaundice
	Frequency unknown	Cholestatic hepatitis, hepatotoxicity[10], increased ALT, AST, gamma-GT, alkaline phosphatase and bilirubin
Skin and subcutaneous tissue disorders	Frequent	Alopecia[11]
	Less frequent	Rash, dermatitis, nail discolouration, skin discolouration[12], Stevens-Johnson syndrome, toxic epidermal necrolysis, radiation erythema, pruritus (including inflammatory itching)
	Frequency unknown	Erythema multiforme, palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome), urticaria, erythema, facial swelling, hyperhidrosis
Musculo-skeletal and connective tissue disorders	Less frequent	Rhabdomyolysis, cramps
	Frequency unknown	Scleroderma, muscle spasms, myalgia, arthralgia

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Renal and urinary tract disorders	Frequent	Cystitis, microhaematuria, haemorrhagic cystitis, macrohematuria
	Less frequent	Sub urethral haemorrhage, bladder wall oedema, bladder fibrosis and sclerosis, renal impairment, blood creatinine increased, renal tubular necrosis.
	Frequency unknown	Renal tubular disorder, nephropathy toxic, haemorrhagic urethritis, bladder contracture, nephrogenic diabetes insipidus, atypical urinary bladder epithelial cells, blood urea nitrogen increased
Pregnancy, puerperium and perinatal conditions	Frequency unknown	Premature labour
Reproductive system and breast disorders	Frequent	Impairment of spermatogenesis
	Less frequent	Ovulation disorder (rarely irreversible), amenorrhea[13], azoospermia/asperima[13], oligospermia[13]
	Frequency unknown	Infertility, ovarian failure, oligomenorrhea, testicular atrophy

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Congenital, familial and genetic disorders	Frequency unknown	Intra-uterine death, foetal malformation, foetal growth retardation, foetal toxicity, carcinogenic effect on offspring
General disorders and administrative site conditions	Frequent	Fever, chills, asthenia, malaise
	Less frequent	Chest pain, headache, pain, multiorgan failure, injection/infusion site reactions (thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema)
Investigations	Less frequent	Blood lactate dehydrogenase increased, C-reactive protein increased, ECG changes, decreased left ventricle ejection fraction (LVEF), lower levels of female sex hormones, weight gain
	Frequency unknown	Blood estrogen level decreased, Blood gonadotropin level increased

[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, Neutropenia, Agranulocytosis, Granulocytopenia, Thrombocytopenia (complicated by bleeding), Leukopenia, Anaemia

[5]manifested as myelopathy, peripheral neuropathy, polyneuropathy,neuralgia, dysaesthesia, hypoesthesia, paraesthesia, 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

Certain complications 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 **CYCLOCORD**.

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 to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Since no specific antidote for **CYCLOCORD** is known, great caution is advised each time it is used.

CYCLOCORD can be dialysed, therefore, rapid haemodialysis is indicated when treating any suicidal or accidental overdose or intoxication.

In the case of overdose, myelosuppression, mostly leukocytopenia, is to be expected, among other reactions. The severity and duration of the myelosuppression depends on the extent of the overdose. Frequent checks of the blood count and monitoring of the patient are necessary. If neutropenia develops, infection prophylaxis must be given and infections must be treated adequately with antibiotics. If thrombocytopenia develops, thrombocyte replacement should be ensured according to need. It is essential that cystitis prophylaxis with mesna be undertaken to avoid any urotoxic effects.

Remark: If a **CYCLOCORD** solution is inadvertently administered by paravenous injection, there is usually no danger of cytostatic tissue damage since such damage is not expected before **CYCLOCORD** has been bioactivated in the liver. If paravasation should occur, nevertheless stop the infusion immediately and aspirate the paravasate with the cannula in place, irrigate the area with saline solution and immobilise the extremity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

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

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ATC code: L01AA01

Cyclophosphamide has been demonstrated to have a cytostatic effect in many tumour types.

Cyclophosphamide engages probably to the S-or G2-phase of the cell cycle.

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.

Following high-dose IV administration within the framework of allogeneic bone marrow transplantation, the plasma concentration of pure cyclophosphamide follows linear first- 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.

6. PHARMACEUTICAL PARTICULARS

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6.1 List of excipients

Mannitol (E421)

Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

2 years

Chemical and physical in-use stability of the reconstituted solution (concentration 20

mg/ml) & diluted solution (concentration 2 mg/ml) has been demonstrated for 48

hours at 2 °C – 8 °C.

From a microbiological point of view, the medicine should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at

2 °C – 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

For single use only.

Any unused solution should be discarded.

Keep out of reach of children.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 ºC).

For storage conditions after reconstitution/dilution of **CYCLOCORD**, see section 6.3.

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6.5 Nature and contents of container

CYCLOCORD 500 mg: 30 ml clear moulded glass vial, grey rubber stopper and plain red flip-off seal.

CYCLOCORD 1 g: 50 ml clear moulded glass vial, grey rubber stopper and plain mist grey flip-off seal.

Pack size: 1 vial per carton

6.6 Special precautions for disposal and other handling

General precautions

If vials are stored at above the recommended temperature, the active substance cyclophosphamide may melt.

Vials containing melted cyclophosphamide can be visually recognised. Cyclophosphamide is a white powder.

Melted cyclophosphamide is a clear or yellowish viscous liquid (usually found as droplets in the affected vials.).

Vials with melted contents should not be used.

Cyclophosphamide is a cytostatic agent. Therefore, the preparation and handling of **CYCLOCORD** should always be in accordance with safety precautions for handling of cytotoxic agents.

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

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.

During the injection of the solvent into the vial an abnormally high pressure is created which disappears when a second sterile needle is inserted through the rubber stopper of the vial. The powder dissolves easily when the vial is shaken well to make a clear solution. If the powder does not dissolve immediately, it is recommended to allow the solution to stand for a few minutes.

The solution is administered as soon as possible after preparation.

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Powder for solution for injection/infusion

For each 100 mg of cyclophosphamide, 5 ml of solvent must be added for reconstitution.

For direct intravenous injection

Reconstitute cyclophosphamide only with 9 mg/ml (0.9 %) sodium chloride solution for injection, using the volumes listed in Table 2 below. Gently swirl the vial around the medicine completely resolve. Do not use sterile water for injection as this will result in a hypotonic solution that should not be injected directly.

Table 2: Reconstitution for direct intravenous injection

Strength	Volume of 9 mg/ml (0.9 %) Sodium Chloride	Cyclophosphamide concentration
500 mg	25 ml	20 mg/ml
1000 mg	50 ml	

For intravenous infusion

Reconstitute cyclophosphamide using 9 mg/ml (0.9 %) sodium chloride solution for injection or sterile water for injection with the volume of solvent listed below in Table 3. Add the solvent to the vial and swirl gently to dissolve the medicine completely.

Table 3: Reconstitution in preparation for intravenous infusion

Strength	Volume of solvent	Cyclophosphamide concentration
500 mg	25 ml	20 mg/ml

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1000 mg	50 ml	

*Dilution of reconstituted **CYCLOCORD***

Further dilute the reconstituted cyclophosphamide solution to a minimum concentration of 2 mg per ml with one of the following solvents:

- 50 mg/ml (5 %) dextrose solution for injection
- 9 mg/ml (0.9 %) sodium chloride Injection

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Limited

Building 2, Tuscany Office Park

6 Coombe Place

Rivonia

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

CYCLOCORD 500 mg: 56/26/0922

CYCLOCORD 1 g: 56/26/0923

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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09 May 2023

10. DATE OF REVISION OF THE TEXT

09 May 2023