

Applicant/HCR: Accord Healthcare (Pty) Ltd
Product name: Cyclocord 500 mg / 1 g
Strength: 500 mg / 1 g vial (Powder for solution for injection/infusion)

Initial submission: 11/10/2021 (0000)

Response to P&A query as per SAHPRA email dated 09/09/2022: submitted 19/09/2022 (0003)

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FINAL APPROVED PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

CYCLOCORD 500 mg

CYCLOCORD 1 g

Powder for solution for injection/infusion

Cyclophosphamide

Sugar-free

Read all of this leaflet carefully before you are given CYCLOCORD

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

What is in this leaflet

1. What **CYCLOCORD** is and what it is used for
2. What you need to know before you are given **CYCLOCORD**
3. How **CYCLOCORD** is given
4. Possible side effects
5. How to store **CYCLOCORD**
6. Contents of the pack and other information

1. What CYCLOCORD is and what it is used for

CYCLOCORD contains the active substance cyclophosphamide. Cyclophosphamide is a cytotoxic medicine or anti-cancer medicine. It works by killing cancer cells, this is sometimes called 'chemotherapy'.

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Your doctor has prescribed **CYCLOCORD** alone or in combination with other medicines to treat the following:

- certain types of cancer of the white blood cells (acute lymphocytic leukaemia, chronic lymphocytic leukaemia)
- different forms of lymphomas that affect the immune system (Hodgkin's disease, non-Hodgkin's lymphoma and multiple myeloma)
- ovarian cancer and breast cancer
- small cell lung cancer
- in the treatment of advanced or metastatic tumour of the central nervous system (neuroblastoma)

CYCLOCORD may be used in preparation for bone marrow transplantation to treat certain types of cancer of the white blood cells (acute lymphoblastic leukaemia, chronic myeloid leukaemia and acute myeloid leukaemia).

Occasionally, doctors may prescribe **CYCLOCORD** for other conditions not related to cancer:

- Life threatening autoimmune diseases: severe progressive forms of lupus nephritis (inflammation of the kidney caused by a disease of the immune system) and Wegener's granulomatosis (a rare form of vasculitis).

2. What you need to know before you are given CYCLOCORD

CYCLOCORD should not be given to you:

- if you are allergic to cyclophosphamide or to any of the other ingredients listed in section 6.1
- if you currently have any infection
- if you have severe bone marrow disorder (in particular after chemotherapy or radiation therapy).

You will have blood tests to check how well your bone marrow is working

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- if you have urinary tract infection, which can be recognised as pain when passing urine (cystitis)
- if you have ever had kidney or bladder problems as a result of previous chemotherapy or radiotherapy
- if you have a condition which decreases your ability to urinate (urinary outflow obstruction)
- if you are pregnant (first trimester pregnancy)
- if you are breast-feeding
- if you have other conditions not related to cancer, except life limiting immune disorders

Warnings and precautions

Tell your doctor or health care provider before being given CYCLOCORD if you have:

- low blood cell counts
- severe infections
- liver or kidney problems. Your doctor will check how well your liver and kidneys are working by doing a blood test
- had your adrenal glands removed
- or already having, or have recently had, radiotherapy or chemotherapy
- heart problems or have had radiotherapy in the area of your heart
- diabetes
- poor general health or are frail
- are elderly
- had surgery less than 10 days ago

Take special care with CYCLOCORD:

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- Potentially life-threatening allergic reactions (anaphylactic reaction) may occur during treatment with cyclophosphamide
- **CYCLOCORD** can have effects on your blood and immune system
- Blood cells are made in your bone marrow. Three different types of blood cell are made:
 - ✓ red blood cells, which carry oxygen around your body
 - ✓ white blood cells, which fight infection
 - ✓ platelets, which help your blood to clot
- After receiving **CYCLOCORD**, your blood count of the three types of cells will drop. This is an unavoidable side effect of **CYCLOCORD**. Your blood count will reach its lowest level about 5 to 10 days after you start receiving **CYCLOCORD** and will stay low until a few days after you finish the course of treatment. Most people recover to a normal blood count within 21 to 28 days. If you have had a lot of chemotherapy in the past, it may take a little longer to return to normal.
- You may be more likely to get infections when your blood count drops. Try to avoid close contact with people who have coughs, colds and other infections. Your doctor will treat you with appropriate medicine if they think you have, or are at risk of an infection
- Your doctor will check that the number of red blood cells, white blood cells and platelets is high enough before and during your treatment with **CYCLOCORD**. They may need to reduce the amount of medicine you are given or delay your next dose.
- **CYCLOCORD** can affect normal wound healing. Keep any cuts clean and dry and check that they are healing normally. It is important to keep your gums healthy, as mouth ulcers and infections can occur. Ask your doctor about it if you are unsure.
- **CYCLOCORD** can damage the lining of your bladder, causing bleeding into your urine and pain on urination. Your doctor knows this can happen and, if necessary, he or she will give you a medicine

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called Mesna which will protect your bladder.

- Mesna can either be given to you as a short injection, or mixed into the drip solution with your **CYCLOCORD** treatment, or as tablets.
- Most people being given **CYCLOCORD** with Mesna do not develop any problems with their bladder, but your doctor may want to test your urine for the presence of blood using a 'dipstick' or microscope. If you notice that you have blood in your urine, you must tell your doctor straight away
- Cancer medicines and radiation therapy can increase the risk of you developing other cancers; this can be a number of years after your treatment has stopped. **CYCLOCORD** has an increased risk of causing cancer in the area of your bladder.
- **CYCLOCORD** can cause damage to your heart or affect the rhythm of its beating. This increases with higher doses of cyclophosphamide, if you are being treated with radiation or other chemotherapy medicines or if you are elderly. Your doctor will monitor your heart closely during treatment.
- **CYCLOCORD** can cause lung problems such as inflammation or scarring in your lungs. This can occur more than six months after your treatment. If you start having difficulty breathing, tell your doctor straight away.
- **CYCLOCORD** can have life threatening effects on your liver. If you have sudden weight gain, liver pain and yellowing of the skin or whites of the eyes (jaundice) tell your doctor straight away.
- Hair thinning or baldness can occur. Your hair should grow back normally though it may be different in texture or colour.
- **CYCLOCORD** can make you feel sick or be sick. This can last for about 24 hours after taking cyclophosphamide. You may need to be given medicines to stop feeling or being sick. Ask your doctor about this.

If any of these apply to you, your doctor may want to change your treatment or give you special

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advice.

Other medicines and CYCLOCORD

Always tell your healthcare provider if you are taking any other medicine.

(This includes complementary or traditional medicines.)

The following medicines may decrease the effect of cyclophosphamide:

- aprepitant, ondansetron (used to prevent being sick)
- bupropion (an anti-depressant)
- busulfan, thiotepa (used to treat cancer)
- ciprofloxacin, chloramphenicol, sulphonamides such as sulfadiazine, sulfasalazine, sulfamethoxazole
- fluconazole, itraconazole (used to treat fungal infections)
- prasugrel (used to prevent blood clots)

The following medicines may increase the effect of cyclophosphamide:

- allopurinol (used to treat gout)
- azathioprine (used to reduce the activity of the immune system),
- chloral hydrate (used to treat insomnia),
- cimetidine (used to reduce stomach acid),
- disulfiram (used to treat alcoholism),
- glycerinaldehyde (used to treat warts)
- dabrafenib (anti-cancer drug)
- medicines that increase liver enzymes such as:
 - ✓ rifampicin (used to treat bacterial infections),

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- ✓ phenobarbital, carbamazepine, phenytoin (used to treat epilepsy),
- ✓ St. John's wort (a herbal remedy for mild depression)
- ✓ corticosteroids (used to treat inflammation),

*Medicines that can increase the toxic effects of **CYCLOCORD** on your blood cells and immunity*

- angiotensin-converting enzyme (ACE) inhibitors, thiazide diuretics such as hydrochlorothiazide or chlortalidone (used to treat high blood pressure or water retention)
- natalizumab (used to treat multiple sclerosis),
- paclitaxel (used to treat cancer),
- zidovudine (used to treat viruses)
- clozapine (used to treat symptoms of some psychiatric disorders)

*Medicines that can increase the toxic effects of **CYCLOCORD** on your heart*

- anthracyclines such as bleomycin, doxorubicin, epirubicin, mitomycin (used to treat cancer)
- cytarabine, pentostatin, trastuzumab (used to treat cancer),
- radiation in the area of your heart

*Medicines that can increase the toxic effects of **CYCLOCORD** on your lungs*

- amiodarone (used to treat irregular heart beat),
- G-CSF, GM-CSF hormones (used to increase white blood cell numbers after chemotherapy).

*Medicines that can affect or be affected by **CYCLOCORD** include*

- etanercept (used to treat rheumatoid arthritis)
- metronidazole (used to treat bacterial or protozoal infections)
- tamoxifen (used to treat breast cancer)
- bupropion (used to help stop smoking)

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- coumarins such as warfarin (used to thin the blood)
- cyclosporine (used to reduce the activity of the immune system)
- succinylcholine (used to relax muscles during medical procedures)
- digoxin, β -acetyldigoxin (used to treat heart conditions)
- vaccines
- verapamil (used to treat high blood pressure, angina or irregular heart beat)
- concomitant use of sulfonylurea derivatives with cyclophosphamide (blood sugar levels may drop)

Please consult your doctor, pharmacist or other healthcare professional for advice.

CYCLOCORD with food, drink and alcohol

Drinking alcohol can increase the nausea and vomiting caused by **CYCLOCORD**.

Grapefruit (fruit or juice) should not be consumed while taking **CYCLOCORD**.

It can interfere with the usual effect of your medicine and may alter the effectiveness of your treatment.

Pregnancy and breast-feeding

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor or pharmacist for further advice before taking CYCLOCORD.

Pregnancy

CYCLOCORD can cause miscarriage or damage to your unborn baby. Considering the available information, use of cyclophosphamide during pregnancy, especially in the first trimester is not recommended.

Breast-feeding

Since **CYCLOCORD** is passed in breast milk, women must not breastfeed during the treatment.

Contraception/Fertility

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If you are a woman, you should not get pregnant during treatment and for the period of 12 months after discontinuation of the treatment.

If you are a man, you should use of an effective contraceptive to ensure that you do not father a child during treatment and for the period of 6 months after discontinuation of the treatment.

CYCLOCORD can affect your ability to have children in the future and may cause infertility. Talk to your doctor about cryo-preservation (freezing) of sperm prior to treatment. If you are considering becoming parents after the treatment, please discuss this with your doctor. Young women with reserved ovarian function may develop premature menopause after receiving cyclophosphamide treatment.

Driving and using machines

After **CYCLOCORD** administration undesirable effects, such as dizziness, blurred vision and visual impairment may occur, which could affect the ability to drive or use machines. The decision if you are allowed to drive or operate machines will be made by your doctor on individual basis.

3. How CYCLOCORD is given

You will not be expected to give yourself **CYCLOCORD**. It will be given to you by a person who is qualified to do so.

The medicine is usually administered in a vein. Duration of administration is typically from 30 minutes to 2 hours, which depends on the volume to be administered.

CYCLOCORD is often given in combination with other anti-cancer medicines or radiotherapy.

Your doctor will decide how much of the medicine you need and when you should be given it.

Duration of treatment and/or treatment intervals depend on the indications for use, the regimen of a

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combination therapy, your general state of health, results of laboratory monitoring and blood cell recovery.

It is advisable to get your treatment administered in the morning. Before, during and after the administration, it is important that you get adequate amounts of fluid, to avoid potential adverse effects on the urinary tract.

If you receive more CYCLOCORD than you should

Since a health care provider will administer **CYCLOCORD**, he / she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If you forget to receive CYCLOCORD

Since a health care provider will administer **CYCLOCORD**, it is unlikely that the dose will be missed.

4. Possible side effects

CYCLOCORD can have side effects.

Not all side effects for CYCLOCORD are included in this leaflet. Should your general health worsen or if you experience any untoward effects while receiving CYCLOCORD, please consult your healthcare professional for advice.

If any of the following happens, stop receiving CYCLOCORD and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Allergic reactions. Signs of these would be shortness of breath, wheezing, increased heart rate, decreased blood pressure (extreme tiredness), rash, itching or swelling of the face and lips. Severe allergic reactions could lead to difficulty in breathing or shock, with a possible fatal outcome (anaphylactic shock, anaphylactic/ anaphylactoid reaction).

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- Getting bruises without knocking yourself, or bleeding from your gums. This may be a sign that the platelet levels in your blood are getting too low
- Severe infection or fever, ulcers in the mouth, coughing, breathlessness, signs of sepsis like fever, rapid breathing, elevated heart rate, confusion and edema. This may be a sign of a lowering of your white blood cell count and antibiotics may be needed to fight infections, breakdown of red blood cells, decreased number of platelets and kidney failure (Haemolytic uremic syndrome).
- Severe hypersensitivity reactions with (high) fever, red spots on the skin, joint pain and/or eye infection (Stevens-Johnson syndrome), severe sudden (hypersensitive) reaction with fever and blisters on the skin/peeling of the skin (toxic epidermal necrolysis)
- Severe pain in the chest

These are all very serious side effects. If you have them, you may have had a serious reaction to **CYCLOCORD**. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Abnormal muscle breakdown which can lead to kidney problems (rhabdomyolysis)
- Different kind of blood disorders (Agranulocytosis)
- Being very pale, feeling fatigued and tired. This may be a sign of low red blood cells (anaemia).
Usually, no treatment is required, your body will eventually replace the red blood cells. If you are very anaemic, you may need a blood transfusion
- Having blood in your urine, pain while passing urine, or passing less urine
- Symptoms like weakness, vision loss, impaired speech, loss of sense of touch

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Tell your doctor if you notice any of the following:

Frequent

- Loss of hair (alopecia)
- Burning sensations or pains during urination and frequent need to urinate (bladder infection).
- Appearance of blood in the urine
- Fever
- Suppression of the immune system
- Infections
- Inflammation of mucous membranes
- Abnormal liver function
- Infertility in men
- Chills
- Feeling of weakness
- Generally feeling unwell
- Decrease in white blood cells and fever (febrile neutropenia)

Less frequent

- Inflammation of the lung (pneumonia)
- Sepsis
- Allergic reactions
- Infertility in women (this can be permanent)
- Chest pain
- Fast heartbeat

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- Heart problems
- Changes in the results of some blood tests
- Redness of the skin (flush)
- Damage to the nerves which can cause numbness, pin, and weakness (neuropathy)
- Pain from your nerves, which can also feel like an aching or burning sensation (neuralgia)
- Loss of appetite (anorexia)
- Deafness
- Increased risk of cancer of the white blood cells (acute leukaemia) and some other cancers (bladder cancer, ureter cancer)
- Ineffective production of a certain type of blood cells (myelodysplastic syndrome)
- Increase in the release of antidiuretic hormone from the pituitary gland. This affects the kidneys causing levels of sodium in your blood (hyponatremia) and water retention resulting in swelling of the brain due to too much water in your blood. Signs of this can be headache, changes in personality or behaviour, confusion, drowsiness.
- Changes in heart beat
- Inflammation of the liver
- Rash
- Inflammation of the skin
- Lack of menstruation (periods)
- Lack of spermia
- Dizziness
- Visual impairment, blurred vision

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- Changes in the color of your nails and skin
- Dehydration
- Convulsion
- Bleedings
- Shock
- Complications that can occur after cancer treatment caused by break-down products of dying cancer cells (tumour lysis syndrome)
- Low levels of sodium in your blood
- High blood pressure (hypertension)
- Low blood pressure (hypotension)
- Angina
- Injury of the lung (acute respiratory distress syndrome)
- Scarring of the lungs which causes shortness of breath (chronic pulmonary interstitial fibrosis)
- Difficulty breathing with wheezing or coughing (bronchospasm)
- Breathlessness (dyspnoea)
- A condition in which the body or a region of the body is deprived of adequate oxygen supply (hypoxia)
- Cough
- Soreness or ulcers in the mouth (stomatitis)
- Feeling sick (nausea) being sick (vomiting) or diarrhoea
- Constipation
- Inflammation of the intestine
- Inflammation of the pancreas

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- Blood clots
- Enlargement of the liver (hepatomegaly)
- Yellow eyes or skin
- Redness of the skin (radiation erythaema)
- Itching
- Impairment of the sense of taste
- Sensation of tingling, tickling, prickling, pricking, or burning (paraesthesia)
- Impairment of the sense of smell
- Cramps
- Problems with your bladder
- Kidney problems, including kidney failure.
- Headache
- Multi organ failure
- Injection/infusion site reactions
- Weight gain
- Confusion
- Conjunctivitis, eye oedema
- Fluid in or around the lungs (pulmonary oedema)
- Accumulation of fluid in the abdominal cavity (ascites)

Frequency unknown

- Different kinds of cancer e.g. blood cancer (Non-Hodgkin's lymphoma), kidney cancer, thyroid cancer
- Sarcoma

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- Different kind of blood disorders (Lymphopenia, Haemoglobin decreased)
- Lacrimation increased
- Tinnitus
- Blockage of the nasal passages (nasal congestion)
- Oropharyngeal pain
- Symptoms of allergies or flu like symptoms (Rhinorrhoea)
- Sneezing
- Conditions causing inflammation of the lungs which can cause breathlessness, cough and raised temperature or scarring of the lungs (pneumonitis, obliterative bronchiolitis, alveolitis allergic), fluid in or around the lungs (pleural effusion) abdominal pain
- Bleeding in stomach or guts
- Intestinal problems/bleeding
- Liver impairment
- Rash, skin reddening, blistering of lips, eyes or mouth, skin peeling (erythema multiforme, urticaria, erythema)
- Hand-foot syndrome
- Facial swelling
- Increased sweating
- Hardening of skin (scleroderma)
- Muscle spasm and pain
- Joint pain
- Inflammation, scarring and contraction of your bladder

Applicant/HCR: Accord Healthcare (Pty) Ltd
Product name: Cyclocord 500 mg / 1 g
Strength: 500 mg / 1 g vial (Powder for solution for injection/infusion)

Initial submission: 11/10/2021 (0000)

Response to P&A query as per SAHPRA email dated 09/09/2022: submitted 19/09/2022 (0003)

Response to Clinical query as per SAHPRA email dated 26/02/2023: submitted 20/03/2023 (0004)

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- Effects on the foetus like damage or death of the foetus, intra-uterine death, foetal malformation, foetal growth retardation, carcinogenic effect on offspring
- Changes in the results of some blood tests (glucose level, hormone levels)
- Effects on the brain (encephalopathy), a syndrome called Reversible posterior
- Leukoencephalopathy syndrome, which can cause swelling of the brain, headache, confusion, fits and loss of sight, changes in your sense of touch (dysesthesia) or loss of sensation (hypoesthesia), shaking (tremor), changes in your sense of taste (dysgeusia) or loss of taste (hypogeusia), changes in your sense of smell (parosmia),
- Decrease in your heart's ability to pump enough blood around your body which may be life threatening (cardiogenic shock, heart failure or cardiac arrest), faster heart beat (tachycardia), which may be life threatening (ventricular tachycardia), slower heart beat (bradycardia), build-up of fluid in the sac around your heart (pericardial effusion), abnormal ECG heart tracing (Electrocardiogram QT prolonged), changes in your heart rhythm (arrhythmia) which may be noticeable (palpitations)
- Changes in the frequency of menstruation
- Salivary gland inflammation
- Anaemia (a low red blood cell count) that can leave you feeling tired and drowsy
- Have easy bruising caused by thrombocytopenia (low platelet count)
- Leukocytopenia (a low white blood cell count)
- Heart attack
- Increase in liver enzymes

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

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Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via the “**6.04 Adverse Drug Reaction**

Reporting Form”, found online under SAHPRA’s publications: <https://www.sahpra.org.za/Publications/Index/8>.

By reporting side effects, you can help provide more information on the safety of **CYCLOCORD**.

5. How to store CYCLOCORD

- Store in a refrigerator (2 °C – 8 °C).
- After opening the product should be used immediately.
- 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.
- For single use only. Discard any unused product.
- Store all medicines out of reach of children.
- Store in original package until use.
- Do not use after the expiry date stated on the label
- Return all unused medicine to your pharmacist
- Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What CYCLOCORD contains

- The active substance is cyclophosphamide

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- 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.
- The other ingredients are mannitol and water for injection

What CYCLOCORD looks like and contents of the pack

- A white lyophilised powder
- **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.
- 1 vial per carton

HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Limited
Building 2, Tuscany Office Park
6 Coombe Place
Rivonia
Johannesburg
South Africa

This leaflet was last revised in

09 May 2023

Registration number

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CYCLOCORD 500 mg: 56/26/0922

CYCLOCORD 1 g: 56/26/0923