Artwork No.	-		Colours Used
Customer		■	Pantone Black
Description			
Market	UK		
Language	English		
Size	720 x 400 mm PIL (FF - 80 x 45 mm)		
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200 mg/ml
Cyclophosphamide
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Cyclophosphamide
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Package leaflet: Information for the patient

Cyclophosphamide 200 mg/ml concentrate for solution for injection/infusion

Read all of this leaflet carefully before this medicine is administered to you because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.
- The full name of this medicine is Cyclophosphamide 200 mg/ml concentrate for solution for injection/infusion but within this leaflet it will be referred to as Cyclophosphamide.

What is in this leaflet:

1. What Cyclophosphamide is and what it is used for

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

Cyclophosphamide is used in chemotherapy alone or in combination with other medicinal products in the following cases:
- 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
- Ewing's sarcoma (a form of bone cancer)
- small cell lung cancer
- advanced or metastatic tumour of the central nervous system (neuroblastoma).

Furthermore, cyclophosphamide is 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, some doctors may prescribe cyclophosphamide 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 take Cyclophosphamide

Do not use Cyclophosphamide if you:
- are allergic to cyclophosphamide or any of its metabolites or any ingredients of this medicine (listed in section 6)
- currently have any infection
- have a 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
- have a urinary tract infection, which can be recognised as pain when passing urine (cystitis)
- have ever had kidney or bladder problems as a result of previous chemotherapy or radiotherapy
- have a condition which decreases your ability to urinate (urinary outflow obstruction)
- are breast-feeding
- have other conditions not related to cancer, except life limiting immune disorders.

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

Take special care with Cyclophosphamide:
- Potentially life-threatening allergic reactions (anaphylactic reaction) may occur during treatment with cyclophosphamide
- Cyclophosphamide 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, and
  - platelets, which help your blood to clot
- After receiving cyclophosphamide, your blood count of the three types of cells will drop. This is an unavoidable side effect of cyclophosphamide. Your blood count will reach its lowest level about 5 to 10 days after you start receiving cyclophosphamide 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 cyclophosphamide. They may need to reduce the amount of medicine you are given or delay your next dose
- Cyclophosphamide 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
- Cyclophosphamide 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 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 cyclophosphamide, or as tablets. More information on Mesna can be found in the Patient Information Leaflet for Mesna injection and Mesna tablets
- Most people being given cyclophosphamide 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. Cyclophosphamide has an increased risk of causing cancer in the area of your bladder
- Cyclophosphamide 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
- Cyclophosphamide 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
- Cyclophosphamide 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
- Cyclophosphamide 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.

Other medicines and Cyclophosphamide
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.
In particular, tell them about the following medicines or treatments as they may not work well with cyclophosphamide:

<u>The following medicines may decrease the effect of cyclophosphamide:</u>
- 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 (used to treat bacterial infections)
- fluconazole, itraconazole (used to treat fungal infections)
- prasugrel (used to thin the blood).

<u>The following medicines may increase the effect of cyclophosphamide:</u>
- 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)
- glyceraldehyde (used to treat warts)
- protease inhibitors (used to treat viruses)
- dabrafenib (anti-cancer drug)
- medicines that increase liver enzymes such as:
  - rifampicin (used to treat bacterial infections)
  - phenobarbital, carbamazepine, phenytoin (used to treat epilepsy)
  - St. John's Wort (a herbal remedy for mild depression)
  - corticosteroids (used to treat inflammation).

<u>Medicines that can increase the toxic effects of cyclophosphamide on your blood cells and immunity:</u>
- 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).

<u>Medicines that can increase the toxic effects of cyclophosphamide on your heart:</u>
- 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.

<u>Medicines that can increase the toxic effects of cyclophosphamide on your lungs:</u>
- amiodarone (used to treat irregular heartbeat)
- G-CSF, GM-CSF hormones (used to increase white blood cell numbers after chemotherapy).

<u>Other medicines that can affect or be affected by cyclophosphamide include:</u>
- 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)
- 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, ß-acetyldigoxin (used to treat heart conditions)
- vaccines
- verapamil (used to treat high blood pressure, angina or irregular heartbeat)
- concomitant use of sulfonylurea derivatives with cyclophosphamide (blood sugar levels may drop).

Cyclophosphamide with food, drink and alcohol
Drinking alcohol can increase the nausea and vomiting caused by cyclophosphamide.

Grapefruit (fruit or juice) should not be consumed while taking cyclophosphamide. It can interfere with the usual effect of your medicine and may alter the effectiveness of cyclophosphamide.

Contraception, pregnancy, breastfeeding and fertility
<u>Contraception in men and women</u>
If you are a woman, you should not get pregnant during treatment with Cyclophosphamide 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 the treatment with Cyclophosphamide and for the period of 6 months after discontinuation of the treatment.

<u>Pregnancy</u>
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Cyclophosphamide 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 and that the doctor will decide if it can be used.

<u>Breast-feeding</u>
Since cyclophosphamide is passed in breast milk, women must not breast-feed during the treatment. See section 2 "Do not use Cyclophosphamide".

<u>Fertility</u>
Cyclophosphamide 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 cyclophosphamide 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.

Cyclophosphamide contains propylene glycol
This medicine contains 34 mg propylene glycol in each 1 ml concentrate vial which is equivalent to 34 mg/ml.

If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.

Cyclophosphamide contains ethanol (alcohol)
This medicine contains 620 mg ethanol per ml of solution, which is equivalent to 13 g per maximal dose of 60 mg/kg. The amount in maximal dose (60 mg/kg in 70 kg patient) of this medicine is equivalent to 323 ml beer or 130 ml wine.

The alcohol in this preparation is likely to affect children. These effects may include feeling sleepy and changes in behaviour. It may also affect their ability to concentrate and take part in physical activities.

The amount of alcohol in this medicine can affect your ability to drive or use machines. This is because it may affect your judgement and how fast you react.

If you have epilepsy or liver problems, talk to your doctor or pharmacist before taking this medicine.

The amount of alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.

If you are pregnant or breast-feeding, talk to your doctor or pharmacist before taking this medicine.

If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

3. How to take Cyclophosphamide

Cyclophosphamide will be given to you by a doctor or nurse experienced in the use of cancer chemotherapy.
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.

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

<u>The recommended dose:</u>
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 combination therapy, your general state of health, results of laboratory monitoring and blood cell recovery.

It is advisable to get cyclophosphamide 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 have any questions on the use of this medicine, ask your doctor or pharmacist.

If you receive more Cyclophosphamide than you should
As cyclophosphamide is given to you under the supervision of your doctor, it is very unlikely that you will receive too much. However, if you experience any side effects after being given cyclophosphamide, tell your doctor immediately. You may need urgent medical attention.

Symptoms of a cyclophosphamide overdose include the side effects listed below in section 4, 'Possible side effects', but are usually of a more severe nature.

If you forget to take Cyclophosphamide
If you have missed administration of the medicine, please consult the doctor immediately.

If you have any questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you experience:

- 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)
- 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 oedema. 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)
- 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
- 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)
- abnormal muscle breakdown which can lead to kidney problems (rhabdomyolysis)
- different kind of blood disorders (agranulocytosis)
- having blood in your urine, pain while passing urine, or passing less urine
- severe pain in the chest
- symptoms like weakness, vision loss, impaired speech, loss of sense of touch.

Other side effects that may occur:

Very common: may affect more than 1 in 10 people
- decrease in the number of blood cells (myelosuppression)
- decrease in white blood cells which are important in fighting infection (leukopenia, neutropenia)
- loss of hair (alopecia)
- burning sensation or pain during urination and frequent need to urinate (bladder infection)
- appearance of blood in the urine
- fever
- suppression of the immune system.

The following information is intended for healthcare professionals only:

Cyclophosphamide should only be used under the supervision of a clinician experienced in the use of cancer chemotherapy. This medicine 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.

<u>Posology</u>
Dosage must be individualised. Doses and duration of treatment and/or treatment intervals depend on the therapeutic indication, the scheme of a combination therapy, the patient's general state of health and organ function, and the results of laboratory monitoring (in particular, blood cell monitoring).

In combination with other cytostatics of similar toxicity, a dose reduction or extension of the therapy-free intervals may be necessary.

Use of haematopoiesis stimulating agents (colony-stimulating factors and erythropoiesis-stimulating agents) may be considered to reduce the risk of myelosuppressive complications and/or help facilitate the delivery of the intended dosing.

Prior, during 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.

It is within the responsibility of the physician to decide on the use of cyclophosphamide according to the operative treatment guidelines.

The doses below can be regarded as general guidelines:

<u>Haematologic and solid tumours</u>
- For daily treatment:
  3 - 6 mg/kg body weight (= 120 - 240 mg/m^2 body surface area), injected intravenously
- For the intermittent treatment:
  10 - 15 mg/kg body weight (= 400 - 600 mg/m^2 body surface area), injected intravenously, with therapy-free intervals of 2 to 5 days
- For high-dose intermittent treatment:
  20 - 40 mg/kg body weight (= 800 - 1600 mg/m^2 body surface area), injected intravenously, with therapy-free intervals of 21 to 28 days.

<u>As preparation for a bone marrow transplantation</u>
2 days 60 mg/kg or 4 days 50 mg/kg body weight injected intravenously.

If a busulfan-cyclophosphamide (Bu/Cy) regimen is applied, the first dose of cyclophosphamide must be administered at least 24 hours after the last dose of busulfan.

<u>Autoimmune diseases</u>
Per month 500 – 1000 mg/m^2 body surface area.

<u>Patients with hepatic impairment</u>
Severe hepatic impairment may be associated with a decreased activation of cyclophosphamide. This may alter the effectiveness of the Cyclophosphamide treatment and should be considered when selecting the dose and estimating response to the medicinal product.

The dose must be reduced in patients with severe hepatic impairment. A dose reduction of 25% is recommended in patients with serum bilirubin concentrations of 3.1 – 5 mg/100 ml (=0.053-0.086 mmol/l).

<u>Patients with renal impairment</u>
In patients with renal impairment, particularly in patients with severe 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 4.4). A dose reduction of 50% for a glomerular filtration rate below 10 ml/minute is recommended.

Cyclophosphamide and its metabolites are dialysable, although there may be differences in clearance depending upon the dialysis system being used. In patients requiring dialysis, consistent interval between dialysis cycles and Cyclophosphamide administration should be considered.

<u>Elderly patients</u>
In elderly patients, monitoring for toxicities and the need for dose adjustment should reflect the higher frequency of decreased hepatic, renal or cardiac function, or other organ function and concomitant diseases or other drug therapy in this population.

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

<u>Dose modification due to myelosuppression</u>
A leukocyte and platelet count should be regularly performed during treatment with cyclophosphamide. It is recommended to adjust the dose, if required, if signs of myelosuppression become evident.
Please refer to the table below. Urinary sediment should also be checked regularly for the presence of erythrocytes.

Leukocyte count [microlitre]	Platelet count [microlitre]	Dosage
more than 4000	more than 100 000	100% of the planned dose
2500 - 4000	50 000 - 100 000	50% of the planned dose
less than 2500	less than 50 000	Omit until values normalise or decide individually

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

<u>Method of administration</u>
Cyclophosphamide is inert until activated by enzymes in the liver. However, as with all cytotoxic agents, it is recommended that dilution should be performed by trained personnel, in a designated area.

<u>Precaution to be taken before handling or administering the product</u>
Those handling the preparation should wear protective gloves. Care should be taken to avoid splashing material into the eyes. The material should not be handled by women who are pregnant or who are breast-feeding.

<u>Intravenous use</u>
Drug products for intravenous use must be inspected visually for particulate matter

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Common: may affect up to 1 in 10 people
- 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).

Uncommon: may affect up to 1 in 100 people
- anaemia (a low red blood cell count) that can leave you feeling tired and drowsy
- have easy bruising caused by thrombocytopenia (low platelet count)
- inflammation of the lung (pneumonia)
- sepsis
- allergic reactions
- infertility in women (this can be permanent)
- chest pain
- fast heartbeat
- heart problems
- changes in the results of some blood tests
- redness of the skin (flush)
- damage to the nerves which can cause numbness, pain, and weakness (neuropathy)
- pain from your nerves, which can also feel like an aching or burning sensation (neuralgia)
- loss of appetite (anorexia)
- deafness.

Rare: may affect up to 1 in 1000 people
- 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 low levels of sodium in your blood (hyponatraemia) 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 heartbeat
- inflammation of the liver
- rash
- inflammation of the skin
- lack of menstruation (periods)
- lack of spermia
- dizziness
- visual impairment, blurred vision
- changes in the colour of your nails and skin
- dehydration
- convulsion
- bleedings.

Very rare: may affect up to 1 in 10000 people
- shock
- complications that can occur after cancer treatment caused by breakdown products of dying cancer cells (tumour lysis syndrome)
- low levels of sodium in your blood
- high blood pressure (hypertension)
- low blood pressure (hypotension)
- angina
- heart attack
- 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
- blood clots
- enlargement of the liver (hepatomegaly)
- activation of viral hepatitis
- yellow eyes or skin
- redness of the skin (radiation recall dermatitis)
- itching, toxic dermatitis
- 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
- ulcerative cystitis
- 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).

Not known: frequency cannot be estimated according to available data
- different kinds of cancer e.g. blood cancer (non-Hodgkin's lymphoma), kidney cancer, thyroid cancer, sarcoma
- 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, allergic alveolitis), fluid in or around the lungs (pleural effusion), abdominal pain
- bleeding in stomach or guts
- intestinal problems/bleeding
- liver impairment
- cytolytic hepatitis
- 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
- 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 heartbeat (tachycardia), which may be life-threatening (ventricular tachycardia), slower heartbeat (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), left ventricular failure, diffuse intramyocardial haemorrhage
- changes in the frequency of menstruation
- salivary gland inflammation
- acute water intoxication
- oedema
- flu-like illness.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cyclophosphamide

Keep this medicine out of the sight and reach of children.
Do not use Cyclophosphamide after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

After opening:
After opening, store partially used multiple-dose vial in the original carton at 2°C - 8°C for up to 28 days. Discard unused portion after 28 days.

After dilution:
Chemical and physical stability of diluted solution has been demonstrated for 7 days at 2°C - 8°C (protected from light) & 24 hours at 20°C - 25°C (normal room light).

From a microbiological point of view, the diluted medicinal product 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 dilution has taken place in controlled and validated aseptic conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cyclophosphamide contains

- The active substance is cyclophosphamide
- The excipients are propylene glycol (E1520), macrogol, monothioglycerol, ethanol anhydrous.

1 ml concentrate contains cyclophosphamide monohydrate equivalent to 200 mg cyclophosphamide.

One vial of 1 ml of concentrate contains cyclophosphamide monohydrate equivalent to 200 mg cyclophosphamide.

One vial of 2.5 ml of concentrate contains cyclophosphamide monohydrate equivalent to 500 mg cyclophosphamide.

One vial of 5 ml of concentrate contains cyclophosphamide monohydrate equivalent to 1000 mg cyclophosphamide.

One vial of 10 ml of concentrate contains cyclophosphamide monohydrate equivalent to 2000 mg cyclophosphamide.

What Cyclophosphamide looks like and contents of the pack

2 ml clear tubular type I colourless glass vial with chlorobutyl rubber stopper and plain flip-off blue seal containing 1 ml of concentrate.

5 ml clear tubular type I colourless glass vial with chlorobutyl rubber stopper and plain flip-off yellow seal containing 2.5 ml of concentrate.

5 ml clear tubular type I colourless glass vial with chlorobutyl rubber stopper and plain flip-off blue seal containing 5 ml of concentrate.

10 ml clear tubular type I colourless glass vial with chlorobutyl rubber stopper and plain flip-off blue seal containing 10 ml of concentrate.

Pack sizes

1 vial
5 vials
6 vials
10 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Accord, Barnstaple, EX32 8NS, UK

Manufacturers
Accord Healthcare Limited
Sage House, 319 Pinner Road
North Harrow, Middlesex
HA1 4HF
United Kingdom

Accord Healthcare Polska Sp.z o.o.
ul. Lutomierska 50,
95-200 Pabianice
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Laboratori Fundació Dau
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Zona Franca, Barcelona, 08040,
Spain

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and discolouration prior to administration whenever solution and container permit.

Infusion:
Intravenous administration should preferably be conducted as an infusion.

If the solution is to be used for IV infusion, Cyclophosphamide is diluted to a minimum concentration of 2 mg per ml by using any of the following diluents:

- 0.9% Sodium Chloride Injection
- 0.45% Sodium Chloride Injection
- 5% Glucose Injection
- 5% Glucose and 0.9% Sodium Chloride Injection.

Direct injection:
If the solution is to be used for direct injection, Cyclophosphamide is diluted to a minimum concentration of 20 mg per ml by using any of the following diluents:

- 0.9% Sodium Chloride Injection
- 0.45% Sodium Chloride Injection
- 5% Glucose Injection
- 5% Glucose and 0.9% Sodium Chloride Injection.

Do not use sterile water for injection for dilution because it results in a hypotonic solution and should not be injected directly.

To reduce the likelihood of adverse reactions that appear to be administration rate-dependent (e.g. facial swelling, headache, nasal congestion, scalp burning), cyclophosphamide should be injected or infused very slowly. Duration of the infusion should be appropriate for the volume and type of carrier fluid to be infused.

Storage and shelf life of the diluted solution

After opening:
After first use, store partially used multiple-dose vial in the original carton at 2°C - 8°C for up to 28 days. Discard unused portion after 28 days.

After dilution:
Chemical and physical stability of diluted solution has been demonstrated for 7 days at 2°C - 8°C (protected from light) & 24 hours at 20°C - 25°C (normal room light).

From a microbiological point of view, the diluted medicinal product 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 dilution has taken place in controlled and validated aseptic conditions.