45 mm

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accord
Cyclophosphamide
500 mg / 1000 mg

45 mm

Cyclophosphamide
500 mg / 1000 mg
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80 mm

Package leaflet: Information for the patient

Cyclophosphamide 500 mg powder for solution for injection/infusion
Cyclophosphamide 1000 mg powder for solution for injection/infusion

Read all of this leaflet carefully before you start using this medicine 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. See section 4.
- The full name of this medicine is Cyclophosphamide 500 mg, 1000 mg powder for solution for injection/infusion but within this leaflet it will be referred to as Cyclophosphamide.

What is in this leaflet:

1. What is Cyclophosphamide 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 case.

- 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
- in the treatment of advanced or metastatic tumor 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 leukemia, chronic myeloid leukemia and acute myeloid leukemia).

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 use 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 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 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 effect with 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 ulfadiazine, 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 heart beat)
- 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 heart beat)
- 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
Contraception in men and women
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.

Pregnancy
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.

Breastfeeding
Since Cyclophosphamide is passed in breast milk, women must not breastfeed during the treatment. See section 2 "Do not use Cyclophosphamide".

Fertility
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.

3. How to use 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 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.

The recommended dose
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

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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.

Posology
Dose should be individually adjusted for each patient. Duration of treatment and/or treatment intervals depend on the indication, the regimen of a combination therapy, the patient's general state of health, results of laboratory monitoring and blood cell recovery.

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 and 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.

Cyclophosphamide is inert until activated by enzymes in the liver. However, as with all cytotoxic agents, it is recommended that reconstitution should be performed by trained personnel, in a designated area.

Handling
The choice of solvent for reconstituting Cyclophosphamide containing Cyclophosphamide depends on the route of administration to be used.

Infusion:
Intravenous administration should preferably be conducted as an infusion.
If the solution is to be used for IV infusion, Cyclophosphamide is reconstituted by adding sterile water for injection or 9 mg/ml (0.9%) sterile sodium chloride solution.

Reconstituted Cyclophosphamide should be further diluted in 50 mg/ml (5%) dextrose or 9 mg/ml (0.9%) sodium chloride solution prior to infusion.

Direct injection:
If the solution is to be used for direct injection, Cyclophosphamide is reconstituted by adding 9 mg/ml (0.9%) sterile sodium chloride solution. Please note that only Cyclophosphamide reconstituted in 9 mg/ml (0.9%) sterile sodium chloride solution is suitable for bolus injection.

Cyclophosphamide reconstituted in water is hypotonic and should not be injected directly.
The following quantities of water for injections or sodium chloride 9 mg/ml (0.9 %) solution are added to the vials containing Cyclophosphamide, powder for solution for injection/infusion

Vial of 500 mg: 25 mL
Vial of 1000 mg: 50 mL

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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 use 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 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).
- 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 of 10 people:
- decrease in the number of blood cells (myelosuppression)
- decrease in white blood cells which are important in fighting infection (leucopenia, neutropenia)
- 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.

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 heart beat
- 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

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 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
- changes in the color 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 break-down products of dying cancer cells (tumor 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)
- 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).

***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 (Rhinorrhea)
- 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
- 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 hearts 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.

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: www.mhra.gov.uk/yellowcard 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 preparation for intravenous administration
Chemical and physical in-use stability of 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 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, if reconstitution has taken place in controlled and validated aseptic conditions.

Do not use this medicine if you notice deterioration of drug product i.e melt back of cake and visible particles in reconstituted/diluted solution.

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 excipient is Mannitol (E421).

Each Cyclophosphamide 500 mg powder for solution for injection/infusion contains 534.5 mg Cyclophosphamide monohydrate equivalent to 500 mg Cyclophosphamide.

Each Cyclophosphamide 1000 mg powder for solution for injection/infusion contains 1069.0 mg Cyclophosphamide monohydrate equivalent to 1000 mg Cyclophosphamide.

What Cyclophosphamide looks like and contents of the pack
Cyclophosphamide 500 mg is a white powder or cake available in 30 mL glass vial.
Cyclophosphamide 1000 mg is a white powder or cake available in 50 mL glass vial.

Pack sizes
1 vial

Marketing Authorisation Holder:
Accord Healthcare Limited
Sage House , 319 Pinner Road, North Harrow, Middlesex
HA1 4HF, United Kingdom

Manufacturer:
Accord Healthcare Polska Sp.z o.o.
ul. Lutomierska 50, 95-200 Pabianice, Poland

Or
Pharmadox Healthcare Ltd.
KW20A, Kordin Industrial Park, Paola, PLA3000, Malta

Or
Laboratori Fundació Dau
C/ C, 12-14 Pol. Ind., Zona Franca, Barcelona, 08040, Spain

Or
Accord Healthcare B.V.
Winthontlaan 200, 3526KV Utrecht, The Netherlands

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Injecting the solvent into the vial for injection creates an abnormally high pressure, which disappears as soon as the second sterile needle has been inserted in the rubber stop of the vial for injection. The powder easily dissolves when the vial for injection is shaken vigorously to produce a clear solution. If the powder does not immediately dissolve, continue to shake the vial vigorously for up to several minutes until complete dissolution of the powder. The solution must be administered as soon as possible following its reconstitution.

Intravenous use
Intravenous administration should preferably be conducted as an infusion.

If Cyclophosphamide , powder for solution for injection/infusion (is stored (e.g. during transport) at the temperature exceeding the maximum temperature, Cyclophosphamide may melt. Vials for injections containing melted Cyclophosphamide can be visually recognised. Cyclophosphamide is a white powder. M*elted Cyclophosphamide* is a *clear or* yellowish viscous liquid (usually found as droplets in the affected vials.). Vials for injections containing melted Cyclophosphamide may no longer be used.

Guidelines for the Safe Handling of Antineoplastic Agents
- The rules and regulations for handling cytotoxic in general must be observed when reconstituting or handling Cyclophosphamide.
- 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. Cytotoxic preparations should not be handled by pregnant staff or who are breast feeding. Trained personnel should dilute the drug.
- This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper.
- Use Luer-lock fittings on all syringes and sets. Large bore needles are recommended to minimize pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle. Any unused contents should be discarded. Adequate care and precaution should be taken in the disposal of items used to dilute Cyclophosphamide. Any unused product or contaminated materials should be placed in a high-risk waste bag. Sharp objects (needles, syringes, vials, etc) should be placed in a suitable rigid container. Personnel concerned with the collection and disposal of this waste should be aware of the hazard involved.
- Any unused product or waste material should be disposed of in accordance with standard procedures applicable to cytotoxic agents.

Storage and shelf life of the reconstituted solution
The reconstituted solution is physico-chemically stable for 48 hours when stored at temperature 2-8° C.
From a microbiological point of view, the 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 reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Note: Artwork requires symbol of Scissor & dotted line. Perforation is not requiring in the artwork.