1.3.1.3 Package Leaflet

Package leaflet: Information for the patient

{[To be completed nationally] 500 mg powder for solution for injection/infusion}
{[To be completed nationally] 1000 mg powder for solution for injection/infusion}
{[To be completed nationally] 2000 mg powder for solution for injection/infusion}

Cyclophosphamide

Read all of this leaflet carefully before you are given 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.
- 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.

What is in this leaflet

1. What [TO BE COMPLETED NATIONALLY] is and what it is used for

[TO BE COMPLETED NATIONALLY] contains an 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 often used alone or together with other anti-cancer drugs or radiotherapy in the treatment of various cancers. These include:
• certain types of cancer of the white blood cells (acute lymphoblastic leukemia, chronic lymphocytic leukemia);
• 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 are given [TO BE COMPLETED NATIONALLY]

You will not be given [TO BE COMPLETED NATIONALLY]:

- if you are allergic to cyclophosphamide or any of its metabolites. An allergic reaction can include shortness of breath, wheezing, rash, itching or swelling of the face and lips.
- if you currently have any infections.
- if your bone marrow is not working properly (especially if you have previously had chemotherapy or radiotherapy). You will have blood tests to check how well your bone marrow is working.
- if you have a urinary tract infection, which can be recognised as pain when passing urine (cystitis)
- 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 breast-feeding

Warnings and precautions
Talk to your doctor before being given [TO BE COMPLETED NATIONALLY] 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.

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.

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 [TO BE COMPLETED NATIONALLY]

Tell your doctor if you are taking, have recently taken or might take any other medicines. In particular, tell them about the following medicines or treatments as they may not work well with Cyclophosphamide:

The following medicines can reduce how effective Cyclophosphamide is:

- aprepitant (used to prevent being sick)
- bupropion (an anti-depressant)
- busulfan, thiotepa (used to treat cancer)
- ciprofloxacin, chloramphenicol (used to treat bacterial infections)
- fluconazole, itraconazole (used to treat fungal infections)
- Prasugrel (used to thin the blood)
- Sulfonamides, such as sulfadiazine, sulfasalazine, sulfamethoxazole (used to treat bacterial infections
- ondansetron (used to prevent being sick)

The following medicines can increase the toxicity 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)
- glyceraldehyde (used to treat warts)
- protease inhibitors (used to treat viruses)
- medicines that increase liver enzymes such as: rifampicin (used to treat bacterial infections), carbamazepine, phenobarbital, phenytoin (used to treat epilepsy), St. John's wort (a herbal remedy for mild depression), Corticosteroids (used to treat inflammation)
- dabrafenib (anti cancer drug)

Medicines that can increase the toxic effects of Cyclophosphamide on your blood cells and immunity:

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

Medicines that can increase the toxic effects of Cyclophosphamide 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 Cyclophosphamide 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 increase the toxic effects of Cyclophosphamide on your kidneys

- amphotericin B (used to treat fungal infections)
- Indomethacin (used to treat pain and inflammation)

Other medicines that can affect or be affected by Cyclophosphamide 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)
- 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)
- Sulfonylurea derivatives (blood sugar levels may drop, if cyclophosphamide and sulfonylurea derivatives are used concomitantly)

[TO BE COMPLETED NATIONALLY] 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.

Pregnancy, breast-feeding and fertility

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

Pregnancy
Cyclophosphamide can cause miscarriage or damage your unborn baby.

If you are a woman, you should not get pregnant during treatment with cyclophsphamide or up to 12 months after treatment.
If you are a man, you should take adequate precautions, including use of an effective contraceptive to ensure that you do not father a child during your treatment with cyclophosphamide or up to 6 months after treatment.

Lactation
Do not breast-feed while being treated with Cyclophosphamide. Ask your doctor for advice.

Fertility
Cyclophosphamide can affect your ability to have children in the future. Talk to your doctor about cryo-preservation (freezing) of sperm or eggs prior to treatment because of the possibility of irreversible infertility due to therapy with cyclophosphamide. If you are considering becoming parents after the treatment please discuss this with your doctor.

Driving and using machines
Some of the side effects of treatment with Cyclophosphamide might affect your ability to drive and use machines safely. Your doctor will decide if it is safe for you to do so.

3. How to use [TO BE COMPLETED NATIONALLY]

Method of administration
For intravenous use

[TO BE COMPLETED NATIONALLY] will be given to you by a a doctor or nurse experienced in the used of cancer chemotherapy [

TO BE COMPLETED NATIONALLY] is given as an injection and will normally be added to a large bag of fluid and will be slowly injected (infused) directly into your vein. The vein can be in your arm, the back of your hand or a large vein under your collar bone.

Depending on your dose, it will usually take between 30-120 minutes to be given as an infusion. Cyclophosphamide is often given in combination with other anti-cancer medicines or radiotherapy.

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The recommended dose
- Your doctor will decide how much of the medicine you need and when you should be given it.
- The amount of cyclophosphamide you will be given depends on:
  – the type of illness you have;
  – how big you are (a combination of your height and weight);
  – your general health;
  – whether you are being given other anti-cancer medicines or having radiotherapy.

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 notice [TO BE COMPLETED NATIONALLY] is working too strong or too weak, talk to your doctor or pharmacist.

Your doctor may need to change the amount of medicine you are given and monitor you more closely if you:
- have problems with your liver or kidneys;
- you are elderly.

Use in children and adolescent
Cyclophosphamide is also indicated in children. The safety profile of cyclophosphamide in children is similar to that of adults.

If you use more [TO BE COMPLETED NATIONALLY] 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 or go to Accident and Emergency at your nearest hospital. You may need urgent medical attention.
Symptoms of a cyclophosphamide overdose include the side effects listed below in the 'Side Effects' section, but are usually of a more severe nature.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, Cyclophosphamide 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.**
- **being very pale, lethargic 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**
- **severe pain in the chest**
- **symptoms like weakness, vision loss, impaired speech, loss of sense of touch**

Cyclophosphamide can also cause the following side-effects:

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 (leucopenia, neutropenia)
- Loss of hair (alopecia)
- Burning sensations during urination and frequent need to urinate (cystitis).
- Appearance of blood in the urine (microhaematuria)
- Fever
- Suppression of the immune system

Common: may affect up to 1 in 10 people

- Infections
- inflammation of mucous membranes (mucositis)
- blood in the urine and painful voiding (haemorrhagic cystitis)
- Appearance of blood in the urine (macrohaematuria)
- 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 (rarely irreversible)
- 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 in the distribution of a nerve (neuralgia)
- anorexia
- deafness

Rare: may affect up to 1 in 1,000 people

- increased risk of cancer of the white blood cells (acute leukaemia)and some other cancers (bladder cancer, ureter cancer)
- ineffective production of the myeloid class of blood cells (myelodysplastic syndrome)
- increase in the release of antidiuretic hormone from the pituitary gland (syndrome of inappropriate antidiuretic hormone secretion). This affects the kidneys causing the low 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 10,000 people

- breakup of red blood cells and kidney failure (Hemolytic uremic syndrome)
- blood clots form throughout the body's small blood vessels (Disseminated intravascular coagulation)
- 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 (hyponatremia)
- high blood pressure (hypertension)
- low blood pressure (hypotension)
- angina
- heart attack
- occlusion of a blood vessel due to a blood clot in the circulatory system, (thromboemboembolism),
- 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 diarrhea
- constipation
- inflammation of the intestine
- inflammation of the pancreas
- blood clot in the liver (veno-occlusive liver disease)
- enlargement of the liver (hepatomegaly)

- yellow eyes or skin
- 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)
- Radiation erythaema
- itching
- impairment of the sense of taste (dysgeusia, hypogeusia)
- sensation of tingling, tickling, prickling, pricking, or burning (paraesthesia)
- impairment of the sense of smell (parosmia)
- abnormal muscle breakdown which can lead to kidney problems (rhabdomyolysis)
- cramps
- problems with your bladder
- kidney problems, including kidney failure.
- Headache
- Multi organ failure
- Injection/infusion site reactions
- Weight gain
- Confusion
- Conjunctivitis, eye oedema
- acute kidney failure with decreased number of red blood cells and platelets (Haemolytic uraemic syndrome)
- respiratory failure due to fluid accumulation in the lung (pulmonary oedema)
- accumulation of fluid in the abdominal cavity (ascites)

Not known: frequency cannot be estimated from the available data

- Different kinds of cancer e.g. blood cancer (Non-Hodgkin's lymphoma), kidney cancer, thyroid cancer
- Sarcoma
- Different kind of blood disorders (Agranulocytosis, Lymphopenia, Haemoglobin decreased)
- occlusion of a blood vessel due to a blood clot in the circulatory system, (thromboembolic events), including the possibility of occlusion of the lung vessels (pulmonary embolism)
- lacrimation increased
- tinnitus
- blockage of the nasal passages (nasal congestion)
- Oropharyngeal pain
- Rhino rhea
- Sneezing
- Pulmonary veno-occlusive disease
- Obliterative bronchiolitis

- Alveolitis allergic
- Pneumonitis
- 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
- damage or death of the foetus
- changes in the results of some blood tests (glucose level, hormone levels)
- disorder of the brain (encephalopathy), neurotoxicity manifested as a syndrome characterized by headache, confusion, seizures and visual loss (posterior reversible encephalopathy syndrome), abnormal sensation (dysesthesia, hypoesthesia,), tremor, impairment of the sense of taste (dysgeusia, hypogeusia), impairment of the sense of smell (parosmia)Different kind of heart disorders (Ventricular tachycardia, Cardiogenic shock, Pericardial effusion, Bradycardia, Palpitations, Electrocardiogram QT prolonged)
- Infertility in women and men
- Changes in the frequency of menstruation
- Intra-uterine death
- Foetal malformation
- Foetal growth retardation
- Carcinogenic effect on offspring
- Salivary gland inflammation (usually in cheek area; parotid gland inflammation)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [TO BE COMPLETED NATIONALLY]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP
The expiry date refers to the last day of that month.

Do not store above 25°C.

After reconstitution for intravenous administration
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C for the reconstituted solution and for the diluted solution.

From a microbiological point of view, the reconstituted and diluted solution should be used immediately, unless reconstitution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions before use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8°C.

Do not throw away any medicines via wastewater. 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 [TO BE COMPLETED NATIONALLY] contains

- The active substance is cyclophosphamide 500 mg.
- The active substance is cyclophosphamide 1000 mg.
- The active substance is cyclophosphamide 2000 mg.

- There are no other ingredients

What [TO BE COMPLETED NATIONALLY] looks like and contents of the pack

[TO BE COMPLETED NATIONALLY] is a white crystalline powder.

[To be completed nationally] 500 mg powder for solution for injection/infusion is packed in boxes containing 1,5 or 10 clear-colourless Type I-glass 50 ml vials with uncoated bromobutyl ~~rubber~~ stopper, and flip-off seal with a red PP button.
[To be completed nationally] 1000 mg powder for solution for injection/infusion is packed in boxes containing 1,5 or 10 clear-colourless Type I-glass 100 ml vials with uncoated bromobutyl ~~rubber~~ stopper, and flip-off seal with a sea green PP button.

[To be completed nationally] 2000 mg powder for solution for injection/infusion is packed in boxes containing 1,5 or 10 clear-colourless Type I-glass 100 ml vials with uncoated bromobutyl ~~rubber~~ stopper, and flip-off seal with a purple PP button.

Not all pack sizes may be marketed.

Vials are packed with or without a protective plastic overwrap (Onco-Safe). “Onco-Safe” does not come into contact with the medicinal product and provides additional transport protection, which increases the safety for the medical and pharmaceutical personnel.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}.>

<[To be completed nationally]>
<Other sources of information>

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The following information is intended for healthcare professionals only:

[TO BE COMPLETED NATIONALLY] should only be used by clinicians experienced in the use of cancer chemotherapy. [TO BE COMPLETED NATIONALLY] 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 and mode of administration
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.

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

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, [TO BE COMPLETED NATIONALLY] 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.

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.

Handling

The choice of solvent for reconstituting [TO BE COMPLETED NATIONALLY] containing cyclophosphamide depends on the route of administration to be used.

Infusion:
If the solution is to be used for IV infusion, [TO BE COMPLETED NATIONALLY] (containing cyclophosphamide) is reconstituted by adding sterile water for injection or 0.9% sterile sodium chloride solution.
Reconstituted [TO BE COMPLETED NATIONALLY] should be further diluted in 5% dextrose or 0.9% sodium chloride solution prior to infusion.

Direct injection:
If the solution is to be used for direct injection, [TO BE COMPLETED NATIONALLY] (containing cyclophosphamide) is reconstituted by adding 0.9% sterile sodium chloride solution.
Please note that only [TO BE COMPLETED NATIONALLY] reconstituted in 0.9% sterile sodium chloride solution is suitable for bolus injection.
[TO BE COMPLETED NATIONALLY] (containing cyclophosphamide) reconstituted in water is hypotonic and should not be injected directly.

The following quantities of water for injections or sodium chloride 0.9 % are added to the vials containing [To be completed nationally], powder for solution for injection/infusion

Vial of 500 mg: 25 ml
Vial of 1000 mg: 50 ml
Vial of 2000 mg: 100 ml

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 y 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.

After reconstitution the solution is clear and colourless to light yellow. Please check the vial before further use. Only clear solutions must be used.
[To be completed nationally], powder for solution for injection/infusion reconstituted in water for injection has an osmolality of 92 mOsm/kg.
[To be completed nationally], powder for solution for injection/infusion reconstituted in 0.9% sodium chloride has an osmolality of 353 mOsm/kg and a pH of 4.6

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

The rules and regulations for handling cytostatics in general must be observed when reconstituting or handling [To be completed nationally]. 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. If [To be completed nationally], 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
Cytotoxic preparations should not be handled by pregnant staff. 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.
Adequate protective gloves, masks and clothing should be worn. Precautions should be taken to avoid the drug accidentally coming into contact with skin or mucous membranes, the affected area should be cleaned thoroughly with soap and water. If accidental contamination occurs with the eyes, they should be wahsed with water thoroughly and immediately.
Use Luer-lock fittings on all syringes and sets. Large bore needles are recommended to minimise 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

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C for the reconstituted solution and for the diluted solution.

From a microbiological point of view, the reconstituted and diluted solution should be used immediately, unless reconstitution has taken place in controlled and validated aseptic conditions. 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

Special precautions for storage

Do not store above 25°C.

For storage conditions after reconstitution of the medicinal product, see above.