

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Cyclophosphamide Injection 1 g.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cyclophosphamide monohydrate equivalent to 1000mg anhydrous cyclophosphamide.

When reconstituted for intravenous use, the solution for administration contains 20mg cyclophosphamide per ml.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A white crystalline powder contained in clear glass injection vials.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Cyclophosphamide is a cytotoxic drug for the treatment of malignant disease in adults and children. As a single agent, it has successfully produced an objective remission in a wide range of malignant conditions. Cyclophosphamide is also frequently used in combination with other cytotoxic drugs, radiotherapy or surgery.

4.2. Posology and method of administration

Cyclophosphamide Injection is for intravenous or oral administration.

Cyclophosphamide should only be used by clinicians experienced in the use of cancer chemotherapy. Cyclophosphamide 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

Dosage must be individualized. 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).

A guide to the dosage regimens used for most indications is given below.

This treatment should be continued until a clear remission or improvement is seen or be interrupted when the extent of leucopenia becomes unacceptable.

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Conventional: 80-300 mg/m² daily as a single i.v. dose or daily divided oral doses.
300-600 mg/m² as a single i.v. dose weekly.

High dose: 600 - 1500 mg/m² as a single i.v. dose or short infusion given at
10-20 day intervals.

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

Activation of cyclophosphamide requires hepatic metabolism; therefore, oral and intravenous administrations are preferred.

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.

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. See Section 4.4.

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.

Patients with Hepatic Impairment

Severe hepatic impairment may be associated with decreased activation of cyclophosphamide. This may alter the effectiveness of cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected.

Patients with Renal Impairment

In patients with renal impairment, particularly in patients with severe renal impairment, decreased renal excretion may result in increased plasma levels of cyclophosphamide and its metabolites. This may result in increased toxicity and should be considered when determining the dosage in such patients.

Cyclophosphamide and its metabolites are dialyzable, although there may be differences in clearance depending upon the dialysis system being used. In patients requiring dialysis, use of a consistent interval between cyclophosphamide administration and dialysis should be considered. See Section 4.4.

Elderly

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

Children

No specific information. Children have received Cyclophosphamide. No adverse reactions specific to this group have been reported.

Method of Administration

Cyclophosphamide is inert until activated by enzymes in the liver. However, as with all cytotoxics, it is suggested 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.

Intravenous administration

Intravenous administration preferably should be conducted as an infusion, usually given directly into the tubing of a fast running i.v. infusion with the patient supine. Care should be taken that extravasation does not take place, however, should it occur, no specific measures need be taken.

Duration of the infusion also should be appropriate for the volume and type of carrier fluid to be infused.

If injected directly, cyclophosphamide for parenteral administration should be reconstituted with physiological saline (0.9% sodium chloride), see section 6.6. The pH of an aqueous solution is between 4 and 6.

Cyclophosphamide, reconstituted in water, is hypotonic and should not be injected directly. For infusion, cyclophosphamide should be reconstituted by adding sterile water and infused in the recommended intravenous solutions.

Before parenteral administration, the substance must be completely dissolved.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Oral administration

For oral use, an elixir may be prepared by dissolving the dry powder in Aromatic Elixir USP.

4.3. Contraindications

Cyclophosphamide is contra-indicated in patients with:

- hypersensitivity to cyclophosphamide or to any of its metabolites.
- acute infections,
- bone-marrow aplasia,
- urinary tract infection
- acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy
- Urinary outflow obstruction.

Cyclophosphamide should not be used in the management of non-malignant disease, except for immunosuppression in life-threatening situations.

Cyclophosphamide is contra-indicated during pregnancy. See section 4.4 and 4.6.

4.4. Special warnings and precautions for use

WARNINGS

Anaphylactic Reactions, Cross-sensitivity with Other Alkylating Agents

Anaphylactic reactions including those with fatal outcomes have been reported in association with cyclophosphamide.

Possible cross-sensitivity with other alkylating agents has been reported.

Myelosuppression, Immunosuppression, Infections

Treatment with cyclophosphamide may cause myelosuppression and significant suppression of immune responses.

Cyclophosphamide-induced myelosuppression can cause leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding events), and anaemia.

Severe immunosuppression has led to serious, sometimes fatal, infections. Sepsis and septic shock have also been reported. Infections reported with cyclophosphamide include pneumonias, as well as other bacterial, fungal, viral, protozoal, and parasitic infections.

Latent infections can be reactivated. Reactivation has been reported for various bacterial, fungal, viral, protozoal, and parasitic infections.

Infections must be treated appropriately.

Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician.

In case of neutropenic fever, antibiotics and/or antimycotics must be given.

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Cyclophosphamide should be used with caution, if at all, in patients with severe impairment of bone marrow function and in patients with severe immunosuppression.

Unless essential, cyclophosphamide should not be administered to patients with a leukocyte count below 2500 cells/microlitre (cells/mm³) and/or a platelet count below 50,000 cells/microlitre (cells/mm³).

Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop a serious infection.

In principle, the fall in the peripheral blood cell and thrombocyte count and the time taken to recover may increase with increasing doses of cyclophosphamide.

The nadirs of the reduction in leukocyte count and thrombocyte count are usually reached in weeks 1 and 2 of treatment. The bone marrow recovers relatively quickly, and the levels of peripheral blood cell counts normalize, as a rule, after approximately 20 days.

Severe myelosuppression must be expected particularly in patients pretreated with and/or receiving concomitant chemotherapy and/or radiation therapy.

Close haematological monitoring is required for all patients during treatment.

Urinary Tract and Renal Toxicity

Hemorrhagic cystitis, pyelitis, ureteritis, and haematuria have been reported with cyclophosphamide therapy. Bladder ulceration/necrosis, fibrosis/contracture and secondary cancer may develop.

Urotoxicity may mandate interruption of treatment.

Cystectomy may become necessary due to fibrosis, bleeding, or secondary malignancy.

Cases of urotoxicity with fatal outcomes have been reported.

Urotoxicity can occur with short-term and long-term use of cyclophosphamide. Hemorrhagic cystitis after single doses of cyclophosphamide has been reported.

Past or concomitant radiation or busulfan treatment may increase the risk for cyclophosphamide-induced hemorrhagic cystitis.

Cystitis is, in general, initially abacterial. Secondary bacterial colonization may follow.

Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions. See Section 4.3.

Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity.

Cyclophosphamide should be used with caution, if at all, in patients with active urinary tract infections.

Adequate treatment with mesna and/or strong hydration to force diuresis can markedly reduce the frequency and severity of bladder toxicity. It is important to ensure that patients empty the bladder at regular intervals.

Hematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist.

It is usually necessary to discontinue cyclophosphamide therapy in instances of severe hemorrhagic cystitis.

Cyclophosphamide has also been associated with nephrotoxicity, including renal tubular necrosis.

Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone) have been reported in association with cyclophosphamide administration. Fatal outcomes have been reported.

Cardiotoxicity, Use in Patients with Cardiac Disease

Myocarditis and myopericarditis, which may be accompanied by significant pericardial effusion and cardiac tamponade, have been reported with cyclophosphamide therapy and have led to severe, sometimes fatal congestive heart failure.

Histopathologic examination has primarily shown hemorrhagic myocarditis. Haemopericardium has occurred secondary to hemorrhagic myocarditis and myocardial necrosis.

Acute cardiac toxicity has been reported with a single dose of less than 2mg/kg cyclophosphamide.

Following exposure to treatment regimens that included cyclophosphamide, supraventricular arrhythmias (including atrial fibrillation and flutter) as well as ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported in patients with and without other signs of cardiotoxicity.

The risk of cyclophosphamide cardiotoxicity may be increased for example, following high doses of cyclophosphamide, in patients with advanced age, and in patients with previous radiation treatment of the cardiac region and/or previous or concomitant treatment with other cardiotoxic agents. See Section 4.5.

Particular caution is necessary in patients with risk factors for cardiotoxicity and in patients with pre-existing cardiac disease.

Pulmonary Toxicity

Pneumonitis and pulmonary fibrosis have been reported during and following treatment with cyclophosphamide. Pulmonary veno-occlusive disease and other forms of pulmonary toxicity have also been reported.

Pulmonary toxicity leading to respiratory failure has been reported.

While the incidence of cyclophosphamide-associated pulmonary toxicity is low, prognosis for affected patients is poor.

Late onset of pneumonitis (greater than 6 months after start of cyclophosphamide) appears to be associated with a particularly high mortality. Pneumonitis may develop even years after treatment with cyclophosphamide.

Acute pulmonary toxicity has been reported after a single cyclophosphamide dose.

Secondary Malignancies

As with all cytotoxic therapy, treatment with cyclophosphamide involves the risk of secondary tumours and their precursors as late sequelae.

The risk of urinary tract cancer as well as the risk of myelodysplastic alterations, partly progressing to acute leukemias, is increased. Other malignancies reported after use of cyclophosphamide or regimens with cyclophosphamide include lymphoma, thyroid cancer, and sarcomas.

In some cases, the second malignancy developed several years after cyclophosphamide treatment had been discontinued. Malignancy has also been reported after *in utero* exposure.

Veno-occlusive Liver Disease

Veno-occlusive liver disease (VOLD) has been reported in patients receiving cyclophosphamide.

A cytoreductive regimen in preparation for bone marrow transplantation that consists of cyclophosphamide in combination with whole-body irradiation, busulfan, or other agents has been identified (see Section 4.5) as a major risk factor for the development of VOLD. After cytoreductive therapy, the clinical syndrome typically develops 1 to 2 weeks after transplantation and is characterized by sudden weight gain, painful hepatomegaly, ascites, and hyperbilirubinemia/jaundice.

However, VOLD has also been reported to develop gradually in patients receiving long-term low-dose immunosuppressive doses of cyclophosphamide.

As a complication of VOLD, hepatorenal syndrome and multiorgan failure may develop. Fatal outcome of cyclophosphamide-associated VOLD has been reported.

Risk factors predisposing a patient to the development of VOLD with high-dose cytoreductive therapy include:

- preexisting disturbances of hepatic function,
- previous radiation therapy of the abdomen, and a
- low performance score.

Genotoxicity

Cyclophosphamide is genotoxic and mutagenic, both in somatic and in male and female germ cells. Therefore, women should not become pregnant and men should not father a child during therapy with cyclophosphamide.

Both women and men should wait at least 6 to 12 months after stopping Cyclophosphamide before attempting to conceive or father a child.

Animal data indicate that exposure of oocytes during follicular development may result in a decreased rate of implantations and viable pregnancies, and in an increased risk of malformations. This effect should be considered in case of intended fertilization or pregnancy after discontinuation of cyclophosphamide therapy. The exact duration of follicular development in humans is not known, but may be longer than 12 months.

Sexually active women and men should use effective methods of contraception during these periods of time.

Fertility, see section 4.6.

Impairment of Wound Healing

Cyclophosphamide may interfere with normal wound healing.

PRECAUTIONS

Alopecia

Alopecia has been reported and may occur more commonly with increasing doses.

Alopecia may progress to baldness.

The hair can be expected to grow back after treatment with the drug or even during continued drug treatment, though it may be different in texture or colour.

Nausea and Vomiting

Administration of cyclophosphamide may cause nausea and vomiting.

Current guidelines on the use of antiemetics for prevention and amelioration of nausea and vomiting should be considered.

Alcohol consumption may increase cyclophosphamide-induced vomiting and nausea.

Stomatitis

Administration of cyclophosphamide may cause stomatitis (oral mucositis).

Current guidelines on measures for prevention and amelioration of stomatitis should be considered.

Paravenous Administration

The cytostatic effect of cyclophosphamide occurs after its activation, which takes place mainly in the liver. Therefore, the risk of tissue injury from accidental paravenous administration is low.

In case of accidental paravenous administration of cyclophosphamide, the infusion should be stopped immediately, the extravascular cyclophosphamide solution should be aspirated with the cannula in place, and other measures should be instituted as appropriate.

Use in Patients with Renal Impairment

In patients with renal impairment, particularly in patients with severe renal impairment, decreased renal excretion may result in increased plasma levels of cyclophosphamide and its metabolites. This may result in increased toxicity and should be considered when determining the dosage in such patients. See Section 4.2.

Use in Patients with Hepatic Impairment

Severe hepatic impairment may be associated with decreased activation of cyclophosphamide. This may alter the effectiveness of cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected.

Use in Adrenalectomized Patients

Patients with adrenal insufficiency may require an increase in corticoid substitution dose when exposed to stress from toxicity due to cytostatics, including cyclophosphamide.

4.5. Interaction with other medicinal products and other forms of interaction

Planned coadministration or sequential administration of other substances or treatments that could increase the likelihood or severity of toxic effects (by means of pharmacodynamic or pharmacokinetic interactions) requires careful individual assessment of the expected benefit and the risks.

Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention. Patients being treated with cyclophosphamide and agents that reduce its activation should be monitored for a potential reduction of therapeutic effectiveness and the need for dose adjustment.

Interactions Affecting the Pharmacokinetics of Cyclophosphamide and its Metabolites

- Reduced activation of cyclophosphamide may alter the effectiveness of cyclophosphamide treatment. Substances that delay activation of cyclophosphamide include:

- Aprepitant
 - Bupropion
 - Busulfan: Cyclophosphamide clearance has been reported to be reduced and half-life prolonged in patients who receive high-dose cyclophosphamide less than 24 hours after high-dose busulfan.
 - Ciprofloxacin: When given prior to the treatment with cyclophosphamide (used for conditioning prior to bone marrow transplantation), ciprofloxacin has been reported to result in a relapse of the underlying disease.
 - Chloramphenicol
 - Fluconazole
 - Itraconazole
 - Prasugrel
 - Sulfonamides
 - Thiotepa: A strong inhibition of cyclophosphamide bioactivation by thiotepa in high-dose chemotherapy regimens has been reported when thiotepa was administered 1 hour prior to cyclophosphamide.
- An increase of the concentration of cytotoxic metabolites may occur with:
 - Allopurinol
 - Chloral hydrate
 - Cimetidine
 - Disulfiram
 - Glyceraldehyde
 - Inducers of human hepatic and extrahepatic microsomal enzymes (e.g., cytochrome P450 enzymes): The potential for hepatic and extrahepatic microsomal enzyme induction must be considered in case of prior or concomitant treatment with substances known to induce an increased activity of such enzymes such as rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, and corticosteroids.
 - Protease inhibitors: Concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites. Use of protease inhibitor-based regimens was found to be associated with a higher incidence of infections and neutropenia in patients receiving cyclophosphamide, doxorubicin, and etoposide (CDE) than use of an NNRTI-based regimen.
 - Ondansetron

There have been reports of a pharmacokinetic interaction between ondansetron and high-dose cyclophosphamide resulting in decreased cyclophosphamide AUC.

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

Combined or sequential use of cyclophosphamide and other agents with similar toxicities can cause combined (increased) toxic effects.

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- Increased hematotoxicity and/or immunosuppression may result from a combined effect of cyclophosphamide and, for example
 - ACE inhibitors: ACE inhibitors can cause leukopenia.
 - Natalizumab
 - Paclitaxel: Increased hematotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion.
 - Thiazide diuretics
 - Zidovudine
 - Clozapine
- Increased cardiotoxicity may result from a combined effect of cyclophosphamide and, for example
 - Anthracyclines
 - Cytarabine
 - Pentostatin
 - Radiation therapy of the cardiac region
 - Trastuzumab
- Increased pulmonary toxicity may result from a combined effect of cyclophosphamide and, for example
 - Amiodarone
 - G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor): Reports suggest an increased risk of pulmonary toxicity in patients treated with cytotoxic chemotherapy that includes cyclophosphamide and G-CSF or GMCSF.
- Increased nephrotoxicity may result from a combined effect of cyclophosphamide and, for example
 - Amphotericin B
 - Indomethacin: Acute water intoxication has been reported with concomitant use of indomethacin.
- Increase in other toxicities
 - Azathioprine: Increased risk of hepatotoxicity (liver necrosis)
 - Busulfan: Increased incidence of hepatic veno-occlusive disease and mucositis has been reported.
 - Protease inhibitors: Increased incidence of mucositis.

Other interactions

- Alcohol

A reduced antitumor activity was observed in tumor-bearing animals during ethanol (alcohol) consumption and concomitant oral low-dose cyclophosphamide medication.

In some patients, alcohol may increase cyclophosphamide-induced vomiting and nausea.

- Etanercept

In patients with Wegener's granulomatosis, the addition of etanercept to standard treatment, including cyclophosphamide, was associated with a higher incidence of non-cutaneous solid malignancies.

- Metronidazole

Acute encephalopathy has been reported in a patient receiving cyclophosphamide and metronidazole. Causal association is unclear.

In an animal study, the combination of cyclophosphamide with metronidazole was associated with increased cyclophosphamide toxicity.

- Tamoxifen

Concomitant use of tamoxifen and chemotherapy may increase the risk of thromboembolic complications.

Interactions Affecting the Pharmacokinetics and/or Actions of Other Drugs

- Bupropion

Cyclophosphamide metabolism by CYP2B6 may inhibit bupropion metabolism.

- Coumarins

Both increased and decreased warfarin effect have been reported in patients receiving warfarin and cyclophosphamide.

- Cyclosporine

Lower serum concentrations of cyclosporine have been observed in patients receiving a combination of cyclophosphamide and cyclosporine than in patients receiving only cyclosporine. This interaction may result in an increased incidence of graft-versus-host disease.

- Depolarizing muscle relaxants

Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity. Prolonged apnea may occur with concurrent depolarizing muscle relaxants (e.g., succinylcholine). If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

- Digoxin, β -acetyldigoxin

Cytotoxic treatment has been reported to impair intestinal absorption of digoxin and β -acetyldigoxin tablets.

- Vaccines

The immunosuppressive effects of cyclophosphamide can be expected to reduce the response to vaccination. Use of live vaccines may lead to vaccine-induced infection.

- Verapamil

Cytotoxic treatment has been reported to impair intestinal absorption of orally administered verapamil

4.6. Pregnancy and lactation

Pregnancy

Cyclophosphamide is contraindicated in pregnancy (see section 4.3).

Cyclophosphamide crosses the placental barrier. Treatment with cyclophosphamide has a genotoxic effect and may cause foetal damage when administered to pregnant women. Both women and men should wait at least 6 to 12 months after stopping Cyclophosphamide before attempting to conceive or father a child.

- Malformations have been reported in children born to mothers treated with cyclophosphamide during the first trimester of pregnancy. However, there are also reports of children without malformations born to women exposed during the first trimester.
- Exposure to cyclophosphamide in utero may cause miscarriage, foetal growth retardation, and foetotoxic effects manifesting in the newborn, including leukopenia, anaemia, pancytopenia, severe bone marrow hypoplasia, and gastroenteritis.
- Animal data suggest that an increased risk of failed pregnancy and malformations may persist after discontinuation of cyclophosphamide as long as oocytes/follicles exist that were exposed to cyclophosphamide during any of their maturation phases. See Section 4.4, Genotoxicity.
- If cyclophosphamide is used during pregnancy, or if the patient becomes pregnant while taking this drug or after treatment (see Section 4.4, Genotoxicity), the patient should be apprised of the potential hazard to a foetus.

Breastfeeding

Cyclophosphamide is passed into the breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhoea have been reported in children breast fed by women treated with cyclophosphamide. Women must not breastfeed during treatment with cyclophosphamide.

Fertility

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Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes.

Development of sterility appears to depend on the dose of cyclophosphamide, duration of therapy, and the state of gonadal function at the time of treatment.

Cyclophosphamide-induced sterility may be irreversible in some patients.

Sexually active women and men should use effective methods of contraception during these periods of time.

- Female patients

Amenorrhea, transient or permanent, associated with decreased oestrogen and increased gonadotrophin secretion develops in a significant proportion of women treated with cyclophosphamide.

For older women, in particular, amenorrhea may be permanent.

Oligomenorrhea has also been reported in association with cyclophosphamide treatment.

Girls treated with cyclophosphamide during prepubescence generally develop secondary sexual characteristics normally and have regular menses.

Girls treated with cyclophosphamide during prepubescence subsequently have conceived.

Girls treated with cyclophosphamide who have retained ovarian function after completing treatment are at increased risk of developing premature menopause (cessation of menses before age of 40 years).

- Male patients

Men treated with cyclophosphamide may develop oligospermia or azoospermia, which are normally associated with increased gonadotrophin but normal testosterone secretion.

Sexual potency and libido generally are unimpaired in these patients.

Boys treated with cyclophosphamide during prepubescence may develop secondary sexual characteristics normally, but may have oligospermia or azoospermia.

Some degree of testicular atrophy may occur.

Cyclophosphamide-induced azoospermia is reversible in some patients, though the reversibility may not occur for several years after cessation of therapy.

4.7. Effects on ability to drive and use machines

Patients undergoing treatment with cyclophosphamide may experience undesirable effects (including, e.g., dizziness, blurred vision, visual impairment) which could affect the ability to drive or use machines. The decision to drive or operate machinery should be made on an individual basis.

4.8. Undesirable effects

Immune system disorders / Vascular disorders (Hypersensitivity reactions)

Hypersensitivity reactions, e.g. accompanied by rash, chills, fever, tachycardia, bronchospasm, dyspnoea, oedema, hot flush and drop in blood pressure may occur uncommonly. Symptoms like conjunctivitis and eye oedema are reported very rarely in connection with hypersensitivity reactions.

In very rare cases, anaphylactoid reactions may progress to anaphylactic shock.

Anorexia, nausea and vomiting and mucosal ulceration can occur. This may be reduced by the prior administration of an anti-emetic agent. Rarely renal and hepatic dysfunction (including jaundice and increased liver enzymes) have been reported.

Alopecia occurs to some degree in about 20% of patients receiving over 100 mg daily and is inevitable following high doses. Epilation commences usually after the first three weeks of treatment, but regrowth is evident after three months in most patients even though they remain on treatment.

The reticulo-endothelial system is depressed, granulopoiesis and lymphopoiesis being more affected than thrombopoiesis and erythropoiesis, but this depression is reversible. When a single dose is given, the fall in the peripheral white cell count reaches its nadir within 5-10 days. Recovery is seen at 10-14 days following administration, with full recovery in most cases by 21-28 days. The fall in the peripheral count and the time taken to recover may increase with increasing doses of Cyclophosphamide.

An alteration in carbohydrate metabolism may be seen in patients on Cyclophosphamide. Hyperglycaemia has been reported.

Azoospermia often occurs in men and is dose dependent. Spontaneous recovery of fertility may occur, and is also dependent on dose. Menstruation in women commonly ceases during therapy, and may be permanent, particularly in older women. Cyclophosphamide may have an adverse effect on prepubertal gonads.

Cardiotoxicity may be induced in patients who have had or are receiving mediastinal irradiation or doxorubicin. It has also been reported with high doses of cyclophosphamide. This mainly occurs as a tachyarrhythmia and may progress in severe cases to intractable heart failure. Following large doses, ECG changes and elevation of LDH, AST and CPK have been reported in some patients.

Haematuria may occur during or after therapy with Cyclophosphamide. Where mesna is not given in conjunction with Cyclophosphamide, acute sterile haemorrhagic cystitis may occur in up to 10% of patients. Late sequelae of this cystitis are bladder contracture and fibrosis.

Cyclophosphamide has been shown to be mutagenic, teratogenic, and carcinogenic in certain laboratory tests and, as with other cytotoxic agents, there have been reports of possible drug-induced neoplasia. There is an excessive risk of acute leukaemia and bladder cancer following cyclophosphamide therapy.

Cyclophosphamide therapy may lead to inappropriate secretion of anti-diuretic hormone with fluid retention and hyponatraemia, and subsequent water intoxication.

Other side-effects, such as pancreatitis, pigmentation, macrocytosis, and induction of hyperglycaemia or hypoglycaemia have been reported. Pneumonitis and pulmonary fibrosis have also occasionally been associated with Cyclophosphamide therapy.

Note:

There are certain complications, such as veno-occlusive disease, thromboembolism, DIC (disseminated intravascular coagulation) or haemolytic uraemic syndrome, that may also be induced by the underlying disease, but which might occur with an increased frequency during chemotherapy that includes Cyclophosphamide.

Side-effects have occasionally occurred after cessation of treatment.

4.9. Overdose

Serious consequences of overdosage include manifestations of dose dependent toxicities such as myelosuppression, urotoxicity, cardiotoxicity (including cardiac failure), veno-occlusive hepatic disease, and stomatitis. See Section 4.4.

Patients who received an overdose should be closely monitored for the development of toxicities, and haematotoxicity in particular.

No specific antidote for cyclophosphamide is known.

Cyclophosphamide and its metabolites are dialysable. Consider haemodialysis in cases of severe overdose presenting early, particularly in patients with renal impairment

Overdosage should be managed with supportive measures, including appropriate, state-of-the-art treatment for any concurrent infection, myelosuppression, or other toxicity, should it occur.

Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with cyclophosphamide overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Cyclophosphamide has been demonstrated to have a cytostatic effect in many tumour types. The active metabolites of cyclophosphamide are alkylating agents which transfer alkyl groups to DNA during the process of cell division, thus preventing normal synthesis of DNA.

5.2. Pharmacokinetic properties

Cyclophosphamide is well absorbed following an oral dose with a mean half-life of 4-8 hours for both oral and parenteral administration.

It is an inactive pro drug with alkylating metabolites produced by hepatic metabolism, reaching peak levels 4-6 hours after an i.v. injection. Hepatic enzymes may be induced. The parent compound binds poorly to plasma protein but the active metabolites are significantly

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protein-bound. The drug is widely distributed and crosses the blood-brain barrier, the placental barrier and is found in ascites. The metabolites are excreted renally.

5.3. Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to the information already stated in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

None.

6.2. Incompatibilities

Benzyl alcohol increases the degradation rate of cyclophosphamide.

6.3. Shelf-life

Unopened
36 months.

After reconstitution for intravenous administration
Chemical and physical in-use stability has been demonstrated (in aqueous, sodium chloride, and glucose solutions) for 48 hours at 2 - 8°C.

From a microbiological point of view, the 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 - 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

After reconstitution in Aromatic Elixir USP for oral administration
At a concentration of 2 mg cyclophosphamide per ml in Aromatic Elixir USP, chemical and physical stability has been demonstrated for 14 days at 2 - 8°C.

6.4. Special precautions for storage

Do not store above 25°C.

Store in original container.

After reconstitution (for either intravenous or oral administration), store at 2 - 8°C and protect from light.

6.5. Nature and contents of container

75 ml type I or type III glass vials with butyl rubber closures and plastic and aluminium caps.

Pack size : 1 vial.

6.6. Special precautions for disposal

For intravenous administration

Prior to administration the contents of a vial should be dissolved in 50 ml physiological saline (0.9% w/v sodium chloride) by introducing the saline into the vial and shaking vigorously until the powder is completely dissolved. Reconstitution results in a clear solution with a pH of between 4 and 6.

Cyclophosphamide Injection is compatible with the following infusion solutions: sodium chloride solution, glucose solution, sodium chloride and glucose solution, sodium chloride and potassium chloride solution, and potassium chloride and glucose solution.

For oral administration

Cyclophosphamide Injection may be dissolved in Aromatic Elixir USP.

General instructions

If vials are stored above the recommended temperature this can cause degradation of the active ingredient, identifiable by a yellow melted appearance to the vial contents. Vials containing melted material should not be used.

Cyclophosphamide is a cytotoxic agent. The handling and preparation of cyclophosphamide should always be in accordance with current guidelines on safe handling of cytotoxic agents. The material should not be handled by women who are pregnant or who are breast-feeding.

Adequate care and precautions should be taken in the disposal of empty vials and items (syringes, needles, etc) used in reconstitution and administration.

7. MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.,
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8. MARKETING AUTHORISATION NUMBER

PL 00116/0388

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

1st May 2003

10. DATE OF REVISION OF THE TEXT

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