Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cyclophosphamide Seacross 500 mg powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Strength after reconstitution: 20 mg cyclophosphamide (anhydrous)/ml solution (for reconstitution volumes, see 6.6.)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion
White crystal or crystalline powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cyclophosphamide may be used alone or in combination with other chemotherapeutic agents, depending on the indication. Cyclophosphamide Seacross is indicated in the treatment of:

- Chronic Lymphocytic Leukaemia (CLL),
- Acute Lymphocytic Leukaemia (ALL),
- As conditioning for a bone marrow transplantation, in the treatment of Acute Lymphoblastic Leukaemia, Chronic Myelogenous Leukaemia and Acute Myelogenous Leukaemia in combination with whole body irradiation or busulfan,
- Hodgkin's lymphoma, Non-Hodgkin's lymphoma and Multiple Myeloma,
- Metastatic ovarian and breast, carcinoma,
- Adjuvant treatment of breast carcinoma,
- Ewing's sarcoma,
- Small cell lung cancer,
- advanced or metastatic neuroblastoma,
- Life-threatening autoimmune diseases: severe progressive forms of lupus nephritis and Wegener's granulomatosis.

4.2 Posology and method of administration

Cyclophosphamide Seacross should only be used by clinicians experienced in the use of cancer chemotherapy. Cyclophosphamide Seacross 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 individualised. Doses and duration of treatment and/or treatment intervals depend on the therapeutic indication, the scheme of a combination therapy, the patient's general state of health and organ function, and the results of laboratory monitoring (in particular, blood cell monitoring).

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

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

Prior, during 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 Seacross should be administered in the morning. See section 4.4.

It is within the responsibility of the physician to decide on the use of Cyclophosphamide according to the operative treatment guidelines.
The doses below can be regarded as general guidelines:

Hematologic and solid tumours
a. For daily treatment:
3 – 6 mg/kg body weight (= 120 – 240 mg/m^2 body surface area), injected intravenously,

b. For intermittent treatment:
10 – 15 mg/kg body weight (= 400 – 600 mg/m^2 body surface area), injected intravenously, with therapy-free intervals of 2 to 5 days.

c. For high-dose- intermittent treatment:
20 – 40 mg/kg body weight (= 800 – 1600 mg/m^2 body surface area), injected intravenously, with therapy-free intervals of 21 to 28 days.

As preparation for a bone marrow transplantation
2 days 60 mg/kg or 4 days 50 mg/kg body weight injected intravenously.
If a busulfan-cyclophosphamide (Bu/Cy) regimen is applied, the first dose of cyclophosphamide must be administered at least 24 hours after the last dose of busulfan (see section 4.4 and 4.5).

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

Patients with Hepatic Impairment
Severe hepatic impairment may be associated with a decreased activation of cyclophosphamide. This may alter the effectiveness of the cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected. (See section 4.4). The dose must be reduced in patients with severe hepatic impairment.

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 4.4). A dose reduction of 50% for a glomerular filtration rate below 10 mL/minute is recommended.

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
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.

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

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

Leukocyte count/µl	**Platelet count /µl**	**Dosage**
> 4000	> 100 000	100% of the planned dose
2500 – 4000	50 000 – 100 000	50 % of the planned dose

< 2500	< 50 000	Omit until values normalise or decide individually

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

Method of administration
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

Precaution to be taken before manipulating or administering the product
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.

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

Infusion:
If the solution is to be used for intravenous infusion, Cyclophosphamide Seacross (containing cyclophosphamide) is reconstituted by adding sterile water for injection or sodium chloride 9 mg/mL (0.9%) solution for injection.

Reconstituted Cyclophosphamide Seacross should be further diluted in 5% glucose or sodium chloride 9 mg/mL (0.9%) solution for infusion prior to infusion.

Direct injection:
If the solution is to be used for direct injection, Cyclophosphamide Seacross (containing cyclophosphamide) is reconstituted by adding sodium chloride 9 mg/mL (0.9%) solution for injection.
Please note that only Cyclophosphamide Seacross reconstituted in sodium chloride 9 mg/mL (0.9%) solution for injection is suitable for bolus injection.
Cyclophosphamide Seacross **(containing cyclophosphamide) reconstituted in water is hypotonic and should not be injected directly.**

Intravenous use
Intravenous administration should preferably be conducted as an infusion.
To reduce the likelihood of adverse reactions that appear to be administration rate-dependent (e.g. facial swelling, headache, nasal congestion, scalp burning), cyclophosphamide should be injected or infused very slowly. Duration of the infusion (ranging from 30 minutes to 2 hours) should be appropriate for the volume and type of carrier fluid to be infused.

For instructions on reconstitution and dilution of Cyclophosphamide Seacross before administration, see section 6.6.

4.3 Contraindications

Cyclophosphamide Seacross is contra-indicated in patients with:

- hypersensitivity to cyclophosphamide, any of its metabolites
- acute infections;
- bone marrow aplasia or bone marrow depression prior to treatment,
- urinary tract infection;
- acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy;
- urinary outflow obstruction
- breastfeeding (see section 4.6)

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

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 (anaemia, leukopenia, neutropenia and thrombocytopenia) and significant suppression of immune responses, which may result in severe, sometimes fatal, infections, sepsis and septic shock. 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 occurring during treatment with cyclophosphamide, including neutropenic fever, 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. Cyclophosphamide must be administered with the necessary caution (or not at all) in patients with severe *functional impairment of bone marrow* and patients with severe immunosuppression.

Close haematological monitoring is required for all patients during treatment. Haematological parameters must be checked prior to each administration and regularly during treatment. More frequent monitoring may be required if leukocyte counts drop below 3000 cells/microlitre (cells/mm^3).
Dose adjustment due to myelosuppression is recommended (see section 4.2)

Unless essential, cyclophosphamide should not be administered to patients with a leukocyte count below 2500 cells/microlitre (cells/ mm^3 and/or a platelet count below 50,000 cells/microlitre (cells/mm^3).

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.

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

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

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. 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. Cystectomy may become necessary due to fibrosis, bleeding, or secondary malignancy. Past or concomitant radiation or busulfan treatment may increase the risk for cyclophosphamide-induced hemorrhagic cystitis. Cystitis is, in general, initially abacterial. Secondary bacterial colonisation 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. 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. Haematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Severe hemorrhagic cystitis usually requires a discontinuation of the treatment with cyclophosphamide.

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 been reported secondary to hemorrhagic myocarditis and myocardial necrosis. Acute cardiac toxicity has been reported with single doses as low as 20 mg/kg of 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 as a result of treatment with cyclophosphamide may, for example, be increased 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 required in patients with risk factors for cardiotoxicity and in patients with a 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 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 lymphomas, 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.
The risk of bladder cancer can be markedly reduced by hemorrhagic cystitis prophylaxis.

Veno-occlusive Liver Disease
Veno-occlusive liver disease (VOLD) has been reported in patients receiving cyclophosphamide, mainly in patients receiving a cytoreductive regimen in preparation for bone marrow transplantation in combination with whole-body irradiation, busulfan, or other agents (see section 4.5). 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 include pre-existing disturbances of hepatic function, previous radiation therapy of the abdomen, and a low performance score. VOLD incidence has been reported to reduce, if a time interval of at least 24 hours is observed between the last administration of busulfan and the first administration of cyclophosphamide (see section 4.2 and 4.5).

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.
Women should not become pregnant during the treatment and for a period of 6 months following discontinuation of the therapy.
Men should not father a child during the treatment and for a period of 3 months following discontinuation of the therapy.

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 malfor-mations. 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 (see section 4.6.).

Fertility
Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes.
Men treated with cyclophosphamide should be informed about sperm preservation prior to treatment (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
Administraton 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 pre-vention 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. The area should subsequently be rinsed with physiological saline solution, and the arm or leg should rest.

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 a decreased effect of cyclophosphamide. This may negatively alter the effectiveness of cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected. See section 4.2. Due to the porphyrogenic effect of Cyclophosphamide patients with acute porphyria should be treated with caution.

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

Use in Patients with Diabetes Mellitus
Caution is also advised in is patients with diabetes mellitus, since cyclophosphamide may interact with insulin and other hypoglycaemic agents (also see section 4.5).

Use in Patients who have recently undergone surgery
In general, cytostatics (among which agents cyclophosphamide) should not be administered to patients who had a surgery less than 10 days ago.

4.5 Interaction with other medicinal products and other forms of interaction

Cyclophosphamide is inactive, but is metabolised in the liver, mainly by CYP2A6, 2B6, 2C9, 2C19 and 3A4, into two active metabolites.

Planned co-administration or sequential administration of other substances or treatments with cyclophosphamide 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 negatively 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: decreased elimination of cyclophosphamide and prolonged half-life has been reported in patients who received high-dose cyclophosphamide less than 24 hours after high-dose busulfan. Increased incidence of hepatic veno-occlusive disease and mucositis has been reported with concomitant administration (see section 4.2 and 4.4).
- Ciprofloxacin: when administered prior to treatment with cyclophosphamide (used for conditioning prior to bone marrow transplant), ciprofloxacin may cause regression of the underlying disease.
- Chloramphenicol
- Azole-antimycotics (Fluconazole, Itraconazole): Azole-antimycotics are known to inhibit cytochrome P450 enzymes. Increased amounts of toxic degradation products of cyclophosphamide have been reported in combination with Itraconazole.
- CYP2B6 and CYP3A4 inhibitors (Nevirapin, Ritonavir): co-administration may reduce the efficacy of cyclophosphamide.
- Prasugrel
- Sulfonamides, e.g. sulfadiazine, sulfamethoxazole and sulfapyridine.
- 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.
- Ondansetron: There have been reports of a pharmacokinetic interaction between ondansetron and high-dose cyclophosphamide resulting in decreased cyclophosphamide AUC.
- Grapefruit (fruit or juice), Rifampicin, St. Johns worth: Co-administration with CYP3A4 Inhibitors or Inducers can reduce the efficacy or increase the toxicity of cyclophosphamide.

An increase of the concentration of cytotoxic metabolites may occur with:
- Allopurinol: an increase of bone marrow suppression was reported.
- Azathioprine: increased risk of hepatotoxicity (liver necrosis).
- Chloral hydrate
- Cimetidine
- Disulfiram
- Glyceraldehyde
- 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. Increased incidence of mucositis is reported in combined therapy of cyclophosphamide (CDE) and saquinavir.
- 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, benzodiazepines and corticosteroids.
- Dabrafenib

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.

- 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 (e.g. hydrochlorothiazide): An increase of bone marrow suppression was reported.
- Zidovudine
- Clozapine

- Increased cardiotoxicity may result from a combined effect of cyclophosphamide and, for example

- Anthracyclines
- Mitomycin
- Cytarabine
- Pentostatin
- Radiation therapy of the cardiac region or a whole-body irradiation in combination with high doses of cyclophosphamide
- 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.

<u>Other interactions</u>

- Alcohol

A reduced antitumor activity was observed in tumour-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.

<u>Interactions Affecting the Pharmacokinetics and/or Actions of Other Drugs</u>

- Bupropion

Cyclophosphamide metabolism by CYP2B6 may inhibit bupropion metabolism.

- Coumarins

Both increased and decreased warfarin effects 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 (GVHD).

- Depolarising muscle relaxants

Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity. Prolonged apnoea may occur with concurrent depolarizing muscle relaxants (e.g. succinylcholine, suxamethonium) as a result of a decreased pseudocholinesterase level. If a patient has been treated with cyclophosphamide within 10 days of general anaesthesia, the anaesthesiologist should be alerted.

- Digoxin, β- acetyldigoxin

Impaired absorption of digoxin and β-acetyldigoxin tablets have been reported during a concomitant cytotoxic treatment

- 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

Impaired intestinal absorption of orally administered verapamil has been reported.

- Sulfonylurea derivatives

Blood sugar levels may drop, if cyclophosphamide and sulfonylurea derivatives are used concomitantly.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
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)

Contraception in males and females
Women should not become pregnant during the treatment and for a period of 6 months following discontinuation of the therapy.
Men should not father a child during the treatment and for a period of 3 months following discontinuation of the therapy.
Sexually active women and men should use effective methods of contraception during these periods of time.

Pregnancy
There are very limited data from the use of cyclophosphamide in pregnant women. There are reports of serious multiple congenital aberrations after use during the first trimester.
Animal studies have shown teratogenicity and other reproduction toxicity (see section 5.3).
Considering the data from human case reports, animal studies and the mechanism of action of cyclophosphamide, its use during pregnancy, in particular during the first trimester, is not recommended.
In each individual case the potential benefit of the treatment should be weighed against the potential risk for the foetus.

Breastfeeding
Cyclophosphamide is excreted into the breast milk and can cause neutropenia, thrombocytopenia, low haemoglobin, and diarrhoea in children. Cyclophosphamide is contraindicated during breastfeeding (see section 4.3).

Fertility
Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes.
In women cyclophosphamide may cause transient or permanent amenorrhea, and in boys treated with cyclophosphamide during prepubescence, oligospermia or azoospermia. Men treated with cyclophosphamide may develop oligospermia or azoospermia. Prior to treatment of men with cyclophosphamide, they should be informed of the possibility to store and keep viable sperm collected before treatment.

4.7 Effects on ability to drive and use machines

Patients undergoing treatment with cyclophosphamide may experience undesirable effects (including nausea, vomiting, 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

The frequency of adverse reactions reported in the table below are derived from clinical trials and from post marketing experience and are defined using the following convention: very common (>1/10), common (> 1/100 to <1/10), uncommon (> 1/1,000 to <1/100), rare (> 1/10,000 to <1/1,000), very rare (< 1/10,000) not known.

Organ System Class (SOC)	Recommended MedDRA term	Frequency
Infections and infestations	Infections[1]	Common
	Pneumonia[2]	Uncommon
	Sepsis[1]	Uncommon
Neoplasms, benign and malignant and unspecified (including cysts and polyps)	Acute leukaemia[3]	Rare
	Myelodysplastic syndrome	Rare
	Secondary malignancies	Rare
	Bladder cancer	Rare
	Ureteric cancer	Rare
	Tumour lysis syndrome	Very rare
	Non-Hodgkin's lymphoma	Not known
	Sarcoma	Not known
	Renal cell carcinoma	Not known
	Renal pelvis cancer	Not known
	Thyroid cancer	Not known
	Neoplasia	Not known
Blood and lymphatic system disorders	Myelosuppression[4]	Very common
	Leukopenia	Very common
	Neutropenia	Very common
	Febrile neutropenia	Common
	Thrombocytopenia	Uncommon
	Anaemia	Uncommon
	Disseminated intravascular coagulation	Very rare
	Haemolytic uremic syndrome	Very rare
	Agranulocytosis	Not known
	Lymphopenia	Not known
	Haemoglobin decreased	Not known
Immune system disorders	Immunosuppression	Very common
	Anaphylactic/Anaphylactoid reaction	Uncommon
	Hypersensitivity reaction	Uncommon
	Anaphylactic shock	Very rare
Endocrine disorders	SIADH (syndrome of inappropriate antidiuretic hormone secretion)	Rare
	Water intoxication	Not known
Metabolism and nutrition disorders	Anorexia	Uncommon
	Dehydration	Rare

	Hyponatremia	Very rare
	Blood glucose increased	Not known
	Blood glucose decreased	Not known
Psychiatric disorders	Confusional state	Very rare
Nervous system disorders	Peripheral neuropathy	Uncommon
	Polyneuropathy	Uncommon
	Neuralgia	Uncommon
	Convulsion	Rare
	Dizziness	Rare
	Dysgeusia	Very rare
	Hypogeusia	Very rare
	Paresthesia	Very rare
	Neurotoxicity[5]	Not known
	Reversible posterior leukoencephalopathy Syndrome[6]	Not known
	Encephalopathy	Not known
Eye disorders	Blurred vision	Rare
	Visual impairment	Rare
	Conjunctivitis	Very rare
	Eye oedema[7]	Very rare
	Lacrimation increased	Not known
Ear and labyrinth disorders	Deafness	Uncommon
	Tinnitus	Not known
	Hearing impaired	Not known
Cardiac disorders	Cardiomyopathy	Uncommon
	Myocarditis	Uncommon
	Heart failure[8]	Uncommon
	Tachycardia	Uncommon
	Ventricular arrhythmia	Rare
	Supraventricular arrhythmia	Rare
	Ventricular fibrillation	Very rare
	Angina	Very rare
	Myocardial infarction	Very rare
	Pericarditis	Very rare
	Atrial fibrillation	Very rare
	Ventricular tachycardia	Not known
	Cardiogenic shock	Not known
	Pericardial effusion	Not known
	Bradycardia	Not known
	Palpitations	Not known
	Electrocardiogram QT prolonged	Not known
	Myocardial haemorrhage	Not known
	Cardiac failure congestive	Not known
	Left ventricular failure	Not known
	Left ventricular dysfunction	Not known
	Carditis	Not known
	Ejection fraction decreased	Not known
Vascular disorders	Flushing	Uncommon
	Haemorrhage	Rare
	Thromboembolism	Very rare
	Hypertension	Very rare
	Hypotension	Very rare
	Pulmonary embolism	Not known
	Venous thrombosis	Not known
	Vasculitis	Not known
	Peripheral ischemia	Not known
	Hot flush	Not known
	Blood pressure decreased	Not known
Respiratory, thoracic and mediastinal disorders[8,9]	Acute respiratory distress syndrome (ARDS)	Very rare

	Chronic pulmonary interstitial fibrosis	Very rare
	Pulmonary oedema	Very rare
	Bronchospasm	Very rare
	Dyspnoea	Very rare
	Hypoxia	Very rare
	Cough	Very rare
	Nasal congestion	Not known
	Oropharyngeal pain	Not known
	Rhinorrhea	Not known
	Sneezing	Not known
	Pulmonary veno-occlusive disease	Not known
	Obliterative bronchiolitis	Not known
	Alveolitis allergic	Not known
	Pneumonitis	Not known
	Pleural effusion	Not known
	Respiratory failure	Not known
	Organizing pneumonia	Not known
	Respiratory distress	Not known
	Pulmonary hypertension	Not known
Gastrointestinal disorders	Mucosal inflammation	Common
	Enterocolitis haemorrhagic	Very rare
	Acute pancreatitis	Very rare
	Ascites	Very rare
	Stomatitis	Very rare
	Diarrhoea	Very rare
	Vomiting	Very rare
	Constipation	Very rare
	Nausea	Very rare
	Abdominal pain	Not known
	Parotid gland inflammation	Not known
	Gastrointestinal haemorrhage	Not known
	Cecitis	Not known
	Colitis	Not known
	Enteritis	Not known
	Abdominal discomfort	Not known
Hepatobiliary disorders	Hepatic function abnormal	Common
	Hepatitis	Rare
	Veno-occlusive liver disease	Very rare
	Hepatomegaly	Very rare
	Jaundice	Very rare
	Cholestatic hepatitis	Not known
	Hepatotoxicity[10]	Not known
	Cytolytic hepatitis	Not known
	Cholestasis	Not known
Skin and subcutaneous tissue disorders	Alopecia[11]	Very common
	Rash	Rare
	Dermatitis	Rare
	Nail discolouration	Rare
	Skin discolouration[12]	Rare
	Stevens-Johnson syndrome	Very rare
	Toxic epidermal necrolysis	Very rare
	Radiation erythema	Very rare
	Pruritus (including itching due to inflammation)	Very rare
	Erythema multiforme	Not known
	Palmar-plantar erythrodysesthesia syndrome (hand- foot syndrome)	Not known
	Urticaria	Not known
	Erythema	Not known
	Facial swelling	Not known
	Hyperhidrosis	Not known

	Toxic skin eruption	Not known
	Blister	Not known
	Nail disorder	Not known
Musculoskeletal and connective tissue disorders	Rhabdomyolysis	Very rare
	Cramps	Very rare
	Scleroderma	Not known
	Muscle spasms	Not known
	Myalgia	Not known
	Arthralgia	Not known
Renal and urinary tract disorders	Cystitis	Very common
	Microhaematuria	Very common
	Haemorrhagic cystitis	Common
	Macrohematuria	Common
	Suburethral haemorrhage	Very rare
	Bladder wall oedema	Very rare
	Bladder fibrosis and sclerosis	Very rare
	Renal impairment	Very rare
	Renal failure	Very rare
	Blood creatinine increased	Very rare
	Renal tubular necrosis	Very rare
	Renal tubular disorder	Not known
	Nephropathy toxic	Not known
	Haemorrhagic ureteritis	Not known
	Bladder contracture	Not known
	Nephrogenic diabetes insipidus	Not known
	Atypical urinary bladder epithelial cells	Not known
	Blood urea nitrogen increased	Not known
	Bladder necrosis	Not known
Pregnancy, puerperium and perinatal conditions	Premature labour	Not known
Reproductive system and breast disorders	Impairment of spermatogenesis	Common
	Ovulation disorder (rarely irreversible)	Uncommon
	Amenorrhea [13]	Rare
	Azoospermia/asperima [13]	Rare
	Oligospermia [13]	Rare
	Infertility	Not known
	Ovarian Failure	Not known
	Oligomenorrhea	Not known
	Testicular atrophy	Not known
	Ovarian disorder	Not known
	Blood oestrogen decreased	Not known
	Blood gonadotrophin increased	Not known
Congenital, familial and geneticdisorders	Intra-uterine death	Not known
	Foetal malformation	Not known
	Foetal growth retardation	Not known
	Foetal damage	Not known
	Carcinogenic effect on offspring	Not known
General disorders and administrative site conditions	Fever	Very common
	Chills	Common
	Asthenia	Common
	Malaise	Common
	Chest pain	Rare
	Headache	Very rare
	Multiorgan failure	Very rare
	Injection/infusion site reactions (thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema)	Very rare Not known
	General physical deterioration	Not known
	Influenza-like illness	Not known
	Pyrexia	Not known

	Oedema Pain Fatigue	Not known Not known
Investigations	Blood lactate dehydrogenase increased C-reactive protein increased ECG changes Decreased LVEF Weight gain Lower levels of female sex hormones Blood oestrogen level decreased Blood gonadotropin level increased	Uncommon Uncommon Uncommon Uncommon Very rare Uncommon Not known Not known

1. An increased risk for and severity of pneumonias (including fatal outcomes), other bacterial, fungal, viral, protozoal, and parasitic infections; reactivation of latent infections, including viral hepatitis, tuberculosis, JC virus with progressive multifocal leukoencephalopathy (including fatal outcomes), pneumocystis jiroveci, herpes zoster, strongyloides, sepsis and septic shock (including fatal outcomes).
2. including fatal outcomes
3. including acute myeloid leukaemia, acute promyelocytic leukaemia
4. manifested as Bone marrow failure, Pancytopenia, Neutropenia, Agranulocytosis, Granulocytopenia, Thrombocytopaenia (complicated by bleeding), Leukopenia, Anaemia
5. manifested as myelopathy, peripheral neuropathy, polyneuropathy, neuralgia, dysesthesia, hypoesthesia, paresthesia, tremor, dysgeusia, hypogeusia, parosmia.
6. manifested as headache, altered mental functioning, seizures and abnormal vision from blurriness to vision loss
7. Observed in connection with an allergic reaction
8. Including fatal outcomes
9. While the incidence of cyclophosphamide-associated pulmonary toxicity is low, prognosis for affected patients is poor.
10. Hepatic failure, Hepatic encephalopathy, Ascites, Hepatomegaly, Jaundice, Blood bilirubin increased, Hepatic enzymes increased (ASAT, ALAT, ALP, gamma-GT)
11. May progress to baldness
12. Of the palms and heels
13. Persistent

Remark:
Certain complication such as thromboembolisms, disseminated intravascular coagulation, and haemolytic uremic syndrome may occur as a result of the underlying disorders, but the frequency of these complications may increase due to chemotherapy with Cyclophosphamide Seacross.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

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 hematotoxicity in particular.
There is no specific antidote for an overdosage of cyclophosphamide.
Cyclophosphamide and its metabolites are dialyzable. Therefore, rapid haemodialysis is indicated when treating any suicidal or accidental overdose or intoxication.
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 can help to prevent or reduce urotoxic effects in case of cyclophosphamide overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and Immunomodulating Agents; Antineoplastic agents.
Alkylating agents. Nitrogen mustard analogues
ATC code: L01AA01.

Cyclophosphamide has been demonstrated to have a cytostatic effect in many tumour types.

Cyclophosphamide engages probably to the S-or G2-phase of the cell cycle.

It remains to be shown whether the cytostatic effect is entirely dependent on the alkylation of DNA or other mechanisms such as inhibition of chromatin transformation processes or inhibition of DNA polymerases play a role. The metabolite acrolein has no antineoplastic activity, but is responsible for the adverse urotoxic effect.

The immunosuppressive effect of cyclophosphamide is based on the fact that cyclophosphamide has an inhibitory effect on B-cells, CD4 + T-cells and to a lesser extent on CD8 +-T-cells. In addition, it is assumed that cyclophosphamide has an inhibitory effect on the suppressor that regulate the IgG2 class of antibodies.
Cross-resistance, especially with structurally related cytotoxic agents, e.g. ifosfamide, as well as other alkylating agents, cannot be excluded.

5.2 Pharmacokinetic properties

Cyclophosphamide is administered as an inactive prodrug that is activated in the liver.

Absorption
Cyclophosphamide is quickly and almost completely absorbed from parenteral sites.

Distribution
Less than 20% of cyclophosphamide is bound to plasma proteins. The protein binding of the metabolites of cyclophosphamide is higher but less than 70%. To what extent the active metabolites protein bound, is not known.

Cyclophosphamide is about in the cerebrospinal fluid and the mother's milk. Cyclophosphamide and metabolites can pass through the placenta.

Metabolism
Cyclophosphamide is activated in the liver to the active metabolites 4-hydroxy-cyclophosphamide and aldofosfamide (tautomeric form of 4-hydroxy-cyclophosphamide) through phase I metabolism by cytochrome P450 (CYP) enzymes. Different CYP isozymes contribute to the bioactivation of cyclophosphamide, including CYP2A6, 2B6, 2C9, 2C19 and 3A4, 2B6 in which the exhibits highest 4-hydroxylase activity. Detoxification is done mainly through glutathione-S-transferases (GSTA1, GSTP1) and alcohol dehydrogenase (ALDH1, ALDH3). Two to four hours after administration of cyclophosphamide, the plasma concentrations of the active metabolites are maximal, after which a rapid decrease of plasma concentrations takes place.

Elimination
The plasma half-life of cyclophosphamide is about 4 to 8 hours in adults and children. The plasma half-lives of the active metabolites are not known.

Following high-dose IV administration within the framework of allogeneic bone marrow transplantation, the plasma concentration of pure cyclophosphamide follows linear first- order kinetics. Compared with conventional cyclophosphamide therapy, there is an increase in inactive metabolites, indicating saturation of activating enzyme systems, but not of the stages of metabolism leading to inactive metabolites. During the course of high-dose cyclophosphamide therapy over several days, there is a decrease in the areas under the plasma concentration-time curve of the parent compound, probably due to auto-induction of microsomal metabolism activity.

Cyclophosphamide and its metabolites are primarily excreted by the kidneys.

5.3 Preclinical safety data

Acute toxicity
The acute toxicity of cyclophosphamide is relatively low. This was demonstrated in studies on mice, guinea pigs, rabbits and dogs.

Chronic toxicity
Chronic administration of toxic doses led to hepatic lesions manifested as fatty degeneration followed by necrosis. The intestinal mucosa was not affected. The threshold for hepatotoxic effects was 100 mg/kg in the rabbit and 10 mg/kg in the dog.

Mutagenicity and carcinogenicity
The mutagenic effects of cyclophosphamide have been demonstrated in various *in-vitro* and *in-vivo* tests. Chromosome aberrations following administration of cyclophosphamide have also been observed in humans. The carcinogenic effects of cyclophosphamide have been demonstrated in animal studies on rats and mice.

Teratogenicity
The teratogenic effects of cyclophosphamide have been demonstrated in various animals (mice, rats, rabbits, rhesus monkeys and dogs). Cyclophosphamide can cause skeletal, tissue as well as other malformations

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

After reconstitution/dilution:
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, unless reconstitution /dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25 °C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 ml colourless type I glass vial sealed with butyl rubber stopper and aluminium flip-off seal with a red polypropylene plastic button, containing 500mg cyclophosphamide.

Pack of 1 vial.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For each 100 mg of cyclophosphamide, 5 ml of solvent must be added for reconstitution.

The choice of diluent for reconstituting Cyclophosphamide Seacross containing cyclophosphamide depends on the route of administration to be used.

Direct injection:
If the solution is to be used for direct injection, Cyclophosphamide Seacross (containing cyclophosphamide) is reconstituted by adding sodium chloride 9 mg/mL (0.9%) solution for injection.

Infusion:
If the solution is to be used for IV infusion, Cyclophosphamide Seacross (containing cyclophosphamide) is reconstituted by adding sterile water for injection or sodium chloride 9 mg/mL (0.9%) solution for infusion.

The following quantities of water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection are added to the vials containing Cyclophosphamide Seacross, powder for solution for injection/infusion

Vial of 200 mg: 10 ml
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 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.

Infusion:
Reconstituted Cyclophosphamide Seacross should be further diluted in 5% glucose or sodium chloride 9 mg/mL (0.9%) solution for infusion prior to infusion, the solution should be diluted to a minimum concentration of 2 mg per ml.

The rules and regulations for handling cytostatics in general must be observed when reconstituting or handling Cyclophosphamide Seacross. 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. Pregnant personnel should not handle this medicinal product. In case of spills, the area must be thoroughly rinsed with water. If Cyclophosphamide Seacross, 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.

Melted 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.

Disposal
Cyclophosphamide Seacross is for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Seacross Pharma (Europe) Limited
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8 MARKETING AUTHORISATION NUMBER

PA22766/013/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th December 2024

10 DATE OF REVISION OF THE TEXT

January 2026