# 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.

*Dosage*
The dose, route of administration and frequency of administration should be determined by the tumour type, tumour stage, general condition of the patient and whether other chemotherapy or radiotherapy is to be administered concurrently.

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.

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.

Elderly: No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

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

*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.

For intravenous use, the contents of the vial should be dissolved in physiological saline (0.9% w/v sodium chloride) prior to administration. The pH of an aqueous solution is between 4 and 6. Cyclophosphamide is 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.

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

A minimum urine output of 100 ml/hour should be maintained during therapy with conventional doses to avoid cystitis. If the larger doses are used, an output of at least this level should be maintained for 24 hours following administration, if necessary by a forced diuresis.

Alkalisation of the urine is not recommended. Cyclophosphamide should be given early in the day and the bladder voided frequently. The patient should be well hydrated and maintained in fluid balance.

Mesna can be used concurrently to reduce urotoxic effects (see Mesna SPC). If mesna is used to reduce urothelial toxicity, frequent emptying of the bladder should be avoided. Anti-emetics given before and during therapy may reduce nausea and vomiting.

Urine should be sent for laboratory analysis before and at the end of each course of treatment and the patient should be monitored for evidence of haematuria at regular intervals throughout the treatment period. The patient should be instructed to report any signs or symptoms of cystitis.

Cyclophosphamide Injection should be avoided in patients with cystitis from any cause until it has been treated.

If the leukocyte count is below $4 \times 10^9$/L and/or the platelet count is below

100 x $10^9$/L, treatment with Cyclophosphamide should be temporarily withheld until the blood count returns to normal levels.

**4.3. Contra-indications**

Cyclophosphamide is contra-indicated in patients with known hypersensitivity to cyclophosphamide, with acute infections, with bone-marrow aplasia, urinary tract infection or with acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy.

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.

**4.4. Special Warnings and Precautions for Use**

Care should be exercised in patients who are elderly, debilitated, have diabetes mellitus or evidence of myelosuppression, or who have recently received, or are receiving, concurrent treatment with radiotherapy or cytotoxic agents.

Cardiotoxicity may be induced in patients who have had, or are receiving, mediastinal irradiation, doxorubicin or pentostatin. It has also been reported with high doses of cyclophosphamide. In such instances cyclophosphamide therapy should be stopped and appropriate treatment instituted.

Cyclophosphamide is not recommended in patients with plasma creatinine greater than 120 micromol/L (1.5 mg/100 ml), bilirubin greater than 17 micromol/L (1 mg/100 ml), or with transaminases or alkaline phosphatase more than 2-3 times the normal value.

Cyclophosphamide may have an adverse effect on the gonads and amenorrhoea and azoospermia often occur which may be irreversible. Appropriate counselling should be given.

**4.5. Interactions with other Medicaments and other forms of Interaction**

Increased myelosuppression may be seen following concurrent administration of other marrow depressant drugs.

Cyclophosphamide potentiates the hypoglycaemic effects of the sulphonylurea compounds. Other clinically significant interactions are of cyclophosphamide with allopurinol (increased incidence of bone marrow depression) and suxamethonium (prolonged apnoea).

**4.6. Pregnancy and Lactation**

Cyclophosphamide should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh the substantial risk to the foetus. Cyclophosphamide has been shown to be teratogenic. Mothers should not breast-feed while being treated with Cyclophosphamide, or for 36 hours after stopping treatment.

Contraception in both sexes is advised during and for at least 3 months after Cyclophosphamide therapy. Patients should receive counselling with respect to subsequent pregnancies.

## 4.7. Effects on Ability to Drive and Use Machines

A patient's ability to drive or operate machinery may be affected by the possible side effects of cyclophosphamide administration, e.g. nausea, vomiting.

## 4.8. Undesirable Effects

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 tachyarrythmia 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

The most serious consequences of overdosage are myelosuppression, haemorrhagic cystitis and cardiotoxicity in the form of arrhythmias and severe heart failure. Myelosuppression usually recovers spontaneously, but until it does, administration of a broad-spectrum antibiotic may be advisable. Transfusion of whole-blood, platelets or white cells is rarely necessary.

If the overdose is recognised within the first 24 hours, and possibly up to 48 hours, i.v. Mesna may be beneficial in ameliorating damage to the urinary system. Normal supportive measures, such as analgesics and maintenance of fluid balance, should be instituted. If, despite these measures, the cystitis does not resolve, more intensive treatment may be necessary and a urological opinion should be sought. No further courses should be given until the patient has fully recovered.

Cyclophosphamide is dialysable.

## 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 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. Instructions for Use/Handling

*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 and should be treated accordingly. 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.,
Caxton Way,
Thetford,
Norfolk,
IP24 3SE
UK

## 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

August 2007