reduced in patients who have or who develop viral, bacterial, fungal, protozoal or helminthic infections.

Others - Rare instances of anaphylactic reactions have been reported but are not typical for cyclophosphamide.

DRUG INTERACTIONS

Concomitant use of antidiabetic drugs with cyclophosphamide, may potentiate the reduction in blood sugar level. There may be an increase in bone marrow depression is Cyclophosphamide and Allopurinol are given concomitantly. Cyclophosphamide potentiates the effect of succinylcholine chloride.

OVERDOSAGE

Myelosuppression (particularly granulocytopenia) and haemorrhagic cystitis are the most serious consequences of overdosage. Recovery from myelosuppression will occur by the 21st day after the overdosage in the great majority of patients (at doses up to 200 mg/kg i.v.) while granulocytopenia is usually seen by day 6 and lasts for a mean period of 12 days (up to 18 days). A broad spectrum antibiotic may be administered until recovery occurs. Transfusion of whole-blood, platelets or white cells and reverse barrier nursing may be necessary.

If the drug has been taken in the form of tablets, early gastric lavage may reduce the amount of drug absorbed.

During the first 24 hours and possibly up to 48 hours after overdosage, i.v. mensa 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 the cystitis does not resolve more intensive treatment may be necessary.

No further courses should be given until the patient has fully recovered.

DIRECTIONS

Injections: Do not store above 25°C. Protect from light.
Tablets: Do not store above 25ºC & protect from moisture.

To be sold on prescription only. Keep out of the reach of children.

PRESENTATION

INJECTION

UNIPHOS 200: is available as a 200mg vial in a unit carton along with package insert.
UNIPHOS 500: is available as a 500mg vial in a unit carton along with package insert.
UNIPHOS 1000: is available as a 1000mg vial in a unit carton along with package insert.

TABLET

UNIPHOS : Available as a strip of 10 tablets. Such 10 strips are packed in a unit carton along with package insert.

Marketed by:

Revive healthcare

503, 5th Floor, Eden Heights, 6 Main Gulberg,
Jail Road, Lahore - Pakistan 54600.

Manufactured by:
United Biotech (P) Limited
Bagbania, Baddi-Nalagarh Road,
Distt. Solan (HP) - 174 101 - India

یونیفوس ۵۰۰ ملی گرام انجیکشن
(سائیکلوفوسفامائیڈ)

دوا کو ۲۵ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔
دوا کو دھوپ اور نمی سے محفوظ رکھیں۔
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
بچوں کی پہنچ سے دور رکھیں۔

EBa01-05

Rx Cyclophosphamide Injection 200mg/500mg/1g
Cyclophosphamide Tablets 50mg
UNIPHOS

PHARMACEUTICALS WORLDWIDE
UNITED BIOTECH
The Emergence of a New Standard

COMPOSITION

INJECTION

Each vial contains :
Cyclophosphamide eq. to anhydrous Cyclophosphamide (U.S.P. Specs.) 200mg

Each vial contains:
Cyclophosphamide eq. to anhydrous Cyclophosphamide (U.S.P. Specs.) 500mg

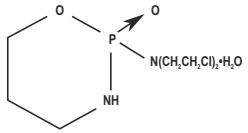
Each vial contains:
Cyclophosphamide eq. to anhydrous Cyclophosphamide (U.S.P. Specs.) 1000mg

TABLETS

Each sugar coated tablet contains :
Cyclophosphamide eq. to anhydrous Cyclophosphamide 50 mg
Colour : Titamium Dioxide

DESCRIPTION

Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. The molecular formula is $C_7H_{15}C_{12}N_2O_2PH_2O$ and. The chemical name for cyclophosphamide is 2-[bis(2-chloroethyl)amino] tetrahydro-2H-13,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide has following structure formula:



CLINICAL PHARMACOLOGY

Mechanism of action Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Pharmacokinetics cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites, but from 5 to 25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide.

INDICATIONS

Cyclophosphamide is indicated concurrently or sequentially with other antineoplastic drugs in the treatment of the following malignancies :- Malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Hodgkin's disease, lymphocytic lymphoma (nodular or diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma, Multiple myeloma, Leukemias : Chronic lymphocytic leukemia, chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis), acute myelogenous and monocytic leukemia, acute lymphoblastic (stem cell) leukemia in children (given during remission is effective in prolonging its duration) Mycosis fungoides (advanced disease), Neuroblastoma (disseminated disease), Adenocarcinoma of the ovary, Retinoblastoma, Carcinoma of the breast.

Nonmalignant Disease : Useful in carefully selected cases of biopsy proven "minimal change" nephrotic syndrome in children but should not be used as primary therapy.

DOSAGE AND ADMINISTRATION

Treatment of Malignancies : Adults and Children : When used as single oncolytic drug therapy, the initial course is usually 40 to 50 mg/kg given intravenously in divided doses over a period of 2 to 5 days. Other intravenous regimens include 10 to 15 mg/kg given every 7 to 10 days or 3 to 5 mg/kg twice weekly.

Oral cyclophosphamide dosing is usually in the range of 1 to 5 mg/kg/day for both initial and maintenance dosing.

Many other regimens of intravenous and oral have been followed. Dosages must be adjusted in accord with evidence of anti-tumor activity and/or leukopenia. The total leukocyte count is a good, objective guide for regulating dosage. Transient decreases in the total white blood cell count to 2000 cells/mm^3 (following short courses) or more persistent reduction to 3000 cells/mm^3 (with continuing therapy) are tolerated without serious risk of infection if there is no marked granulocytopenia. When Cyclophosphamide is included in combined cytotoxic regimens, it may be necessary to reduce the dose of cyclophosphamide as well as that of the other drugs.

Treatment of Nonmalignant Diseases : Biopsy Proven "Minimal Change" Nephrotic Syndrome in Children: An oral dose of 2.5 to 3 mg/kg daily for a period of 60 to 90 days is recommended. In males, the incidence of oligospermia and azoospermia increases if the duration of Cyclophosphamide.

Dilution : Add sterile water for injection to the vial and shaking to dissolve. Use the quantity of diluent shown below to reconstitute the product.

DOSE	QUANTITY OF DILUENT
100 mg	5 ml
200 mg	10 ml
500 mg	20 -25 ml
1 g	50 ml

Cyclophosphamide may be injected intravenously, intramuscularly, intraperitoneally, or intrapleurally or they may be infused intravenously in the following:

Dextrose Injection (5% dextrose)

Dextrose and Sodium Chloride Injection (5% dextrose and 0.9% sodium chloride)

5% Dextrose and Ringer's Injection

Lactated Ringer's Injection

Sodium Chloride Injection, (0.45% sodium chloride)

Sodium Lactate Injection (1/6 molar sodium lactate)

Store in refrigerator (2°to8°C), Avoid long exposure to temperature above 30°C. The solution should be used immediately after preparation as it deteriorates on storage.

The osmolarities of solutions of sterile cyclophosphamide and normal saline are found in the following table :

Sterile Cyclophosphamide	mOsm/L
4 mL diluent per 100 mg cyclophosphamide	**219**
5 mL diluent per 100 mg cyclophosphamide	**172**

Initial treatment is given by intravenous injection. After satisfactory remission maintenance therapy with tablets is recommended.

CONTRAINDICATIONS

Cyclophosphamide should not be taken in patients with known hypersensivity to oxazaphosphorines or in cases of severe bone marrow depression.

WARNING AND PRECAUTIONS

1. Special attention to the possible development of toxicity should be exercised in patients being treated with cyclophosphamide if any of the following conditions are present :- Leukopenia, Thrombocytopenia, Tumor cell infiltration of bone marrow, Previous X-ray therapy, Previous therapy with other cytotoxic agents, Impaired hepatic function , Impaired renal function.
2. Laboratory Tests : During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression. Urine should also be examined regularly for red cells which may precede hemorrhagic cystitis.
3. Myelosuppression is frequently encountered with Cyclophosphamide therapy. Therefore, during treatment, the haematologic profile especially neutrophils and platelets should be monitored regularly to determine the degree of haematopoietic suppression.
4. Patients with impaired renal and hepatic function must be monitored carefully. In cases of patients with severe renal impairment cyclophosphamide dosage reduction may be required.
5. Adrenalectomy : Since cyclophosphamide has been reported to be more toxic in adrenalectomized drugs, adjustment of the doses of both replacement steroids and cyclophosphamide may be necessary for the adrenalectomized patient.
6. Urinary System : Hemorrhagic cystitis may develop in patients treated with cyclophosphamide.Rarely, this condition can be severe and even fatal. Fibrosis of the urinary bladder, sometimes extensive, also may develop with or without accompanying cystitis. Atypical urinary bladder epithelial cells may appear in the urine. These adverse effects appear to depend on the dose of cyclophosphamide and the duration of therapy. Such bladder injury is thought to be due to cyclophosphamide metabolites excreted in the urine. Forced fluid intake helps to assure an ample output of urine, necessitates frequent voiding, and reduces the time the drug remains in the bladder. This helps to prevent cystitis. Hematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Medical and/or surgical supportive treatment may be required, rarely, to treat protracted cases of severe hemorrhagic cystitis. It is usually necessary to discontinue cyclophosphamide therapy in instances of severe hemorrhagic cystitis.
7. Cardiac Toxicity: Acute cardiac toxicity has been reported with doses as low as 2.4 g/m^2 to as high as 26 g/m^2. In a few instances with high doses of cyclophosphamide, severe, and sometimes fatal, congestive heart failure has occurred after the first cyclophosphamide dose. Histopathologic examination has primarily shown hemorrhagic myocarditis. Hemopericardium has occurred secondary to hemorrhagic myocarditis and myocardial necrosis. Pericarditis has been reported independent of any hemopericardium. Cyclophosphamide has been reported to potentiate doxorubicin-induced cardiotoxicity.
8. Infections : Treatment with cyclophosphamide may cause significant suppression of immune responses. Serious, sometimes fatal, infections may develop in severely immunosuppressed patients. Cyclophosphamide treatment may not be indicated or should be interrupted or the dose reduced in patients who have or who develop viral, bacterial, fungal, protozoan, or helminthic infections.
9. Other : Anaphylactic reactions have been reported; death has also been reported in association with this event. Possible cross-sensitivity with other alkylating agents has been reported.

PREGNANCY & LACTATION

Pregnancy this product should not normally be administered to patients who are pregnant. Alkylating agents, including cyclophosphamide, have been shown to possess mutagenic, teratogenic and carcinogenic potential. Pregnancy should therefore be avoided during cyclophosphamide therapy and for three months thereafter.

Lactation cyclophosphamide is excreted in breast milk. Because of the potential for serious adverse reactions and the potential for tumorigenicity shown for cyclophosphamide in humans, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE EFFECTS

Haematologic - Prolonged use of high dose may induce myelosuppression especially leuopenia. Leucocyte count less than 2000 cells/mm3 develops commonly in patients treated with an initial loading dose and less frequently in patients maintained on small doses. Thrombocytopenia and anemia develop occasionally in patients treated with cyclophosphamide. These effects can be reversed by reducing the drug dose by interrupting treatment. Recovery from leucopenia usually begins after 7 to 10 days of cessation of therapy.

Gastrointestinal - Nausea and vomiting commonly occur with cyclophosphamide therapy. Anorexia and less frequently, abdominal discomfort or pain and diarrhoea may occur. Antiemetic therapy should be initated to reduce the incidence of nausea and vomiting.

Dermatologic - Alopecia occurs commonly in patients treated with cyclophosphamide but is reversible. Pigmentation of the skin and changes in nails can occur.

Urologic - Hemorrhagic cystitis may develop in patients treated with cyclophosphamide. These adverse effects appear to depend on dose of cyclophosphamide and the duration of therapy and is thought to be due to cyclophosphamide metabolites excreted in urine. Ample fluid intake during or immediately after administration of cyclophosphamide and increased diuresis help to prevent the development of haemorrhagic cystitis. Haematuria usually resolves in a few days after cyclophosphamide treatment is stopped but may persist in few cases. In patients receiving doses of 10 mg/kg or more and in high risk patients, concomitant administration of Mesna for protection of urinary bladder, is advisable.

Interference with gonadal function - 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 start of treatment.

Infections - Treatment with cyclophosmide may cause significant suppression of immune responses. Serious, sometimes fatal infections may develop in severely immunosuppressed patients. Cyclophosphamide treatment may not be indicated or should be interrupted or the dose