Cyphos

Cyclophosphamide USP Injection

DRUG INTERNATIONAL LTD.

Composition :

Cyphos-200mg Injection: Each vial contains Cyclophosphamide 200mg (As Cyclophosphamide Monohydrate USP) Lyophilized Powder for Solution for IV Infusion.

Cyphos-1gm Injection: Each vial contains Cyclophosphamide 1gm (As Cyclophosphamide Monohydrate USP) Lyophilized Powder for Solution for IV Infusion.

Clinical Pharmacology

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.

Pharmacodynamics/Kinetics:

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. Although elevated levels of metabolites of Cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

Indications

Malignant diseases: Cyclophosphamide, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to Cyclophosphamide treatment:

1. 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.
2. Multiple myeloma.
3. 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 (Cyclophosphamide given during remission is effective in prolonging its duration).
4. Mycosis fungoides (advanced disease).
5. Neuroblastoma (disseminated disease).
6. Retinoblastoma.
7. Metastasizing and non-metastasizing malignant solid tumors: Ovarian cancer, testicular cancer, breast cancer, small cell lung cancer, neuroblastoma, Ewing's sarcoma.
8. Progressive autoimmune diseases: Rheumatoid arthritis, psoriatic arthropathy, systemic lupus erythematosus, scleroderma, systemic vasculitides, certain types of glomerulonephritis, myasthenia gravis, autoimmune hemolytic anemia, cold agglutinin disease.

Nonmalignant Disease

Biopsy Proven "Minimal Change" Nephrotic Syndrome in Children

Cyclophosphamide is useful in carefully selected cases of biopsy proven "minimal change" nephrotic syndrome in children but should not be used as primary therapy. In children whose disease fails to respond adequately to appropriate adrenocorticosteroid therapy or in whom the adrenocorticosteroid therapy produces or threatens to produce intolerable side effects, Cyclophosphamide may induce a remission. Cyclophosphamide is not indicated for the nephrotic syndrome in adults or for any other renal disease.

Dosage and administration:

Cyclophosphamide should only be administered by physicians experienced with this drug. The dosage must be adapted to each patient individually. The following dose recommendations mainly apply to the treatment with Cyclophosphamide as a monotherapy. In combination with other cytostatics of similar toxicity, a dose reduction or extension of the therapy-free intervals may be necessary.

Unless otherwise prescribed the following dosages are recommended:

1. For continuous treatment in adults and children 3 to 6 mg/kg body weight daily (equivalent to 120 to 240 mg /m2 body surface).
2. For intermittent treatment 10 to 15 mg/kg body weight (equivalent to 400 to 600 mg /m2 body surface) at intervals of 2 to 5 days.

3. For high-dose intermittent treatment, e.g. 20 to 40 mg/kg body weight (equivalent to 800 to 1600 mg/m2 body surface) and higher doses (e.g. for conditioning prior to bone-marrow transplantation) at intervals of 21 to 28 days.

Bone marrow transplantation

2 days 60 mg/kg or 4 days 50 mg/kg body weight injected intravenously.

Autoimmune diseases

Per month 500 – 1000 mg/m2 body surface area.

Paediatric population

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

Recommendations for dose reduction in patients with myelosuppression

Leukocyte count [µl]	Platelet count [µl]	Dosage
> 4000	> 100 000	100% of the planned dose
4000-2500	100000 -50000	50% of the planned dose
<2500	< 50000	Adjustment until values normalize or specific decision is made

Recommendations for dose adjustment in patients with hepatic and renal insufficiency.

Severe hepatic or renal insufficiency requires a dose reduction. A dose reduction of 25% for serum bilirubin from 3.1 to 5 mg/100 ml and a 50% for a glomerular filtration rate below 10 ml/minute is recommended. Cyclophosphamide is dialyzable.

Duration of therapy and intervals will depend on the indication, the applied combination chemotherapy schedule, the patient's general state of health, the laboratory parameters and the recovery of blood cell counts.

Preparation and Handling of solution:

Handle and dispose of cyclophosphamide in a manner consistent with other cytotoxic drugs. Caution should be exercised when handling and preparing Cyclophosphamide for Injection, USP (lyophilized powder), To minimize the risk of dermal exposure, always wear gloves when handiling vials containing Cyclophosphamide for Injection, USP (lyophilized powder)

Intravenous Administration:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use cyclophosphamide vials if there are signs of melting. Melted cyclophosphamide is a clear or yellowish viscous liquid usually found as a connected phase or in droplets in the affected vials.

Cyclophosphamide dose not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions.

Reconstitute Cyclophosphamide with 0.9% Sodium Chloride Injection, USP only, using the volumes listed below in Table. Gently swirl the vial to dissolve the drug completely. Do not use Sterile Water for Injection, USP because it results in a hypotonic solution and should not be injected directly.

Strength	Volume of 0.9% Sodium Chloride	Cyclophosphamide Concentration
200mg	10ml	20 mg per ml
1000mg	50 ml	

Dilution of Reconstituted Cyclophosphamide:

Further dilute the reconstituted Cyclophosphamide solution to a minimum concentration of 2 mg per ml with any of the following diluents:

* 5% Dextrose Injection, USP
* 5% Dextrose and 0.9% Sodium Chloride Injection, USP
* 0.45% Sodium Chloride Injection, USP

Storage of Reconstituted and Diluted Cyclophosphamide Solution:

Unopened vials of cyclophosphamide are stable until the date (indicated on the package when stored at of below 250C (770F). If not used immediately, for microbiological integrity, cyclophosphamide solutions should be stored as described in below.

Storage of Cyclophosphamide Solutions

Diluent	Storage	
	Room Temperature	Refrigerated
Reconstituted Solution (Without Further Dilution)		
0.9% Sodium Chloride Injection, USP	up to 24 hrs	up to 6 days
Sterile Water for Injection, USP	Do not store, use immediately	
Diluted Solutions		
0.45% Sodium Chloride Injection, USP	up to 24 hrs	up to 6 days
5% Dextrose Injection, USP	up to 24 hrs	up to 36 days
5% Dextrose and 0.9% Sodium Chloride Injection, USP	up to 24 hrs	up to 36 days

* Storage time is the total time cyclophosphamide is in solution including the time it is reconstituted in 0.9% Sterile Sodium Chloride Injection, USP Or Sterile Water for Injection, USP.

Adverse Effects

Information on adverse reactions associated with the use of Cyclophosphamide is arranged according to body system affected or type of reaction. The adverse reactions are listed in order of decreasing incidence.

Digestive System

Nausea and vomiting commonly occur with Cyclophosphamide therapy. Anorexia and less frequently abdominal discomfort or pain and diarrhea may occur. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy.

Skin and its Structures

Alopecia occurs commonly in patients treated with Cyclophosphamide. 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 color. Skin rash occurs occasionally in patients receiving the drug. Pigmentation of the skin and changes in nails can occur.

Hematopoietic System

Leukopenia occurs in patients treated with Cyclophosphamide, is related to the dose of drug, and can be used as a dosage guide. Leukopenia of less than 2000 cells/mm3 deevelops commonly in patients treated with an initial loading dose of the drug, and less frequently in patients maintained on smaller doses. The degree of neutropenia is particularly important because it correlates with a reduction in resistance to infections. Fever without documented infection has been reported in neutropenic patients.

Thrombocytopenia or anemia develops occasionally in patients treated with Cyclophosphamide. These hematologic effects usually can be reversed by reducing the drug dose or by interrupting treatment. Recovery from leukopenia usually begins in 7 to 10 days after cessation of therapy.

Urinary System

Hemorrhagic ureteritis and renal tubular necrosis have been reported to occur in patients treated with Cyclophosphamide. Such lesions usually resolve following cessation of therapy.

Respiratory System

Interstitial pneumonitis has been reported as part of the postmarketing experience. Interstitial pulmonary fibrosis has been reported in patients receiving high doses of Cyclophosphamide over a prolonged period.

Use in Pregnancy

Pregnancy Category D

Use in Lactation

Cyclophosphamide is excreted in breast milk. Because of the potential for serious adverse reactions and the potential for tumourigenicity 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.

Contraindications

Continued use of Cyclophosphamide is contraindicated in patients with severely depressed bone marrow function. Cyclophosphamide is contraindicated in patients with Known hypersensitivity to Cyclophosphamide, Severly impaired bone marrow function (particularly in patients who have been pretreated with cytotoxic agents and radiotherapy), inflammation of the bladder (Cystitis) and active infections.

Precautions

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.

1. Leukopenia
2. Thrombocytopenia
3. Tumor cell infiltration of bone marrow
4. Previous X-ray therapy
5. Previous therapy with other cytotoxic agents
6. Impaired hepatic function
7. Impaired renal function

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.

Drug Interactions

The rate of metabolism and the leukopenic activity of Cyclophosphamide reportedly are increased by chronic administration of high doses of phenobarbital.

The physician should be alert for possible combined drug actions, desirable or undesirable, involving Cyclophosphamide even though Cycloposphamide has been used successfully concurrently with other drugs including other cytotoxic drugs.

Cyclophosphamide treatment, which causes a marked and persistent inhibition of cholinesterase activity, potentiates the effect of succinylcholine chloride.

If a patient has been treated with Cyclophosphamide with 10 days of general anaesthesia, the anaesthesiologist should be alerted.

Overdose

No specific antidote for Cyclophosphamide is known. Overdosage should be managed with supportive measures, including appropriate treatment for any concurrent infection, myelosuppression, or cardiac toxicity should it occur.

Pharmaceutical Information

Storage condition

Do not store above 25oC. It should be stored at controlled temperature between 15oc to 25oc. Protect from heat and light. Keep out of reach of children.

Packing : Cyphos-200mg Injection: Each box contains 1 vial of Cyclophosphamide 200mg lyophilized Powder.

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