Cyclotox

Cyclophosphamide Injection

COMPOSITION

Cyclotox Injection: Each vial contains Cyclophosphamide BP equivalent to Anhydrous Cyclophosphamide 1g as lyophilized powder.
Cyclotox 200 Injection: Each vial contains Cyclophosphamide BP equivalent to Anhydrous Cyclophosphamide 200 mg as lyophilized powder.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Pharmacodynamics

Cyclophosphamide is bio transformed 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.

Pharmacokinetics

Following IV administration, elimination half-life (t) ranges from 3 to 12 hours with total body clearance (CL) values of 4 to 5.6 L/h. Pharmacokinetics are linear over the dose range used clinically.

Absorption

After oral administration, peak concentrations of cyclophosphamide occurred at one hour. Area under the curve ratio for the drug after oral and IV administration (AUCpo: AUC iv) ranged from 0.87 to 0.96.

Distribution

Volume of distribution approximates total body water (30 to 50 L).

Metabolism

The liver is the major site of cyclophosphamide activation. Approximately 75% of the administered dose of cyclophosphamide is activated by hepatic microsomal cytochrome P450s including CYP2A6, 2B6, 3A4, 3A5, 2C9, 2C18 and 2C19, with 2B6 displaying the highest 4-hydroxylase activity.

Elimination

Cyclophosphamide is primarily excreted as metabolites. 10 to 20% is excreted unchanged in the urine and 4% is excreted in the bile following IV administration.

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

• 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 (Cyclophosphamide given during remission is effective in prolonging its duration).
• Mycosis fungoides (advanced disease).
• Neuroblastoma (disseminated disease).
• Retinoblastoma.
• Metastasizing and non-metastasizing malignant solid tumors: Ovarian cancer, testicular cancer, breast cancer, small cell lung cancer, neuroblastoma, Ewing's sarcoma.
• 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. The handling and preparation of cytostatic should always be in accordance with the safety precautions used for the handling of cytotoxic agents.

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 /m^2 body surface).
2. For intermittent treatment 10 to 15 mg/kg body weight (equivalent to 400 to 600 mg /m^2 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.

Preparation, Handling and Administration

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

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 does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions. Use aseptic technique.

For Direct Intravenous Injection

Reconstitute Cyclophosphamide with 0.9% Sodium Chloride Injection, BP only, using the volumes listed below in Table 1. Gently swirl the vial to dissolve the drug completely. Do not use Sterile Water for Injection, BP because it results in a hypotonic solution and should not be injected directly.

Table 1: Reconstitution for Direct Intravenous Injection

Strength	Volume of 0.9% Sodium Chloride	Cyclophosphamide Concentration
200 mg	10 mL	20 mg/mL
1 gm	50 mL	

FOR INTRAVENOUS INFUSION

Reconstitution of Cyclophosphamide

Reconstitute Cyclophosphamide using 0.9% Sodium Chloride Injection, BP or Sterile Water for Injection, BP with the volume of diluent listed below in Table 2. Add the diluent to the vial and gently swirl to dissolve the drug completely.

Reconstitution in preparation for Intravenous Infusion

Strength	Volume of 0.9% Sodium Chlorid	Cyclophosphamide Concentration
200 mg	10 mL	20 mg/mL
1 gm	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, BP
• 5% Dextrose and 0.9% Sodium Chloride Injection, BP
• 0.45% Sodium Chloride Injection, BP

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 also should be appropriate for the volume and type of carrier fluid to be infused.
Storage of Reconstituted and Diluted Cyclophosphamide Solution
If not used immediately, for microbiological integrity, cyclophosphamide solutions should be stored as described in: Reconstituted Solution (Without further dilution)
Storage of Cyclophosphamide Solutions

Diluent	Storage	
	Room Temperature	Refrigerator
0.9% Sodium Chloride Injection, BP	up to 24 hrs	up to 6 days
Sterile Water for Injection, BP	Do not store; use immediately	
Reconstituted Solution (Without Further Dilution)		

Diluted Solutions

0.45% Sodium Chloride Injection, BP	up to 24 hrs	up to 6 days
5% Dextrose Injection, BP	up to 24 hrs	up to 36 hrs
5% Dextrose and 0.9% Sodium Chloride Injection, BP	up to 24 hrs	up to 36 hrs Refrigerated

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

CONTRAINDICATIONS

Hypersensitivity

Cyclophosphamide is contraindicated in patients who have a history of severe hypersensitivity reactions to it, any of its metabolites, or to other components of the product. Anaphylactic reactions including death have been reported with cyclophosphamide. Possible cross-sensitivity with other alkylating agents can occur.

Urinary Outflow Obstruction

Cyclophosphamide is contraindicated in patients with urinary outflow obstruction

WARNINGS AND PRECAUTIONS

Myelosuppression, Immunosuppression, Bone Marrow Failure and Infections
Cyclophosphamide can cause myelosuppression (leukopenia, neutropenia, thrombocytopenia and anemia), bone marrow failure, and severe immunosuppression which may lead to serious and sometimes fatal infections, including sepsis and septic shock. Cyclophosphamide should not be administered to patients with neutrophils =1,500/mm and platelets < 50,000/mm.

Urinary Tract and Renal Toxicity

Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with cyclophosphamide.

Cardiotoxicity

Myocarditis, myopericarditis, pericardial effusion including cardiac tamponade, and congestive heart failure, which may be fatal, have been reported with cyclophosphamide therapy Supraventricular arrhythmias (including atrial fibrillation and flutter) and ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported after treatment with regimens that included cyclophosphamide.

Pulmonary Toxicity

Pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease and other forms of pulmonary toxicity leading to respiratory failure have been reported during and following treatment with cyclophosphamide.

Secondary Malignancies

Cyclophosphamide is genotoxic [see Nonclinical Toxicology. Secondary malignancies (urinary tract cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported in patients treated with cyclophosphamide-containing regimens.

Veno-occlusive Liver Disease

Veno-occlusive liver disease (VOD) including fatal outcome has been reported in patients receiving cyclophosphamide-containing regimens.

Embryo-Fetal Toxicity

Cyclophosphamide can cause fetal harm when administered to a pregnant woman exposure to cyclophosphamide during pregnancy may cause birth defects, miscarriage, fetal growth retardation, and fetotoxic effects in the newborn.

Impairment of Wound Healing

Cyclophosphamide may interfere with normal wound healing.

Hyponatremia

Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone), which may be fatal, has been reported.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling.

Hematopoietic system

Neutropenia occurs in patients treated with cyclophosphamide. 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.

Gastrointestinal system

Nausea and vomiting 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 in patients treated with cyclophosphamide. Skin rash occurs occasionally in patients receiving the drug. Pigmentation of the skin and changes in nails can occur.
• Hypersensitivity
• Myelosuppression, Immunosuppression, Bone Marrow Failure, and Infections
• Urinary Tract and Renal Toxicity
• Cardiotoxicity
• Pulmonary Toxicity
• Secondary Malignancies

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D

Nursing Mothers

Cyclophosphamide is present in breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhea have been reported in infants breast fed by women treated with cyclophosphamide.

Infertility

Females Amenorrhea, transient or permanent, associated with decreased estrogen and increased gonadotropin secretion develops in a proportion of women treated with cyclophosphamide.

Use in Patients with Renal Impairment

In patients with severe renal impairment, decreased renal excretion may result in increased plasma levels of cyclophosphamide and its metabolites.

Use in Patients with Hepatic Impairment

Patients with severe hepatic impairment have reduced conversion of cyclophosphamide to the active 4hydroxyl metabolite, potentially reducing efficacy.

DRUG INTERACTIONS

Cyclophosphamide is a pro-drug that is activated by cytochrome P450s An increase of the concentration of cytotoxic metabolites may occur with:
• Protease inhibitors: Concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites. Combined or sequential use of cyclophosphamide and other agents with similar toxicities can potentiate toxicities.
• Increased hepatotoxicity and/or immunosuppression may result from a combined effect of cyclophosphamide and, for example:
• ACE inhibitors: ACE inhibitors can cause leukopenia.
• Natalizumab
• Paclitaxel: Increased hepatotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion.
• Thiazide diuretics
• Zidovudine
• Increased cardiotoxicity may result from a combined effect of cyclophosphamide and, for example:
• Anthracyclines
• Cytarabine
• Pentostatin
• Radiation therapy of the cardiac region
• Trastuzumab
•Increased pulmonary toxicity may result from a combined effect of cyclophosphamide and, for example:
• Amiodarone
• G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony- stimulating factor).
• Increased nephrotoxicity may result from a combined effect of cyclophosphamide and, for example:
• Amphotericin B
• Indomethacin: Acute water intoxication has been reported with concomitant use of indomethacin
• Increase in other toxicities:
• Azathioprine: Increased risk of hepatotoxicity (liver necrosis)
• Busulfan: Increased incidence of hepatic veno-occlusive disease and mucositis has been reported.
• Protease inhibitors: Increased incidence of mucositis
• Increased risk of hemorrhagic cystitis may result from a combined effect of cyclophosphamide and past or concomitant radiation treatment.

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. Common

PHARMACEUTICAL INFORMATION

Storage condition

Store the vial in original carton at 2°C to 8°C, away from light. Keep out of the reach of children.

Packaging & Presentation

Cyclotox Injection: Each commercial box contains 1 vial of Cyclophosphamide BP equivalent to Anhydrous Cyclophosphamide 1 g as lyophilized powder.

Cyclotox 200 Injection: Each commercial box contains 1 vial of Cyclophosphamide BP equivalent to anhydrous Cyclophosphamide 200 mg as lyophilized powder.

Manufactured by-
BEACON® Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

LF31501

সাইক্লোটক্স

সাইক্লোফস্ফামাইড ইনজেকশন

উপাদান

সাইক্লোটক্স ইনজেকশনঃ প্রতিটি ভায়ালে আছে সাইক্লোফসফামাইড বিপি যা ১ গ্রাম এনহাইড্রাস সাইক্লোফসফামাইডের সমতূল্য।

সাইক্লোটক্স ২০০ ইনজেকশন

প্রতিটি ভায়ালে আছে সাইক্লোফসফামাইড বিপি যা ২০০ মিলিগ্রাম এনডাইড্রাস সাইক্লোফসফামাইডের সমতূল্য।

ফার্মাকোলজী

ঔষধের কার্যপদ্ধতি

সাইক্লোফসফামাইড একটি অ্যালকাইলেটিং ড্রাগ যা লিভারের ইনজাইম দ্বারা সক্রিয় এবং ক্যান্সার কোষের অস্বাভাবিক বৃদ্ধিকে বাধা প্রদান করে। DNA ক্রস লিংকং এর মাধ্যমে ক্যান্সার কোষ ধ্বংস করে।

নির্দেশনা

সাইক্লোফসফামাইড বিভিন্ন ম্যালিগন্যান্ট রোগে ব্যবহৃত হয়। অন্যান্য নিওপ্লাস্টিক ঔষধের সাথে বহুল ব্যবহার আছে যা নিম্নে দেওয়া হলো

১. ম্যালিগন্যান্ট ফিফোমা, হজকিন'স ডিজিস, লিম্ফোসাইটিক লিম্ফোমা, মিক্সড সেল লিম্ফোমা, হিস্টোলাইটিক লিম্ফোমা, বুরুকিটস লিম্ফোমা
২. মাল্টিপল মায়েলোমা
৩. লিউকেমিয়া; ক্রনিক লিম্ফোসাইটিক লিম্ফোমা, ক্রনিক গ্র্যানুলোসাইটক লিউকেমিয়া, একিউট মায়েলোজেনাস এবং মনোসাইটক, শিশুদের একিউট লিম্ফোব্লাস্টিক লিউকেমিয়া
৪. মাইকোসিস ফানজাইডস
৫. নিউরোব্লাস্টমা
৬. রেটিনোব্লাস্টোমা
৭. মেটস্টেটাইজিং এবং নন-মেটস্টেটাইজিং সলিড টিউমারৎ ওভারিয়ান ক্যান্সার, টেস্টিকুলার ক্যান্সার, ব্রেস্ট ক্যান্সার, স্মল সেল ফুসফুসের ক্যান্সার, নিউরোব্লাস্টোমা, কোন্ড অ্যাগ্লুটিনিন ডিজিস
৮. প্রগ্রেসিভ অটোইম্যুনো ডিজিসঃ রিউমাটয়েড আরথ্রাইটিস, সোরিয়াটিক এট্রপ্যাথি, এসএলই, স্ক্লেরোডারমা, সিস্টেমিক ভাসকুলাইটিডিস, বিভিন্ন ধরনের গ্লোমেউলোনেফ্রোইটিস, মায়াসথেনিয়া গ্রাভিস, অটোইমিউনো হেমোলাইটক এনেমিয়া, কোল্ড অ্যাগ্লুটিনিন ডিজিস

ননম্যালিগন্যান্ট ডিজিস

বায়েপ্সি দ্বারা নির্ধারিত নেফ্রেটিক সিনড্রোম। কিন্তু শিশুদের ক্ষেত্রে প্রাথমিক চিকিৎসা হিসেবে ব্যবহার করা উচিৎ নয়।

সেবনমাত্রা ও বিধি

শুধুমাত্রা অভিজ্ঞ চিকিৎসকের পরামর্শে সাইক্লোফসমাইড সেবন করা যাবে। ঔষধ প্রস্তুতির সময় প্রয়োজনীয় সতর্কতা অবলম্বন করুন।

সাইক্লোফসমাইড এককভাবে ব্যবহারে নিম্নোক্ত মাত্রা নির্দেশিত

১) বিরতিহীন চিকিৎসার জন্য প্রাপ্ত বয়স্ক ও শিশুদের জন্য দৈনিক ৩-৬ মিগ্রা/কেজি নির্দেশিত
২) অন্তরবর্তীকালীন চিকিৎসার জন্য ১০-১৫ মিগ্রা/কেজি নির্দেশিত
৩) উচ্চ মাত্রায় অন্তবর্তীকালীন ব্যবহারের জন্য ২০-৪০ মিগ্রা/কেজি নির্দেশিত

সাইক্লোফসফাইমাইড দ্রবণ প্রস্তুতি

আইসোটনিক সলিউশন প্রস্তুতির জন্য লায়োফিলাইজড পাউডারের সথে নিম্নোক্ত পরিমাণ ফিজিওলজক্যাল স্যালাইন যোগ করুন।

সাইক্লোফসফামাইড ভায়াল	সাইক্লোফসফামাইড ২০০ ইনজেকশন	সাইক্লোফসফামাইড ১ গ্রাম ইনজেকশন
ফিজিওলজিক্যাল স্যালাইন	১০ মিলি	৫০ মিলি

ঔষুধের দ্রবণ প্রস্তুতির পরে কোন অদ্রবনীয় কণা আছে কিনা এবং বর্ণ পরিবর্তন হয়েছে কিনা তা চোখে দেখে পরীক্ষা করে নিতে হবে। প্রস্তুতির পরে হালকা হলুদাভ দ্রবণ তৈরী হবে।
প্রস্তুতকৃত দ্রবণ রিংগার্স সলিউশন, সরমাল স্যালাইন, ডেক্সট্রোজের মাধ্যমে ইনফিউশন এর মাধ্যমে ৩০ মিনিট হতে ২ ঘন্টার মধ্যে প্রয়োগ করতে হবে।

ফার্মাকোকাইনেটিক বৈশিষ্ট্য

বিতরণ

ভলিউম অফ ডিস্ট্রিবিউশন প্রায় ৩০-৫০ লিটার।

বিপাক

লিভারের মাধ্যমে সাইক্লোফসফামাইড সক্রিয় হয়। ৭৫ ভাগ সক্রিয় হয় হেপাটিক মাইক্রোসোমাল সাইটোক্রম p450 দ্বারা। এছাড়াও ৪-হাইড্রক্সিলের সাথে CYP2A, 2B6, 3A4, 3A5, 2C9, 2C18 এনজাউম সর্বোচ্চ সক্রিয়াতা দেখায়।

নিষ্কাশন

সাইক্লোফসফামাইড অপরিবর্তিত অবস্থায় মেটাবোলাইট হিসেবে নিষ্কাশন হয়। ১০-২০% মূত্রের মাধ্যমে অপরিবপর্তিত অবস্থায় বের হয়ে যায় এবং ৪% নিষ্কাশন হয় পিত্তরশের সাহায্যে।

প্রতিনির্দেশনা

বোন ম্যারো সমস্যা তীব্র হলে নিয়মিত সাইক্লোফসমাইড ব্যাবহার থেকে বিরত থাকতে হবে। রোগীর নিম্নোক্ত লক্ষণে সাইক্লোফসফামাইড ব্যবহার থেকে বিরত থাকতে হবে-
হাইপারসেনসিটিভিটি
বোন ম্যারো সমস্যা
মূত্রাশয়ে প্রদাহ
ইনফেকশন

সতর্কতা

সাইক্লোফসফোমাইড ব্যবহারের সময় ও আগে নিম্নলিখিত সতর্কতা ও সাবধারতা অবলম্বন করা উচিত।
লিউকোপেনিয়া, থ্রম্বোসাইটোপেনিয়া, টিউমার সেল যুক্ত বোনমেরো, পূর্বের এক্সরে থেরাপি, পূর্বে ব্যবহার করা সাইটোটক্সিক ড্রাগ, লিভারের সমস্যা, কিডনীর সমস্যা।

বিরূপ প্রভাব

সাইক্লোফসফামাইড ব্যবহারে রোগীর নিম্নলিখিত বিরূপ প্রভাবের মধ্যে- বমি বমি ভাব, বশি হওয়া, খাবারে অরুচি হেমোরেজিক কোলাইটিস, মুখগহবরে ক্ষত, জন্ডিস, চুল গড়া, চুলে র বর্ণ পরিবর্তন, লিউকোপেনিয়া, থ্রম্বোসাইটপেনিয়া, হেমোরেজিক ইউরোথ্রাইটিস, রেনাল টিবিউলার নেক্রোসিস, ইন্টারস্টিশাল নিউমোনাইটিস, ইন্টারস্টিশাল পালমোনারি ফাইব্রোসিস হতে পারে। এছাড়া এনাফাইলেকটিক রিএকশন হতে পারে।
এছাড়াও হাইপারসেনসিটিভিটি, মায়েলোসাপরেশন, ইমিউনসাপ্রেশন বোনম্যারো ফেইলিউর, ইনফেকশন, কার্ডিওটক্সিসিট, রেনাল ও ইউরিনারি টক্সিসিটি, সেকেভারী ম্যালিগন্যান্সি হতে পারে।

বিশেষ ব্যবহার

গর্ভকালীন ব্যবহার

প্রেগন্যানসি ক্যাটাগরি **D**

অন্যান্য ওষুধের সাথে প্রতিক্রিয়া

প্রোটিয়েজ ইনহিবিটর, ACE ইনহিবিটর, নাটালিজুমাব, প্যাকলিট্যাক্সেল, থায়াজাইড ডাই-ইউরেটিক্স, জিডভুডিন, এনথ্রাসাইক্লিন, সাইটারাবিন, ট্রাসটুজুমার, এমিওডেরন, এম্ফোটারিসিন-বি, এন্ডোমথাসিন, এজাথায়োপ্রিণ এর সাথে ব্যবহারে হেপাটাটক্সিসিটি, মিউরোটক্সিসিটি, মিউকোসাইটিস, হেমাটটক্সিসিটি হতে পারে।

ওষুধের মাত্রাতিরিক্ত ব্যবহার

সাইক্লোফসফোমাইডের কোন সুনির্দিষ্ট এন্টিডট নেই।

সংরক্ষণ

অব্যবহৃত ভায়ালটি সরবরাহকৃত মোড়কে ২°-৮° সেলসিয়াস তাপমাত্রায়, শুকনা স্থানে ও আলো থেকে দূরে রাখুন। সকল ঔষধ শিশুদের নাগালের বাইরে রাখুন।

সরবরাহ

সাইক্লোটক্স ইনজেকশন

প্রতি মোড়কে ১টি সাইক্লোফসফামাইড ১ গ্রাম লায়োফিলাইজড পাউডার এর ভায়াল রয়েছে।

সাইক্লোটক্স ২০০ ইনজেকশন

প্রতি মোড়কে ১টি সাইক্লোফসফামাইড ২০০ মিলিগ্রাম লায়োফিলাইজড পাউডার এর ভায়াল রয়েছে।

প্রস্তুতকারক
বীকন ফার্মাসিউটিক্যালস্ লিমিটেড
ভালুকা, ময়মনসিংহ, বাংলাদেশ

Cyclotox

Cyclophosphamide Injection

COMPOSITION

Cyclotox Injection: Each vial contains Cyclophosphamide BP equivalent to Anhydrous Cyclophosphamide 1g as lyophilized powder.

Cyclotox 200 Injection: Each vial contains Cyclophosphamide BP equivalent to Anhydrous Cyclophosphamide 200 mg as lyophilized powder.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Pharmacodynamics

Cyclophosphamide is bio transformed 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.

Pharmacokinetics

Following IV administration, elimination half-life (t) ranges from 3 to 12 hours with total body clearance (CL) values of 4 to 5.6 L/h. Pharmacokinetics are linear over the dose range used clinically.

Absorption

After oral administration, peak concentrations of cyclophosphamide occurred at one hour. Area under the curve ratio for the drug after oral and IV administration (AUCpo: AUC iv) ranged from 0.87 to 0.96.

Distribution

Volume of distribution approximates total body water (30 to 50 L).

Metabolism

The liver is the major site of cyclophosphamide activation. Approximately 75% of the administered dose of cyclophosphamide is activated by hepatic microsomal cytochrome P450s including CYP2A6, 2B6, 3A4, 3A5, 2C9, 2C18 and 2C19, with 2B6 displaying the highest 4-hydroxylase activity.

Elimination

Cyclophosphamide is primarily excreted as metabolites. 10 to 20% is excreted unchanged in the urine and 4% is excreted in the bile following IV administration.

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

• 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 (Cyclophosphamide given during remission is effective in prolonging its duration).
• Mycosis fungoides (advanced disease).
• Neuroblastoma (disseminated disease).
• Retinoblastoma.
• Metastasizing and non-metastasizing malignant solid tumors: Ovarian cancer, testicular cancer, breast cancer, small cell lung cancer, neuroblastoma, Ewing's sarcoma.
• 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. The handling and preparation of cytostatic should always be in accordance with the safety precautions used for the handling of cytotoxic agents.

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 /m^2 body surface).
2. For intermittent treatment 10 to 15 mg/kg body weight (equivalent to 400 to 600 mg /m^2 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.

Preparation, Handling and Administration

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

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 does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions. Use aseptic technique.

For Direct Intravenous Injection

Reconstitute Cyclophosphamide with 0.9% Sodium Chloride Injection, BP only, using the volumes listed below in Table 1. Gently swirl the vial to dissolve the drug completely. Do not use Sterile Water for Injection, BP because it results in a hypotonic solution and should not be injected directly.

Table 1: Reconstitution for Direct Intravenous Injection

Strength	Volume of 0.9% Sodium Chloride	Cyclophosphamide Concentration
200 mg	10 mL	20 mg/mL
1 gm	50 mL	

FOR INTRAVENOUS INFUSION

Reconstitution of Cyclophosphamide

Reconstitute Cyclophosphamide using 0.9% Sodium Chloride Injection, BP or Sterile Water for Injection, BP with the volume of diluent listed below in Table 2. Add the diluent to the vial and gently swirl to dissolve the drug completely.

Reconstitution in preparation for Intravenous Infusion

Strength	Volume of 0.9% Sodium Chlorid	Cyclophosphamide Concentration
200 mg	10 mL	20 mg/mL
1 gm	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, BP
• 5% Dextrose and 0.9% Sodium Chloride Injection, BP
• 0.45% Sodium Chloride Injection, BP

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 also should be appropriate for the volume and type of carrier fluid to be infused.
Storage of Reconstituted and Diluted Cyclophosphamide Solution
If not used immediately, for microbiological integrity, cyclophosphamide solutions should be stored as described in: Reconstituted Solution (Without further dilution)
Storage of Cyclophosphamide Solutions

Diluent	Storage	
	Room Temperature	Refrigerator

0.9% Sodium Chloride Injection, BP	up to 24 hrs	up to 6 days
Sterile Water for Injection, BP	Do not store; use immediately	
Reconstituted Solution (Without Further Dilution)		

Diluted Solutions

0.45% Sodium Chloride Injection, BP	up to 24 hrs	up to 6 days
5% Dextrose Injection, BP	up to 24 hrs	up to 36 hrs
5% Dextrose and 0.9% Sodium Chloride Injection, BP	up to 24 hrs	up to 36 hrs Refrigerated

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

CONTRAINDICATIONS

Hypersensitivity

Cyclophosphamide is contraindicated in patients who have a history of severe hypersensitivity reactions to it, any of its metabolites, or to other components of the product. Anaphylactic reactions including death have been reported with cyclophosphamide. Possible cross-sensitivity with other alkylating agents can occur.

Urinary Outflow Obstruction

Cyclophosphamide is contraindicated in patients with urinary outflow obstruction

WARNINGS AND PRECAUTIONS

Myelosuppression, Immunosuppression, Bone Marrow Failure and Infections Cyclophosphamide can cause myelosuppression (leukopenia, neutropenia, thrombocytopenia and anemia), bone marrow failure, and severe immunosuppression which may lead to serious and sometimes fatal infections, including sepsis and septic shock. Cyclophosphamide should not be administered to patients with neutrophils =1,500/mm and platelets < 50,000/mm.

Urinary Tract and Renal Toxicity

Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with cyclophosphamide.

Cardiotoxicity

Myocarditis, myopericarditis, pericardial effusion including cardiac tamponade, and congestive heart failure, which may be fatal, have been reported with cyclophosphamide therapy Supraventricular arrhythmias (including atrial fibrillation and flutter) and ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported after treatment with regimens that included cyclophosphamide.

Pulmonary Toxicity

Pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease and other forms of pulmonary toxicity leading to respiratory failure have been reported during and following treatment with cyclophosphamide.

Secondary Malignancies

Cyclophosphamide is genotoxic [see Nonclinical Toxicology. Secondary malignancies (urinary tract cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported in patients treated with cyclophosphamide-containing regimens.

Veno-occlusive Liver Disease

Veno-occlusive liver disease (VOD) including fatal outcome has been reported in patients receiving cyclophosphamide-containing regimens.

Embryo-Fetal Toxicity

Cyclophosphamide can cause fetal harm when administered to a pregnant woman exposure to cyclophosphamide during pregnancy may cause birth defects, miscarriage, fetal growth retardation, and fetotoxic effects in the newborn.

Impairment of Wound Healing

Cyclophosphamide may interfere with normal wound healing.

Hyponatremia

Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone), which may be fatal, has been reported.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling.

Hematopoietic system

Neutropenia occurs in patients treated with cyclophosphamide. 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.

Gastrointestinal system

Nausea and vomiting 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 in patients treated with cyclophosphamide. Skin rash occurs occasionally in patients receiving the drug. Pigmentation of the skin and changes in nails can occur.
• Hypersensitivity
• Myelosuppression, Immunosuppression, Bone Marrow Failure, and Infections
• Urinary Tract and Renal Toxicity
• Cardiotoxicity
• Pulmonary Toxicity
• Secondary Malignancies

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D

Nursing Mothers

Cyclophosphamide is present in breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhea have been reported in infants breast fed by women treated with cyclophosphamide.

Infertility

Females Amenorrhea, transient or permanent, associated with decreased estrogen and increased gonadotropin secretion develops in a proportion of women treated with cyclophosphamide.

Use in Patients with Renal Impairment

In patients with severe renal impairment, decreased renal excretion may result in increased plasma levels of cyclophosphamide and its metabolites.

Use in Patients with Hepatic Impairment

Patients with severe hepatic impairment have reduced conversion of cyclophosphamide to the active 4hydroxyl metabolite, potentially reducing efficacy.

DRUG INTERACTIONS

Cyclophosphamide is a pro-drug that is activated by cytochrome P450s An increase of the concentration of cytotoxic metabolites may occur with:
• Protease inhibitors: Concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites. Combined or sequential use of cyclophosphamide and other agents with similar toxicities can potentiate toxicities.
• Increased hepatotoxicity and/or immunosuppression may result from a combined effect of cyclophosphamide and, for example:
• ACE inhibitors: ACE inhibitors can cause leukopenia.
• Natalizumab
• Paclitaxel: Increased hepatotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion.
• Thiazide diuretics
• Zidovudine
• Increased cardiotoxicity may result from a combined effect of cyclophosphamide and, for example:
• Anthracyclines
• Cytarabine
• Pentostatin
• Radiation therapy of the cardiac region
• Trastuzumab
•Increased pulmonary toxicity may result from a combined effect of cyclophosphamide and, for example:
• Amiodarone
• G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony- stimulating factor).
• Increased nephrotoxicity may result from a combined effect of cyclophosphamide and, for example:
• Amphotericin B
• Indomethacin: Acute water intoxication has been reported with concomitant use of indomethacin
• Increase in other toxicities:
• Azathioprine: Increased risk of hepatotoxicity (liver necrosis)
• Busulfan: Increased incidence of hepatic veno-occlusive disease and mucositis has been reported.
• Protease inhibitors: Increased incidence of mucositis
• Increased risk of hemorrhagic cystitis may result from a combined effect of cyclophosphamide and past or concomitant radiation treatment.

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. Common

PHARMACEUTICAL INFORMATION

Storage condition

Store the vial in original carton at 2°C to 8°C, away from light. Keep out of the reach of children.

Packaging & Presentation

Cyclotox Injection: Each commercial box contains 1 vial of Cyclophosphamide BP equivalent to Anhydrous Cyclophosphamide 1 g as lyophilized powder.

Cyclotox 200 Injection: Each commercial box contains 1 vial of Cyclophosphamide BP equivalent to anhydrous Cyclophosphamide 200 mg as lyophilized powder.

Manufactured by-
BEACON®
Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

LF31501