Cycloph™ IV Injection

Cyclophosphamide USP Injection

DESCRIPTION

Cycloph™ is a preparation of Cyclophosphamide. The mechanism of action is thought to involve cross-linking of tumor cell DNA. 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.

INDICATIONS

Cyclophosphamide is indicated for the treatment of:

- 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 (cyclophosphamide 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

Cyclophosphamide, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs.

DOSAGE AND ADMINISTRATION

During or 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 should be administered in the morning.

Dosing for Malignant Diseases

Adults and Pediatric Patients

Intravenous

When used as the only oncolytic drug therapy, the initial course of cyclophosphamide for patients with no hematologic deficiency usually consists of 40 mg per kg to 50 mg per kg given intravenously in divided doses over a period of 2 to 5 days. Other intravenous regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly.

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.

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 Injection. To minimize the risk of dermal exposure, always wear gloves when handling vials containing Cyclophosphamide Injection.

Cyclophosphamide Injection

Intravenous Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. 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

Aseptically withdraw the prescribed dose from the vial. Dilute the prescribed dose of Cyclophosphamide Injection to a concentration of 20 mg per mL by using any of the following diluents:

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

Do not use Sterile Water for Injection, USP because it results in a hypotonic solution and should not be injected directly.

For Intravenous Infusion

Aseptically withdraw the prescribed dose from the vial. Dilute the prescribed dose of Cyclophosphamide Injection to a concentration of 2 mg per mL by using any of the following diluents:

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

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 Diluted Cyclophosphamide Solution:

If not used immediately, for microbiological integrity, cyclophosphamide solutions should be stored as described in Table 1:

Diluent	Storage	
	Room Temperature	Refrigerated
Diluted solutions (20 mg/mL)		
0.9% Sodium Chloride Injection, USP	up to 24 hrs	Up to 6 days
0.45% Sodium Chloride Injection, USP	up to 24 hrs	Up to 6 days
5% Dextrose Injection, USP	up to 24 hrs	Up to 6 days
5% Dextrose and 0.9% Sodium chloride Injection, USP	up to 24 hrs	Up to 6 days
Diluted Solutions (2 mg/mL)		
0.9% Sodium Chloride Injection, USP	up to 24 hrs	Up to 6 days
0.45% Sodium Chloride Injection, USP	up to 24 hrs	up to 6 days
5% Dextrose Injection, USP	up to 24 hrs	up to 6 days
5% Dextrose and 0.9% Sodium chloride Injection, USP	up to 24 hrs	up to 6 days

Storage of Undiluted Cyclophosphamide Solution:
After first use, store partially used multiple-dose vial in the original carton at 2°C to 8°C (36°F to 46°F) for up to 28 days. Discard unused portion after 28 days.

CONTRAINDICATIONS

- History of hypersensitivity
- Urinary outflow obstruction

SIDE EFFECTS

- Neutropenia, febrile neutropenia
- Fever
- Alopecia
- Nausea, vomiting, diarrhea, anorexia

WARNING AND PRECAUTION

- Myelosuppression, Immunosuppression, Bone Marrow Failure and Infections – (Severe immunosuppression may lead to serious and sometimes fatal infections. Close hematological monitoring is required.)
- Urinary Tract and Renal Toxicity - Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria can occur. Exclude or correct any urinary tract obstructions prior to treatment.
- Cardiotoxicity - Myocarditis, myopericarditis, pericardial effusion, Cardiac tamponade and congestive heart failure, which may be fatal, have been reported. Monitor patients, especially those with risk factors for cardio toxicity or pre-existing cardiac disease.
- Pulmonary Toxicity - Pneumonitis, pulmonary fibrosis and pulmonary veno-occlusive disease leading to respiratory failure may occur. Monitor patients for signs and symptoms of pulmonary toxicity.
- Secondary Malignancies
- Veno-occlusive Liver Disease - Fatal outcome can occur.
- Alcohol Content - The alcohol content in a dose of Cyclophosphamide Injection may affect the central nervous system. This may include impairment of a patient's ability to drive or use machines immediately after infusion..
- Embryo-Fetal Toxicity - Can cause fetal harm. Advise patients of the potential risk to the fetus and to use effective contraception.
- Infertility
- Impairment of wound healing
- Hyponatremia

Common Adverse Reactions
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

USE IN SPECIFIC POPULATION

- Lactation: Advise not to breastfeed.
- Females and Males of Reproductive Potential: Verify pregnancy status of females prior to initiation of Cyclophosphamide Injection. May impair fertility.
- Renal Patients: Monitor for toxicity in patients with moderate and severe renal impairment.

PHARMACEUTICAL STORAGE

Store at 2-8 °C temperature in a refrigerator. Keep away from light and wet place. Keep out of reach of children.

PACKAGING

Cycloph™ 200 Injection: Each vial contains Cyclophosphamide USP equivalent to Anhydrous Cyclophosphamide 200 mg (200 mg/mL)
Cycloph™ 500 Injection: Each vial contains Cyclophosphamide USP equivalent to Anhydrous Cyclophosphamide 500 mg (200 mg/mL)
Cycloph™ 1 gm Injection: Each vial contains Cyclophosphamide USP equivalent to Anhydrous Cyclophosphamide 1000 mg (200 mg/mL)

SK+F ONCOLOGY
Manufactured by
ESKAYEF PHARMACEUTICALS LIMITED
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R/PM2038 V01