Neoclomide®

Cyclophosphamide USP

Presentation

Neoclomide® Injection 200 mg: Each vial contains Cyclophosphamide (Monohydrate) USP 213.80 mg equivalent to Anhydrous Cyclophosphamide USP is supplied in vial containing 200 mg as sterile, preservative-free lyophilized powder for reconstitution.

Neoclomide® Injection 500 mg: Each vial contains Cyclophosphamide (Monohydrate) USP 534.50 mg equivalent to Anhydrous Cyclophosphamide USP is supplied in vial containing 500 mg as sterile, preservative-free lyophilized powder for reconstitution.

Neoclomide® Injection 1 g: Each vial contains Cyclophosphamide (Monohydrate) USP 1.069 g equivalent to Anhydrous Cyclophosphamide USP is supplied in vial containing 1 g as sterile, preservative-free lyophilized powder for reconstitution.

Neoclomide® Tablet 50 mg: Each tablet contains Cyclophosphamide (Monohydrate) USP 53.45 mg equivalent to Anhydrous Cyclophosphamide USP 50 mg.

Description

Cyclophosphamide for Injection, USP is a sterile white powder containing Cyclophosphamide Monohydrate. Cyclophosphamide Tablets, USP are for oral use and contain 25 mg or 50 mg Cyclophosphamide (Anhydrous). Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder with the molecular formula C7H15Cl2N2O2P•H2O and a molecular weight of 279.1. The chemical name for cyclophosphamide is 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is soluble in water, saline, or ethanol and has the following structural formula:

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. 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 1 Reference ID: 3110030 cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

Indications and usage

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. Adenocarcinoma of the ovary.
7. Retinoblastoma.
8. Carcinoma of the breast.

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.

Contraindications

Continued use of cyclophosphamide is contraindicated in patients with severely depressed bone marrow function. Cyclophosphamide is contraindicated in patients who 2 Reference ID: 3110030 have demonstrated a previous hypersensitivity to it.

Dosage and administration

Treatment of Malignant Diseases

Adults and Children When used as the only oncolytic drug therapy, the initial course of cyclophosphamide for patients with no hematologic deficiency usually consists of 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 cyclophosphamide have been reported. Dosages must be adjusted in accord with evidence of antitumor 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/mm3 (following short courses) or more persistent reduction to 3000 cells/mm3 (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.

Cyclophosphamide and its metabolites are dialyzable although there are probably quantitative differences depending upon the dialysis system being used. Patients with compromised renal function may show some measurable changes in pharmacokinetic parameters of cyclophosphamide metabolism, but there is no consistent evidence indicating a need for cyclophosphamide dosage modification in patients with renal function impairment.

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 treatment exceeds 60 days. Treatment beyond 90 days increases the probability of sterility. Adrenocorticosteroid therapy may be tapered and discontinued during the course of cyclophosphamide therapy.

Cyclophosphamide for Injection

Preparation and Handling of Solutions

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

Cyclophosphamide may be prepared for intravenous administration using any of the following methods. Add the diluent to the vial and shake it vigorously to dissolve. If the powder fails to dissolve immediately and completely, it is advisable to allow the vial to stand for a few minutes. Use the quantity of diluent shown below to reconstitute the product:

Dosage Strength	Contain Cyclophosphamide Monohydrate	Quantity of Diluent	Approximate Cyclophosphamide Concentration
200 mg	213.68 mg	10 ml	2% (20 mg per ml)
500 mg	534.5 mg	25 ml	
1 g	1069.0 mg	50 ml	

Unopened vials of cyclophosphamide are stable until the date indicated on the package when stored at or below 25°C (77°F). If not used immediately, for microbiological integrity, cyclophosphamide solutions should be stored as follows:

Diluent	Storage	
	Room Temperature	Refrigerated
Reconstituted Solution (Without Further Dilution)		
0.9% Sterile Sodium Chloride	up to 24 hrs	up to 6 days
Further Diluted Solutions[1]		
Sodium Chloride Injection, USP (0.45% sterile sodium chloride)	up to 24 hrs	up to 6 days
Dextrose Injection, USP (5% dextrose)	up to 24 hrs	up to 36 hrs
Dextrose and Sodium Chloride Injection, USP (5% dextrose and 0.9% sterile sodium chloride)	up to 24 hrs	up to 36 hrs

[1] Storage time is the total time cyclophosphamide is in solution (including reconstitution).

Precautions

General

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 cyclophosphamide 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 within 10 days of general anesthesia, the anesthesiologist should be alerted.

Pregnancy

Pregnancy Category D.

Nursing Mothers

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.

Pediatric use

The safety profile of cyclophosphamide in pediatric patients is similar to that of the adult population.

Geriatric use

Insufficient data from clinical studies of cyclophosphamide for malignant lymphoma, multiple myeloma, leukemia, mycosis fungoides, neuroblastoma, retinoblastoma, and breast carcinoma are available for patients 65 years of age and older to determine whether they respond differently than younger patients. In two clinical trials in which cyclophosphamide was compared with paclitaxel, each in combination with cisplatin, for the treatment of advanced ovarian carcinoma, 154 (28%) of 552 patients who received cyclophosphamide plus cisplatin were 65 years or older. Subset analyses (65 years) from these trials, published reports of clinical trials of cyclophosphamide containing regimens in breast cancer and non-Hodgkin's lymphoma, and post marketing experience suggest that elderly patients may be more susceptible to cyclophosphamide toxicities. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and adjusting as necessary based on patient response.

Adverse reactions

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. These adverse drug effects generally remit when cyclophosphamide treatment is stopped.

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. Very rare reports of Stevens-Johnson syndrome and toxic epidermal necrolysis have been received during post marketing surveillance; due to the nature of spontaneous adverse event reporting, a definitive causal relationship to cyclophosphamide has not been established.

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/mm^3 develops 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. 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. SIADH (syndrome of inappropriate ADH secretion) has been reported with the use of cyclophosphamide. Malaise and asthenia have been reported as part of the postmarketing experience.

Overdosage

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.

Storage

Store at temperature not exceeding 25°C in a dry place. Protect from light and moisture. Do not freeze.

Packaging

Neoclomide® Injection 200 mg: Each pack contains 1 vial of Anhydrous Cyclophosphamide USP 200 mg & 1 vial of 0.9% NaCl solution BP.

Neoclomide® Injection 500 mg: Each pack contains 1 vial of Anhydrous Cyclophosphamide USP 500 mg & 1 vial of 0.9% NaCl solution BP.

Neoclomide® Injection 1 g: Each pack contains 1 vial of Anhydrous Cyclophosphamide USP 1 g & 1 vial of 0.9% NaCl solution BP.

Neoclomide® Tablet 50 mg: Each box contains 3x10's Anhydrous Cyclophosphamide USP 50 mg tablets in Alu-Alu blister.

Medicine: Keep out of reach of children

For further information, please contact: 01977 158 926
(9.00 am - 5.00 pm)

Healthcare

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HP 52428