Cyclophosphamide Injection IP

ZUVIPHOS

COMPOSITION:

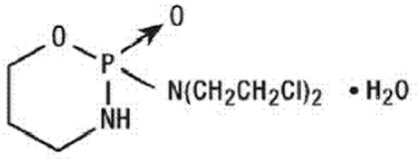
Each vial contains

Strength	200 mg	500 mg	1000 mg
Cyclophosphamide I.P. Equivalent to anhydrous Cyclophosphamide	200 mg	500 mg	1000 mg

DESCRIPTION:

Zuviphos is cyclophosphamide for injection. It is a white powder having a low melting point of 49.5 to 50 C. Cyclophosphamide is chemically 2 - [bis-(2-chloroethyl) - amino] tetrahydro-2H-1, 3,2-oxazaphosphorine-2-oxide, corresponding to the molecular formula C7H15C12N2O2PH2O and a molecular weight of cyclophosphamide is 279.1. Cyclophosphamide is a pro-drug and needs to be converted into an active metabolite in the liver. It is an anticancer drug with a broad-spectrum activity exerting its effect by interfering with G2 & S-phase of the cell cycle.

A powerful immune suppressant, Cyclophosphamide is a component of conditioning regimens for organ and tissue transplants. It has also been used in the treatment of some autoimmune disease such as refractory rheumatoid arthritis, systemic lupus erythematosus, autoimmune haemolytic anaemia, nephrotic syndrome, only after failure with conventional therapy. Cyclophosphamide is preferably administered by the intravenous route. It has been suggested to avoid IM injection because of inconsistent absorption, and delayed activation. For IV administration, a solution containing 20 mg/mL concentrations is generally recommended. It may be diluted further for infusion. The solution may be infused IV in D5W, or D5NS. It is a low melting substance and hence needs to be stored below 25 C. Although the aqueous solutions may be kept for a few hours at 25 C, at temperatures above 30 C cyclophosphamide gets hydrolyzed with loss of chlorine atom and hence loss of activity. Even the oral formulation of Cyclophosphamide needs to be preserved at temperatures less than 25 C. Zuviphos should be stored at controlled temperature between +15°C to +25°C.



MECHANISM of ACTION:

Cyclophosphamide is activated to the alkylating and cytotoxic metabolites in the liver by the mixed function oxidases to form the active 4-hydroxycyclophosphamide derivative which is in equilibrium with the aldophosphamide. The aldophosphamide may get converted in to phosphoramide mustard, which is responsible for biological effects of cyclophosphamide. It interferes with normal DNA function through alkylation and cross-linking the strands of DNA. Cyclophosphamide is a powerful immune suppressive agent.

PHARMACOKINETIC:

Absorption: oral: excellent 80 to100%.

Distribution: Crosses placenta and secreted in breast milk. CSF levels achieved are not adequate to be of value in the treatment of meningeal leukemia.

Serum Half-life: 3 to 12 hrs after IV administration. C max of metabolites: 2 to 3 hrs.

Metabolism: It is a pro-drug, which needs to be metabolized in the liver to the active metabolites.

Excretion: As unchanged drug as well as metabolites. 30 to 96% is excreted in urine over 72 hrs, 5 to 30% of which is unchanged drug.

INDICATIONS:

Zuviphos is indicated in combination with other anticancer drugs in the treatment of metastatic breast cancer, ovarian cancer, cancer of the uterine cervix and endometrium, the Gestational Trophoblastic tumors, Oat Cell Bronchogenic Carcinoma, and Seminoma. It may also be used in the treatment of childhood malignancies such as Neuroblastoma, Retinoblastoma, and Wilm's tumor. Cyclophosphamide has also been successfully used in the treatment of Burkitt's lymphoma, Hodgkin's disease, non-Hodgkin's Lymphomas, the Chronic Lymphoblastic, Acute Myelogenous Leukemia, Plasmocytoma, Multiple Myeloma, Mycosis Fungoides, and Waldenstrom's disease. It has been also indicated for the treatment of the Osteosarcoma and Ewing's sarcoma. It may also be used for the treatment of biopsy proven, minimal change nephritic syndrome. DESCRIPTION:

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DOSAGE & ADMINISTRATION:

Reconstitution:

*Reconstitute with Sterile Water for Injection to achieve a concentration of 20mg/ml as follows:

Cyclophosphamide	200 mg	500 mg	1000 mg
Sterile Water For Injection volume	10 ml	25 ml	50 ml
Conc. Achieved	(20mg/ml)	(20mg/ml)	(20mg/ml)

May be used as such or diluted further in a compatible diluent.

Mode of administration: Zuviphos is ideally administered IV only. It is recommended that freshly prepared solution of Zuviphos should be used. The reconstituted solution- as described above by shaking the vial contents till complete dissolution in Sterile Water for Injection- yields a 20mg/ml solution. The re-constituted solutions may be injected

directly or further diluted with a compatible IV infusion solution for intravenous infusion. For example, a solution thus prepared is added to 250ml of 5% dextrose and administered as an infusion over 30 minutes. (*Do not use Isotonic saline for reconstitution).

A number of protocols incorporating cyclophosphamide are in vogue. Individual protocol should be referred for guidelines on dosing schedule and reduction in dose, if any, based on myelosuppression due to chemotherapy or radiation therapy.

Dosage:

Induction Therapy:

· Initiated with an intravenous Cyclophosphamide 40-50 mg/kg (1.5 to 1.8 g/m2), usually in divided doses given over 2 to 5 days. The dose may be repeated after 3 to 4 weeks, depending upon the response and toxicity.

· (Alternative regimens such as 10 to 15 mg/kg given every 7 to 10 days or 3 to 5 mg/kg twice weekly may also be used).

It case of compromised bone marrow function the dose requires reduction which may range from 33 to 50 %, depending upon the status of the patient.

Special Precautions:

Morning administration may be preferred so as to allow for ample fluid intake and bladder emptying several times so as to diminish the likelihood of cystitis.

Cyclophosphamide Injection in combination chemotherapy

Dosages described above refer to monotherapy. Consider prolongation of interval between cycles (rather than dose reduction) when using combination of Cyclophosphamide Injection with other chemotherapeutic drugs with similar toxicity (for instance bone marrow depression). Refer to individual protocols.

WARNINGS &

1. Cyclophosphamide, like other alkylating agents, is carcinogenic, mutagenic and may cause infertility. It may interfere with wound healing as well. It also has a low Therapeutic Index.

2. Sensitivity & possibility of cross resistance to other alkylating agents has been reported.

10. Since cyclophosphamide is secreted in human milk, breastfeeding should be terminated prior to initiating cyclophosphamide therapy.

3. Terminate cyclophosphamide therapy or reduce dose in patients who develop bacterial/fungal, viral or protozoa infection. This is particularly relevant to patients who are on corticosteroid therapy or have received corticosteroids in the recent past.

4. There are reports of use of multiple anticancer drugs including cyclophosphamide, paclitaxel, carboplatin and other anticancer drugs during pregnancy1-3 such as in Burkit's lymphoma, and even ovarian and breast cancer. Cyclophosphamide has also been used to treat severe lupus4 during pregnancy. Pregnancies exposed to cyclophosphamide for severe lupus flare have resulted in a higher rate of fetal losses than pregnancies with severe lupus but not requiring the drug (100% versus 31.25%). Considering the positive evidence of human fetal risk, the benefits from use in pregnant women may be acceptable despite the risk only if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective.

PRECAUTIONS:

1. Anaphylaxis, skin rash, pigmentation and changes in nail (ridging, retardation of growth) may occur.

2. Since myelosuppression is an adverse effect associated with cyclophosphamide, during treatment with Zuviphos, monitor neutrophil and platelet count to determine the extent of hematopoietic suppression and possible dose adjustments.

4. Cardiac toxicity although uncommon at usual doses, may occur with high dose cyclophosphamide therapy. Thus caution is indicated when doxorubicin like cardiotoxic drugs are used concomitantly with Zuviphos.

7. Development of secondary malignancies such as bladder cancer, or myeloproliferative and lymphoproliferative malignancies have been reported in patients treated with cyclophosphamide alone or in combination with other antineoplastic drugs.

8. Urinary bladder malignancies are most common in patients who experienced hemorrhagic cystitis. Use of MESNA is recommended with high dose cyclophosphamide therapy to prevent bladder toxicity.

ADVERSE EFFECTS:

· Severe leucopenia necessitating dosage reduction or even interruption of therapy may occur following high doses cyclophosphamide therapy. However, thrombopoieses and erythropoieses are generally not affected to any great extent.

· At high doses, cyclophosphamide is associated with a peculiar toxicity such as water retention and dilutional hyponatremia. Pediatric patients are especially prone to this toxicity manifested as decreased urine flow, decreased serum osmolarity and sodium and increased urine osmolarity, occurring 4 to 12 hours after cyclophosphamide. Presumably related to a direct toxic effect of alkylating metabolites on distal renal tubules and collecting ducts, it may resolve at 20 to 24 hours post therapy. CONTRA-INDICATIONS:

· Zuviphos is contraindicated in case of known hypersensitivity to Cyclophosphamide.

· During first three months of pregnancy Zuviphos is absolutely contraindicated as abnormalities have been reported in infants born to women having received cyclophosphamide during pregnancy.

· Patients from reproductive age group should take contraceptives or abstain from intercourse during and for the 3 months after cessation of Cyclophosphamide therapy.

· Zuviphos is contraindicated in florid ulcerations of the GI tract, severe bone marrow depression, liver and kidney dysfunction and in patients with severe heart failure.

Pregnancy: During pregnancy, it may be used only in life threatening situations, or severe disease for which safer drugs are either cannot be used or ineffective.

Pediatric precautions: Safety profile in children is similar to that observed in adult patients.

Carcinogenicity: The possibility may be considered for weighing possible benefits versus risk ratio.

DRUG INTERACTIONS:

- Concomitant administration of anti-diabetic drugs with Zuviphos may cause further reduction in blood sugar level.

- Concomitant administration of Cyclophosphamide and allopurinol may enhance bone marrow depression.

- Since cyclophosphamide causes marked inhibition of cholinesterase activity, caution is indicated when anesthetic agents such as halothane, nitrous oxide, or succinylcholine are administered concomitantly.

- Cimetidine inhibits hepatic enzymes thereby reducing the activation of cyclophosphamide.

- Induction of hepatic enzymes by phenobarbital and phenytoin causes rapid metabolization of cyclophosphamide resulting in a concurrent decrease in serum half-life.

- Cyclophosphamide -Amphotericin are incompatible via Y-site injection.

OVERDOSAGE:

Myelosuppression, nausea and vomiting are the major symptoms of cyclophosphamide overdose. Although dialyzable, no specific studies are reported. There is no specific antidote for cyclophsphamide overdose. The patient needs to be hospitalized and the treatment is essentially supportive therapy. Alopecia may also be observed.

CONTRA-INDICATIONS:

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STORAGE

Store below 25° C .Protect from light.

PRESENTATION:

ZUVIPHOS Injection 200mg vial, 500mg vial or 1g vial.

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
www.zuviuslifesciences.in