hemorrhagic myocarditis and myocardial necrosis. Pericarditis has also been reported independent of any hemopericardium. No residual cardiac abnormalities, as evidenced by electrocardiogram or echocardiogram appear to be present in patients surviving episodes of apparent cardiac toxicity associated with high doses of cyclophosphamide.

Cyclophosphamide has been reported to potentiate doxorubicin induced cardiotoxicity. Treatment with cyclophosphamide may cause significant suppression of immune responses; serious, sometimes fatal, infections may develop in severely immunosuppressed patients. Cyclophosphamide treatment may not be indicated or should be interrupted or the dose reduced in patients who have or who develop viral, bacterial, fungal, protozoan or helminthic infections.

Anaphylactic reactions rarely resulting in death and possible cross sensitivity with other alkylating agents has been reported.

PRECAUTION(S)

Special attention to the possible development of toxicity should be exercised in patients being treated with cyclophosphamide if Leukopenia / Thrombocytopenia / Tumor cell infiltration of bone marrow / Previous X-ray therapy / Previous therapy with other cytotoxic agents / Impaired hepatic function / Impaired renal function is present. 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.

Pregnancy - Category D

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. The safety profile of CYPHOS™ (cyclophosphamide) in pediatric patients is similar to that of the adult population. 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. Postmarketing experience suggest that elderly patients may be more susceptible to cyclophosphamide toxicities. In general the 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.

DRUG INTERACTION(S)

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 alerted 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 may cause a marked and persistent inhibition of cholinesterase activity and potentiate the effect of succinylcholine chloride. The anaesthesiologist should be alerted if a patient has been treated with cyclophosphamide within 10 days of general anesthesia. Cyclophosphamide has been reported to be more toxic in adrenalectomized dogs hence adjustment of doses of both replacement steroids and cyclophosphamide may be necessary for the adrenalectomized patient. Cyclophosphamide may interfere with normal wound healing.

OVERDOSAGE(S)

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 between 20-25 °C (68-77 °F). Protect from light. Retain in carton until time of use. Store the vials between 20-25 °C (68-77 °F). During transport or storage of CYPHOS™ vials, temperature influences can lead to melting of the active ingredient, cyclophosphamide. Vials containing melted substance can be visually differentiated. Melted cyclophosphamide is a clear or yellowish viscous liquid usually found as a connected phase or in droplets in the affected vials. Do not use CYPHOS™ vials if there are signs of melting.

PRESENTATION

CYPHOS™ (Cyclophosphamide injection IP) contains cyclophosphamide monohydrate supplied in 200 mg / 500 mg / 1 g vial for single dose only.

HANDLING & DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines have been published on proper handling and disposal of anticancer drugs however there is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing CYPHOS™, sterile powder for injection. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

Manufactured by:
Getwell Pharmaceuticals
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0700DCY

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Cyclophosphamide Injection IP

CYPHOS™

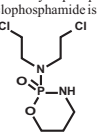
Antineoplastic Agent
FOR INTRAVENOUS USE ONLY
Rx only

WARNING

CYPHOS™ should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Treatment with cyclophosphamide may cause significant suppression of immune responses; hemorrhagic cystitis may develop in patients treated with cyclophosphamide. Cyclophosphamide can cause fetal harm when administered to pregnant women and may interfere with oogenesis, spermatogenesis or cause fertility in both sexes.

DESCRIPTION

CYPHOS™ (Cyclophosphamide injection IP) is a sterile white crystalline powder containing cyclophosphamide monohydrate. Cyclophosphamide is a synthetic antineoplastic drug also known as cytophosphane, a nitrogen mustard alkylating agent from the oxazophorines group. An alkylating agent adds an alkyl group (C_nH_{2n+1}) to DNA; hence cyclophosphamide attaches the alkyl group to the guanine base of DNA, at the number 7 nitrogen atom of the imidozole ring. Cyclophosphamide is a *prodrug* and it is converted in the liver to active forms that have chemotherapeutic activity. Cyclophosphamide has the molecular formula $C_7H_{15}C_{l2}N_2O_2P.H_2O$ and a molecular weight of 279.1. Chemically cyclophosphamide is 2 - [bis (2 - chloroethyl) amino] tetrahydro - 2 H - 1, 3, 2 - oxazaphosphorine 2 - oxide monohydrate. Cyclophosphamide is soluble in water, saline and ethanol. The structural formula of cyclophosphamide is



COMPOSITION

Each vial of CYPHOS™ 200 mg contains	
Cyclophosphamide IP equivalent to anhydrous Cyclophosphamide	200 mg
Sodium Chloride IP	90 mg
Each vial of CYPHOS™ 500 mg contains	
Cyclophosphamide IP equivalent to anhydrous Cyclophosphamide	500 mg
Sodium Chloride IP	225 mg
Each vial of CYPHOS™ 1 g contains	
Cyclophosphamide IP equivalent to anhydrous Cyclophosphamide	1 g
Sodium Chloride IP	450 mg

CLINICAL PHARMACOLOGY & MECHANISM OF ACTION

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 and thus the mechanism of action is thought to involve cross-linking of tumor cell DNA. The main active metabolite of cyclophosphamide is 4-hydroxycyclophosphamide, which exists in equilibrium with its tautomer, aldophosphamide. Most of the aldophosphamide is oxidised by the enzyme aldehyde dehydrogenase (ALDH) to make carboxyphosphamide. A small proportion of aldophosphamide is converted into phosphoramide mustard and acrolein. Acrolein is toxic to the bladder epithelium and can lead to hemorrhagic cystitis. This can be prevented through the use of aggressive hydration and or Mesna.

Recent clinical studies have shown that cyclophosphamide can induce beneficial immunomodulatory effects in the context of adoptive immunotherapy. Although the mechanisms underlying these effects are not fully understood, several mechanisms have been suggested based on potential modulation of the host environment, including:

Elimination of T regulatory cells ($CD_4 + CD_{25} +$ T cells) in naive and tumor bearing hosts

Induction of T cell growth factors such as type I IFNs and or

Enhanced grafting of adoptively transferred tumor reactive effector T cells by the creation of an immunologic space niche.

PHARMACOKINETICS & PHARMACODYNAMICS

Cyclophosphamide is well absorbed after oral administration and bioavailability is often reported to be greater than 75 %. The unchanged drug is primarily eliminated in the form of metabolites, has an elimination 1/2 life of 3-12 hours and as much as 5-25 % of the dose is excreted in urine. Reports suggest that several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2-3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to greater than 60 %. It has however 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.

INDICATION(S)

Malignant Diseases

CYPHOS™, effective for the treatment of susceptible malignancies, is more frequently used concurrently and or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to CYPHOS™ treatment:

Malignant lymphomas (stage III & IV of Ann Arbor staging system), Hodgkin's disease, lymphocytic lymphoma (nodular or diffuse), mixed cell type lymphoma, histiocytic lymphoma and Burkitt's lymphoma

Multiple myeloma

Leukemias: Chronic lymphocytic leukemia, chronic granulocytic leukemia (usually ineffective in acute blastic crisis), acute myelogenous, monocytic leukemia and acute lymphoblastic (stem cell) leukemia in children

Mycosis fungoides (advanced) - the most common form of cutaneous T-cell lymphoma

Neuroblastoma (disseminated)
Adenocarcinoma of the ovary
Retinoblastoma
Carcinoma of the breast

Nonmalignant Disease

CYPHOS™ is useful in carefully selected cases of biopsy proven "minimal change" nephrotic syndrome in children but should not be used as primary therapy. Cyclophosphamide may induce a remission 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 is not indicated for the nephrotic syndrome in adults or for any other renal disease.

DOSAGE & ADMINISTRATION

Treatment of Malignant Diseases in Adults and Children

When used as mono oncolytic drug therapy, the initial course of CYPHOS™ for patients with no hematologic deficiency is usually 40-50 mg/kg given intravenously in divided doses over a period of 2-5 days. Other intravenous regimen includes 10-15 mg/kg given every 7-10 days or 3-5 mg/kg twice weekly. Oral dosage of CYPHOS™ is usually 1-5 mg/kg/day for both initial and maintenance dosing. Although many regimens of intravenous and oral CYPHOS™ have been reported, the dosage must be adjusted in accordance with evidence of antitumor activity and/or leukopenia. Total leukocyte count is a good, objective guide for regulating dosage. Transient decrease in total white blood cell count to 2000 cells/mm^3 (following short courses) or more persistent reduction to 3000 cells/mm^3 (with continuing therapy) are tolerated without serious risk of infection if there is no marked granulocytopenia. An oral dose of 2.5-3 mg/kg daily for a period of 60 to 90 days is usually recommended for the treatment of nonmalignant diseases - biopsy proven "minimal change" nephrotic syndrome in children.

When CYPHOS™ is included in combined cytotoxic regimens, it may be necessary to reduce the dose of CYPHOS™ as well as that of the other drugs. CYPHOS™ 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 CYPHOS™ metabolism, but there is no consistent evidence indicating a need for CYPHOS™ dosage modification in patients with renal function impairment.

In male pateints the incidence of oligospermia and azoospermia increases if the duration of CYPHOS™ treatment exceeds 60 days. Treatment beyond 90 days increases the probability of sterility. Adrenocorticosteroid therapy may be tapered and discontinued during the course of CYPHOS™ therapy.

Preparation and handling of solutions

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. It is recommended to add the diluent to the vial and shake 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 constitute the product.

Dosage strength	CYPHOS ™ contains Cyclophosphamide Monohydrate	Quantity of Diluent
200 mg	213.8 mg	10 ml
500 mg	534.5 mg	25 ml
1 g	1.069 g	50 ml

For direct injection (parenteral use) CYPHOS™ should be prepared by the addition of 0.9 % sterile sodium chloride solution. Solutions of CYPHOS™ may be injected intravenously, intramuscularly, intraperitoneally or intrapleurally if constituted by adding 0.9 % sterile sodium chloride solution.

For infusion CYPHOS™ (cyclophosphamide) may be prepared by the following methods:

CYPHOS™ constituted with 0.9 % sterile sodium chloride infused without further dilution.

CYPHOS™ constituted with 0.9 % sterile sodium chloride may be infused following further dilution in -

- Dextrose Injection USP (5 % dextrose)
- Dextrose and Sodium Chloride Injection USP (5 % dextrose and 0.9 % sterile sodium chloride)
- 5 % Dextrose and Ringer's Injection
- Lactated Ringer's Injection USP
- Sodium Chloride Injection USP (0.45 % sterile sodium chloride)
- Sodium Lactate Injection USP (1/6 molar sodium lactate)

CYPHOS™ sterile powder may be prepared for parenteral use by infusion by adding Sterile Water for Injection USP. CYPHOS™ *constituted in water, is hypotonic and should not be injected directly.* Prior to infusion solution of CYPHOS™ sterile powder constituted in Sterile Water for Injection USP must be further diluted in one of the following:

- Dextrose Injection USP (5 % dextrose)
- Dextrose and Sodium Chloride Injection USP (5 % dextrose and 0.9 % sterile sodium chloride)
- 5 % Dextrose and Ringer's Injection
- Lactated Ringer's Injection USP
- Sodium Chloride Injection USP (0.45 % sterile sodium chloride)
- Sodium Lactate Injection USP (1/6 molar sodium lactate)

Stability of constituted parenteral solution: CYPHOS™ (prepared for either direct injection or infusion) is chemically and physically stable for 24 hours at room temperature or for six days in the refrigerator; it does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions. The osmolarities of solutions of CYPHOS™ constituted with water and 0.9 % sterile sodium chloride solution are as follows

CYPHOS ™ and Diluent	mOsmL
5 ml water per 100 mg cyclophosphamide (anhydrous)	74
5 ml 0.9 % sterile sodium chloride solution per 100 mg cyclophosphamide (anhydrous)	374

Isotonic 0.9 % sterile sodium chloride solution has an osmolarity of 289 mOsm/L.

For oral administration extemporaneous liquid preparations of CYPHOS™ may be prepared by dissolving CYPHOS™ in Aromatic Elixir N.F. Such preparations should be stored under refrigeration in glass containers and used within 14 days.

CONTRAINDICATION(S)

Continued use of cyclophosphamide is contraindicated in patients with severely depressed bone marrow function and in patients who have demonstrated a previous hypersensitivity.

ADVERSE REACTION(S)

Adverse reactions reported with the use cyclophosphamide are listed in order of decreasing incidence and based on the body system affected or type of reaction.

Digestive system: Nausea and vomiting commonly occur with cyclophosphamide therapy. Anorexia, less frequently abdominal discomfort or pain and diarrhea may occur. There have been 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: Alopecia occurs commonly in patients treated with cyclophosphamide. However hair is 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 cyclophosphamide. Pigmentation of the skin and changes in nails has also been reported. Post marketing surveillance suggest very rare occurrence of Stevens-Johnson syndrome and toxic epidermal necrolysis.

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, 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 may develop occasionally in patients treated with cyclophosphamide. These hematologic effects can be usually 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 while interstitial pulmonary fibrosis has been reported in patients receiving high doses of cyclophosphamide over a prolonged period.

Other reactions include anaphylactic reactions which has 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.

WARNING(S)

Cyclophosphamide can cause fetal harm when administered to pregnant women. Reports claim development of abnormalities in infants and fetus born to women treated with cyclophosphamide. Ectrodactylia may be seen in rare cases. If cyclophosphamide is used during pregnancy or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant. Cyclophosphamide may also interfere with oogenesis, spermatogenesis and may cause sterility in both sexes. Development of sterility appears to depend on the dose of cyclophosphamide, duration of therapy and the state of gonadal function at the time of treatment. Cyclophosphamide induced sterility may be irreversible in some patients. Amenorrhea associated with decreased estrogen and increased gonadotropin secretion may develop in a significant proportion of women treated with cyclophosphamide; in affected patients the menstrual cycle may generally resume within a few months after cessation of therapy. Girls treated with cyclophosphamide during pre-pubescence generally develop secondary sexual characteristics normally and tend to have regular menstrual cycle; girls treated with cyclophosphamide during prepubescence subsequently have conceived. Ovarian fibrosis with apparently complete loss of germ cells after prolonged cyclophosphamide treatment in late prepubescence has been reported. Men treated with cyclophosphamide may develop oligospermia or azoospermia associated with increased gonadotropin but normal testosterone secretion however sexual potency and libido are often unimpaired in such patients. Boys treated with cyclophosphamide during prepubescence develop secondary sexual characteristics normally, but may tend to have oligospermia or azoospermia, increased gonadotropin secretion while some degree of testicular atrophy may occur. Cyclophosphamide induced azoospermia is reversible in some patients, though the reversibility may not occur for several years after cessation of therapy. Reports suggest that men temporarily rendered sterile by cyclophosphamide have subsequently fathered normal children.

Reports suggest that malignancies have developed in some patients treated with cyclophosphamide used alone or in association with other antineoplastic drugs and/or modalities. These most frequently include the urinary bladder, myeloproliferative or lymphoproliferative malignancies. Second malignancies are most frequently detected in patients treated for primary myeloproliferative or lymphoproliferative malignancies or nonmalignant disease in which immune processes are believed to be involved pathologically. Second malignancy may also develop several years after cyclophosphamide treatment had been discontinued. Report from breast cancer trial utilizing two to four times the standard dose of cyclophosphamide in conjunction with doxorubicin states the occurrence of secondary acute myeloid leukemia within two years of treatment initiation. Urinary bladder malignancies generally occurred in patients who previously had hemorrhagic cystitis. Patients treated with cyclophosphamide containing regimens for a variety of solid tumors may develop secondary malignancies. The possibility of cyclophosphamide induced malignancy should be considered in the benefit to risk assessment for use of the drug.

Hemorrhagic cystitis may develop in patients treated with cyclophosphamide and rarely this condition can be severe or even fatal. Fibrosis of the urinary bladder, sometimes extensive may develop with or without accompanying cystitis and atypical urinary bladder epithelial cells may appear in urine. Such bladder injury is thought to be due to cyclophosphamide metabolites excreted in the urine. Reports testify that these adverse effects appear to depend on the dose of cyclophosphamide and the duration of therapy. Forced fluid intake helps to assure an ample output of urine, necessitates frequent voiding and reduces the time the drug remains in the bladder and helps prevent cystitis. Hematuria usually resolves within few days after cessation of cyclophosphamide treatment but it may persist at times. Medical and/or surgical supportive treatment may be required, rarely, to treat protracted cases of severe hemorrhagic cystitis and it is often necessary to discontinue cyclophosphamide therapy in instances of severe hemorrhagic cystitis.

Few instances of cardiac dysfunction have been reported following use of recommended doses of cyclophosphamide but no causal relationship has been established. When used as a portion of an intensive antineoplastic multi-drug regimen or in conjunction with transplantation procedures acute cardiac toxicity has been reported with doses between 2.4 g/m^2 to 26 g/m^2. With high doses of cyclophosphamide, severe and sometimes fatal congestive heart failure has occurred after the first dose. Histopathologic examination primarily shows hemorrhagic myocarditis while hemopericardium occurrs secondary to