PRODUCT MONOGRAPH

CYTOXAN*

(cyclophosphamide)

Sterile powder 100, 750, 1000 and 2000 mg, U.S.P.

Tablets 25 and 50 mg, U.S.P.

Antineoplastic Agent

Bristol-Myers Squibb Canada
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THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CAUTION

CYTOXAN IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). IN THOSE PATIENTS WHO DEVELOP BACTERIAL, FUNGAL, OR VIRAL INFECTIONS, MODIFICATION OF DOSAGE SHOULD BE CONSIDERED. BLOOD COUNTS SHOULD BE TAKEN AT REGULAR INTERVALS.

ACTION AND CLINICAL PHARMACOLOGY

Cyclophosphamide is activated by metabolism in the liver by the mixed-function oxidase system of the smooth endoplasmic reticulum. The hepatic cytochrome P-450 mixed-function converts cyclophosphamide to 4-hydroxycyclophosphamide, which is in a steady state with the acyclic tautomer, aldophosphamide. The drug and its metabolites are distributed throughout the body including the brain.

Cyclophosphamide, which is biologically relatively inactive, is eliminated from the body very slowly. The activated metabolites alkylate the target sites in susceptible cells in an "all-or-none" type of reaction or are detoxicated by formation of inactive metabolites that are rapidly excreted by the kidneys.

INDICATIONS AND CLINICAL USES

A. Frequently responsive myeloproliferative and lymphoproliferative disorders:

1. Malignant lymphomas (Stages II to IV)
   a) Hodgkin's disease
   b) Mixed-cell type lymphoma
   c) Lymphocytic lymphoma
   d) Histiocytic lymphoma
   e) Lymphoblastic lymphosarcoma
   f) Burkitt's lymphoma

2. Multiple myeloma.

3. Leukemias:
   a) Chronic lymphocytic leukemia
   b) Chronic granulocytic leukemia (it is ineffective in acute blastic crises)

c) Acute myelogenous and monocytic leukemia
d) Acute lymphoblastic (stem-cell) leukemia in children (cyclophosphamide given during remission is effective in prolonging its duration)

4. Mycosis fungoides (advanced disease).

B. Frequently responsive solid malignancies:
1. Neuroblastoma (in patients with disseminated disease)
2. Adenocarcinoma of the ovary
3. Retinoblastoma

C. Infrequently responsive malignancies:
1. Carcinoma of the breast
2. Malignant neoplasms of the lung

CONTRAINDICATIONS

CYTOXAN is contraindicated in those people who are sensitive to cyclophosphamide or any ingredients in the dosage form. It is also contraindicated in severe leukopenia, thrombocytopenia, and hepatic or renal dysfunction.

WARNINGS

Since cyclophosphamide is an inhibitor of serum cholinesterase, patients receiving this drug may exhibit increased sensitivity to neuromuscular blocking agents, such as succinylcholine. If a patient receiving cyclophosphamide is undergoing surgery, advise the anaesthesiologist

The rate of metabolism and the leukopenic activity of CYTOXAN 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 CYTOXAN even though CYTOXAN has been used successfully concurrently with other drugs, including other cytotoxic drugs.

CYTOXAN has been reported to have oncogenic activity in rats and mice. The possibility that it may have oncogenic potential in humans should be considered. CYTOXAN may interfere with normal wound healing.

Use in pregnancy: CYTOXAN (cyclophosphamide) can be teratogenic or cause fetal resorption in experimental animals. It should not be used in pregnancy, particularly in early pregnancy, unless in the judgement of the physician the potential benefits outweigh the possible risks. CYTOXAN is excreted in breast milk and breast feeding should be terminated prior to institution of CYTOXAN therapy.

Because of the mutagenic potential of the drug, adequate methods of contraception should be used by patients (both male and female) during and at least four months after discontinuance of cyclophosphamide therapy.

Since CYTOXAN has been reported to be more toxic in adrenalectomized dogs, adjustment of the doses of both replacement steroids and CYTOXAN may be necessary for the adrenalectomized patient.

PRECAUTIONS

CYTOXAN should be given cautiously to patients with any of the following conditions:

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

Because CYTOXAN (cyclophosphamide) may exert a suppressive action in immune mechanisms, the interruption or modification of dosage should be considered for patients who develop bacterial, fungal or viral infections. This is especially true for patients receiving concomitant steroid therapy and perhaps those with a recent history of steroid therapy, since infections in some of these patients have been fatal. Varicella-Zoster infections appear to be particularly dangerous under these circumstances.

It is recommended that patients being considered as candidates for long term therapy have their renal function monitored prior to treatment. Urine should also be examined regularly for red cells which may precede hemorrhagic cystitis.

Carcinogenesis

Second malignancies have developed in some patients treated with cyclophosphamide used alone or in association with other antineoplastic therapies. Most frequently, they have been urinary bladder, myeloproliferative or lymphoproliferative malignancies. Second malignancies most frequently were detected in patients treated for primary myeloproliferative or lymphoproliferative malignancies or non-malignant disease in which pathologic immune processes are believed to be involved . In some cases, the second malignancy developed several years after cyclophosphamide treatment had been discontinued. Urinary bladder malignancies generally have occurred in patients who previously had hemorrhagic cystitis. One case of carcinoma of the renal pelvis was reported in a patient receiving long-term cyclophosphamide therapy for cerebral vasculitis. The possibility of cyclophosphamide-induced malignancy should be considered in any benefit-to-risk assessment for use of the drug.

Girls treated with cyclophosphamide during prepubescence generally develop secondary sexual characteristics normally and have regular menses. Ovarian fibrosis with apparently complete loss of germ cells after prolonged cyclophosphamide treatment in late prepubescence has been reported. Girls treated with cyclophosphamide during prepubescence subsequently have conceived.

Men treated with cyclophosphamide may develop oligospermia or azoospermia associated with increased gonadotropin but normal testosterone secretion. Sexual potency and libido are unimpaired in these patients. Boys treated with cyclophosphamide during prepubescence develop secondary sexual characteristics normally but may have oligospermia or azoospermia and increased gonadotropin secretion. 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. Men temporarily rendered sterile by cyclophosphamide have subsequently fathered normal children.

Urinary System

Sterile hemorrhagic cystitis can result from the administration of CYTOXAN (cyclophosphamide). This can be severe, even fatal, and is probably due to metabolites in the urine. Nonhemorrhagic cystitis and/or fibrosis of the bladder also have been reported to result from CYTOXAN administration. Atypical epithelial cells may be found in the urinary sediment. Ample fluid intake and frequent voiding help to prevent the development of cystitis, but when it occurs it is ordinarily necessary to interrupt CYTOXAN therapy. Hematuria usually resolves spontaneously within a few days after CYTOXAN therapy is discontinued, but may persist for several months. In severe cases, replacement of blood loss may be required. The application of electrocautery to telangiectatic areas of the bladder and diversion of urine flow have been successful methods used in treatment of protracted cases. Cryo-surgery has also been used. Nephrotoxicity, including hemorrhage and clot formation in the renal pelvis, have been reported. Hemorrhagic ureteritis and tubular necrosis have been reported in patients treated with CYTOXAN.

ADVERSE REACTIONS

Digestive System

Anorexia, nausea, or vomiting are common and related to dose as well as individual susceptibility. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy.

Skin and Its Structures

It is ordinarily advisable to inform patients in advance of possible alopecia, a frequent complication of CYTOXAN therapy. Regrowth of hair can be expected although occasionally the new hair may be of a different colour or texture. The skin and fingernails may become darker during therapy. Non-specific dermatitis has been reported to occur with CYTOXAN. Very rare reports of Stevens-Johnson syndrome and toxic epidermal necrolysis have been received during postmarketing surveillance; a causal relationship to cyclophosphamide has not been definitively established.

Hematopoietic System

Leukopenia is an expected effect and ordinarily is used as a guide to therapy. Thrombocytopenia or anemia may occur in a few patients. These effects are almost always reversible when therapy is interrupted. Fever without documented infection has been reported in neutropenic patients.

Respiratory System

Postmarketing reports of interstitial pneumonia/pneumonitis have been received. Interstitial pulmonary fibrosis has been reported in patients receiving high doses of CYTOXAN over a prolonged period. There have been reported cases of cyclophosphamide-induced pneumonitis which may continue for one or more months after discontinuation of therapy.

Cardiac Toxicity

Acute cardiac toxicity has been reported with doses from approximately 65 mg/kg usually as a portion of an intensive antineoplastic multi-drug regimen or in conjunction with transplantation procedures. In a few instances with high doses of CYTOXAN, severe, and sometimes fatal, congestive heart failure has occurred after the first CYTOXAN dose. Histopathologic

examination has primarily shown hemorrhagic myocarditis. Pericarditis has 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 CYTOXAN.

CYTOXAN has been reported to potentiate doxorubicin-induced cardiotoxicity.

Other

Other adverse reactions that have been noted with CYTOXAN include: anaphylactic reaction (death has been reported in association with this event); possible cross-sensitivity with other alkylating agents; the syndrome of inappropriate antidiuretic hormone (SIADH) secretion; headache; dizziness; hypoprothrombinemia; diabetes mellitus; malaise and asthenia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No specific antidote for CYTOXAN (cyclophosphamide) is known. Management of overdosage would include general supportive measures to sustain the patient through any period of toxicity that might occur.

Concurrent administration of the uroprotective agent Mesna will aid largely in the prevention of bladder toxicity.

DOSAGE AND ADMINISTRATION

Chemotherapy with CYTOXAN (cyclophosphamide), as with other drugs used in cancer chemotherapy, is potentially hazardous and fatal complications can occur. It is recommended that it be administered only by physicians aware of the associated risks. Therapy may be aimed at either induction or maintenance of remission.

Induction Therapy: The usual initial loading dose for patients with no hematologic deficiency is 40-50 mg/kg, usually given intravenously. This can be given at the rate of 10-20 mg/kg/day for 2-5 days depending on tolerance by the patient.

Patients with any previous treatment that may have compromised the functional capacity of the bone marrow, such as X-ray or cytotoxic drugs, and patients with tumor infiltration of the bone marrow may require reduction of the initial loading dose by 1/3 to 1/2.

A marked leukopenia is usually associated with the above doses, but recovery usually begins after 7-10 days. The white blood cell count should be monitored closely during induction therapy.

If initial therapy is given orally, a dose of 1-5 mg/kg/day can be administered depending on tolerance by the patient.

Maintenance Therapy: It is frequently necessary to maintain chemotherapy in order to suppress or retard neoplastic growth. A variety of schedules has been used:

(1) 1- 5 mg/kg orally, daily
(2) 10-15 mg/kg intravenously, every 7-10 days
(3) 3- 5 mg/kg intravenously, twice weekly.

Unless the disease is usually sensitive to CYTOXAN, it is advisable to give the largest maintenance dose that can be reasonably tolerated by the patient. The total leukocyte count is a good objective guide for regulating the maintenance dose. Ordinarily a leukopenia of 3000-4000 cells/mm^3. can be maintained without undue risk of serious infection or other complications.

PHARMACEUTICAL INFORMATION

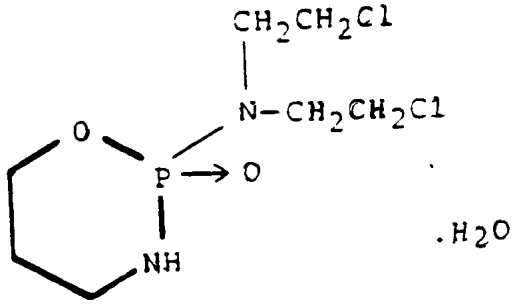
I. DRUG SUBSTANCE

Trade Name: CYTOXAN

Proper Name: Cyclophosphamide

Chemical Name: 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxaza-phosphorine 2-oxide monohydrate

Structural Formula:



Molecular Formula: $C_7H_{15}Cl_2N_2O_2P.H_2O$

Molecular Weight: 279.11

Description: White crystalline powder, soluble in water, saline and alcohol, pH 3.9-7.1 (1% w/v solution), melting point 49.5-53°C.

II. COMPOSITION

Sterile CYTOXAN Powder for Injection - contains cyclophosphamide monohydrate and is supplied in vials for single dose use.

CYTOXAN Tablets - contains cyclophosphamide (anhydrous), acacia, corn starch, FD&C Blue #1, D&C Yellow #10 Aluminum Lake, lactose, magnesium stearate, stearic acid and talc.

III. STABILITY AND STORAGE RECOMMENDATIONS

Sterile CYTOXAN Powder for Injection: Do not store at temperatures above 25°C. During transport or storage of CYTOXAN 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 CYTOXAN vials if there are signs of melting.

CYTOXAN Tablets: Do not store at temperature above 25°C.

IV. PREPARATION AND HANDLING OF SOLUTIONS

As with all parenteral products, intravenous drug admixtures should be inspected visually for clarity, particulate matter precipitate discoloration and leakage prior to administration, whenever solution and container permit.

Prepared solutions should be used for single dose administration and any unused solution discarded.

CYTOXAN should be prepared for parenteral use by adding 0.9% sterile sodium chloride solution if injected directly.

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. Heating should not be used to facilitate dissolution. Use the quantity of diluent shown below to constitute the product:

Reconstitution Table

Dosage Strength	CYTOXAN Contains Cyclophosphamide Monohydrate	Quantity of Diluent
100 mg	107 mg	5 mL
750 mg	801.75	37.5 mL
1 g	1069.0 mg	50 mL
2 g	2138.0 mg	100 mL

Solutions of CYTOXAN may be injected intravenously, intramuscularly, intraperitoneally, or intrapleurally if constituted by adding 0.9% sodium chloride solution.

Solutions of CYTOXAN may be infused intravenously in the following:

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

CYTOXAN should be prepared for parenteral use by infusion by adding Sterile Water for Injection, USP. *CYTOXAN, constituted in water, is hypotonic and should not be injected directly.*

The osmolarities of solutions of CYTOXAN constituted with water or 0.9% sodium chloride solution are found in the following table:

CYTOXAN and Diluent	mOsm/L
5 mL water per 100 mg cyclophosphamide (anhydrous)	74
5 mL 0.9% sodium chloride solution per 100 mg cyclophosphamide (anhydrous)	374

Isotonic 0.9% sodium chloride solution has an osmolarity of 289 mOsm/L. CYTOXAN solution in water is hypotonic.

Stability of Solutions

Constituted CYTOXAN is chemically and physically stable for 24 hours at room temperature or for six (6) days in the refrigerator; it does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions.

Extemporaneous liquid preparations of CYTOXAN for oral administration may be prepared by dissolving CYTOXAN in Aromatic Elixir, N.F. Such preparations should be stored under refrigeration in glass containers and used within 14 days.

V. SPECIAL INSTRUCTIONS

Handling and disposal

1. Preparation of CYTOXAN should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

2. Personnel preparing CYTOXAN should wear PVC gloves, safety glasses, disposable gowns and masks.

3. All needles, syringes, vials and other materials which have come in contact with CYTOXAN should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the Manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

4. Personnel regularly involved in the preparation and handling of CYTOXAN should have bi-annual blood examinations.

AVAILABILITY OF DOSAGE FORMS

Sterile CYTOXAN for Injection (Cyclophosphamide for Injection U.S.P.) is supplied in vials for single use:

100 mg vials
750 mg vials

1000 mg vials
2000 mg vials.

CYTOXAN (Cyclophosphamide Tablets U.S.P.):

25 mg, bottle of 100
50 mg, bottle of 100 or 1000.

PHARMACOLOGY

Cyclosphosphamide is absorbed from the gastrointestinal tract and from parenteral sites. It appears to be absorbed also when it is supplied topically to neoplastic tissues, situated on the surface of the body.

Cyclophosphamide is metabolized in the body initially by the mixed function oxidase enzymes of the liver microsomes; several toxic metabolites have been identified.

There is much more variability in the rate of metabolism of cyclophosphamide among different human subjects than there is in non-human species. The plasma half-life of the unchanged drug is apparently independent of age, nationality, sensitivity or resistance to the drug, diagnosis, or dosage. In patients who had received no drug therapy known to affect microsomal metabolic rates, the apparent average half-life of unchanged Cyclophosphamide was between 5.0 and 6.5 hours after intravenous administration of ^{14}C-labelled Cyclophosphamide.

Peak plasma concentrations of metabolites have been found to be almost proportional to the administered dose, but relatively wide individual variations have been reported. Peak plasma alkylating metabolite levels generally are reached at 2 to 3 hours after administration of the drug reaching maximum values of only one-half to three-quarters of those obtained in rats given comparable doses.

The average plasma alkylating metabolite concentrations at 8 hours after intravenous administration of the drug was about 77% of the peak level when studied in 12 patients without prior drug exposure.

In fact, Cyclophosphamide does not bind to human plasma proteins in appreciable amounts but on single intravenous doses of a ^{14}C-labelled Cyclophosphamide, it resulted in 14 $\pm$ 2.5% and 12 $\pm$ 5% of total radioactivity being bound to plasma proteins at plasma Cyclophosphamide concentrations of 10 and 200 mμ moles/mL. Repeated doses increased the amount of radioactivity bound to plasma. Following five doses of 40 mg/kg about 56% of the plasma radioactivity was bound.

The tissue distribution of Cyclophosphamide had been examined in cancer patients following intravenous administration. It was found that both unchanged drug and metabolites pass the blood-brain barrier. Cerebral tissue contained radioactivity in a concentration range similar to that found in blood.

Biopsies performed 2 hours after administration of the drug revealed that about 30% more radioactivity was present in lymph nodes than in muscle, adipose tissue, or skin, but the relative proportion of unchanged drug metabolites was not established.

In experimental animals, Cyclophosphamide inhibits immune phenomena, inflammatory processes, delayed hypersensitivity reactions, experimental allergic inflammatory disease and

bodily defenses to infectious micro-organisms. Although immuno-suppressive and anti-inflammatory actions for Cyclophosphamide have not been demonstrated conclusively in man, they may be associated with the therapeutic use of the drug.

In man, a generally higher proportion of the administered dose is excreted in the urine as metabolites. Recovery of radioactivity after intravenously administered labelled Cyclophosphamide ranged from 37% to 82%, with 20% to 45% of that recovered attributable to the unchanged drug. The total urinary excretion of unchanged Cyclophosphamide ranged from 3% to 30% of the dose with most cases in the upper half of the range.

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