**CYTOXAN® Tablets (cyclophosphamide tablets, USP)**

**DESCRIPTION**

CYTOXAN® (cyclophosphamide for injection, USP) is a sterile white powder containing cyclophosphamide monohydrate. CYTOXAN Tablets (cyclophosphamide tablets, USP) are for oral use and contain 25 mg or 50 mg cyclophosphamide (anhydrous). Inactive ingredients in CYTOXAN Tablets are: acacia, FD&C Blue No. 1, D&C Yellow No. 10 Aluminum Lake, lactose, magnesium stearate, starch, stearic acid, and talc. CYTOXAN 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:

\[
\text{NH}_2\text{CH}_2\text{Cl}_2\text{N}_2\text{O}_2\text{P}\cdot\text{H}_2\text{O}
\]

**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% 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 to 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 cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

**INDICATIONS AND USAGE**

Malignant Diseases

CYTOXAN, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to CYTOXAN 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 blast crisis), acute myelogenous and monocytic leukemia, acute lymphocytic (stem-cell) leukemia in children (CYTOXAN given during remission is effective in prolonging its duration).
5. Neuroblastoma (disseminated disease).
6. Adenocarcinoma of the ovary.
7. Renal fibrosarcoma.
8. Carcinoma of the breast.

Nonmalignant Disease

Biox Proven “Minimal Change” Nephrotic Syndrome in Children:

CYTOXAN 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 adrenocorticosteroid therapy or in whom the adrenocorticosteroid therapy produces or threatens to produce intolerable side effects, CYTOXAN may induce a remission. CYTOXAN is not indicated for the treatment of 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 have demonstrated a previous hypersensitivity to it. See WARNINGS and PRECAUTIONS.

**WARNINGS**

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Secondary malignancies may develop in patients treated with cyclophosphamide used alone or in association with other antineoplastic drugs and/or modalities. Most frequently, they have been urinary bladder, myeloproliferative, or lymphoproliferative malignancies. Secondary malignancies most frequently were observed after treatment with CYTOXAN tablets in patients treated for primary myeloproliferative or lymphoproliferative malignancies or nonmalignant disease in which immune processes are believed to be involved pathologically. In some cases, the secondary malignancy developed several years after cyclophosphamide treatment had been discontinued. In a single breast cancer trial utilizing two to four times the standard dose of cyclophosphamide in patients surviving episodes of apparent cardiac toxicity associated with high doses of cyclophosphamide. CYTOXAN 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 hemorrhagic infections.

**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.

**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. Acute myelogenous leukemia
4. Transfusion requirements
5. Previous X-ray therapy
6. Previous therapy with other cytotoxic agents
7. Impaired hepatic function
8. 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 hematocytic malignancies.

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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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.

Pregnancy

**Category D**

See WARNINGS.

**Geriatric Use**

**Pediatric Use**

**Pregnancy**

**Category D**
CYTOXAN (cyclophosphamide) may be prepared for parenteral use by infusion using any of the following methods:

1. CYTOXAN constituted with 0.9% sterile sodium chloride may be infused without further dilution.

2. CYTOXAN constituted with 0.9% sterile sodium chloride may be infused following further dilution in the following:

   a. Dextrose Injection, USP (5% dextrose)
   b. Dextrose and Sodium Chloride Injection, USP (5% dextrose and 0.9% sterile sodium chloride)

For Oral Administration

Extemporaneous liquid preparations of CYTOXAN for oral administration may be prepared by dissolving CYTOXAN in water or 5% dextrose solution. Such preparations should be stored under refrigeration at controlled room temperature and used within 14 days.

REFERENCES


