Cyclophosphamide (Cytoxan®)

Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. Cyclophosphamide also possesses potent immunosuppressive activity.

Resources from Manufacturer

Full Prescribing Information

FDA-Approved Indications and Dosing in Rheumatology

Cyclophosphamide is indicated for malignant diseases, including lymphomas, leukemias, blastomas, and other carcinomas.

Cyclophosphamide can be used off-label for severe disease:

- Systemic lupus erythematosus and lupus nephritis
- Systemic sclerosis
- Rheumatoid arthritis
- Polymyositis, dermatomyositis, and other forms of vasculitis or myopathies

Dosing:

Systemic Lupus Erythematosus (SLE) and lupus nephritis

- **IV**
  - ❏ Low dose regimen (preferred): 500 mg IV every 2 weeks for 6 doses, then transition to alternative immunosuppressive agent.
  - ❏ High dose regimen: 500–1,000 mg/m2 once every month for 6 doses, then transition to alternative immunosuppressive agent. Maximum dose not established, however some recommend max 1,000 mg/dose.
- **Oral:** 1-1.5 mg/kg once daily. May increase by 0.5 mg/kg/day every week to 2 mg/kg once daily if needed based on response. Maximum dose 150 mg/day and treatment duration up to 2-4 months once dose stabilized, then transition to alternate immunosuppressive agent.

Systemic Sclerosis

- **IV (preferred):** 600 mg/m2 once every 4 weeks. Maximum dose not established, however some recommend max 1,200 mg/dose.
- **Oral:** 1 mg/kg/day. May increase by 25 mg once monthly up to 2 mg/kg/day if needed based on response. Maximum dose not established, however some recommend maximum 200 mg/day.

Contraindications

- Hypersensitivity to cyclophosphamide.
- Urinary outflow obstruction.

Warnings and Precautions

- Myelosuppression, Immunosuppression, bone marrow failure, and infections–May lead to serious and sometimes fatal infections, including sepsis and septic shock. Latent infections can also be reactivated. Monitoring of CBC is essential, including dose adjustments if needed and held if neutrophils ≤ 1,500/mm3 and platelets ≤ 50,000/mm3. Antimicrobial prophylaxis may be indicated in certain cases of neutropenia, and G-CSF may be administered to reduce the risk of neutropenia complications. In case of neutropenic fever, antibiotic therapy is indicated. Antimycotics and/or antivirals may also be indicated. The nadirs of the reduction in leukocyte count and thrombocyte count are usually reached in weeks 1 and 2 of treatment, and recovery of platelets and neutrophil nadirs is expected after ~20 days.
- Urinary Tract and Renal Toxicity–Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with cyclophosphamide and may require medical and/or surgical supportive treatment. Urotoxicity can occur with short-term or long-term use, and can be fatal. Urinary tract obstructions and infections should be excluded prior to use, and aggressive hydration and mesna may be used to prevent severe bladder toxicity. Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of urotoxicity and/or nephrotoxicity. Cyclophosphamide Injection should be used with caution, if at all, in patients with active urinary tract infections. Aggressive hydration with forced diuresis and frequent bladder emptying can reduce the frequency and severity of bladder toxicity. Mesna has been used to prevent severe bladder toxicity.
- Cardiotoxicity–Cardiotoxicity–Myocarditis, myopericarditis, pericardial effusion, arrhythmia, and congestive heart failure, which may be fatal, have been reported with cyclophosphamide. Risk may be increased with high doses of cyclophosphamide, patients with advanced age, or previously received cardiotoxic agents. Monitor patients, especially those with risk factors for cardiotoxicity or pre-existing cardiac disease.
- Pulmonary Toxicity–Pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease and other forms of pulmonary toxicity leading to respiratory failure have been reported during and following treatment with cyclophosphamide. Late onset pneumonitis (greater than 6 months after start of cyclophosphamide) appears to be associated with increased mortality. Pneumonitis may develop years after treatment with cyclophosphamide.
- Secondary malignancies–Secondary malignancies (urinary tract cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported in patients treated with cyclophosphamide-containing regimens. The risk of bladder cancer may be reduced by prevention of hemorrhagic cystitis.
- Veno-occlusive liver disease (VOD) including fatal outcome has been reported in patients receiving cyclophosphamide-containing regimens. A cytoreductive regimen in preparation for bone marrow transplantation that consists of cyclophosphamide in combination with whole-body irradiation, busulfan, or other agents has been identified as a major risk factor. VOD has also been reported to develop gradually in patients receiving long-term low-dose immunosuppressive doses of cyclophosphamide. Other risk factors predisposing to the development of VOD include preexisting disturbances of hepatic function, previous radiation therapy of the abdomen, and a low performance status. Fatal outcomes can occur.
- Alcohol Content–The alcohol content in a dose of Cyclophosphamide Injection may affect the central nervous system. This may include impairment of a patient's ability to drive or use machines immediately after infusion. Each administration of Cyclophosphamide Injection at 50 mg per kg delivers 0.17 g/kg of ethanol.

continued

Warnings and Precautions *continued*

- Embryo-Fetal Toxicity–Embryo-fetal toxicity–Exposure to cyclophosphamide during pregnancy may cause birth defects, miscarriage, fetal growth retardation, and fetotoxic effects to the newborn. Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Effective contraception is recommended in females of reproductive potential during treatment and for 1 year after, as well as male patients with female partners of reproductive potential during treatment and for 4 months after.
- Infertility–Male and female reproductive function and fertility may be impaired as cyclophosphamide interferes with oogenesis and spermatogenesis. Cyclophosphamide-induced sterility often depends on dose, duration, and state of gonadal function during treatment and may be irreversible in some patients.
- Lactation: Advise not to breastfeed.
- Renal Patients: Monitor for toxicity in patients with moderate and severe renal impairment.

Adverse Reactions

Common: See full prescribing information for all reported adverse events reported in clinical studies and post-marketing surveillance.

- Neutropenia
- Febrile neutropenia
- Fever
- Nausea and vomiting
- Diarrhea
- Alopecia

Medication Strength and Preparations

- Oral capsule and tablets: 25 mg and 50 mg
- Solution for IV infusion: 500 mg/2.5 mL, 1 g/5 mL, 2 g/10 mL
- Powder for reconstitution [for IV infusion]: 500 mg, 1 g, 2 g

Medication Administration and Storage

- Store oral tablets and capsules at room temperature
- Store powder for reconstitution at room temperature
- Store IV solution at 2°C to 8°C [36°F to 46°F]–do not freeze

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