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

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. No difference has been found between oral and IV therapy, 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.
- Cardiotoxicity–Myocarditis, myopericarditis, pericardial effusion, arrhythmia, and congestive heart failure have been reported with cyclophosphamide. Risk may be increased with high doses of cyclophosphamide, patients with advanced age, or previously received cardiotoxic agents.
- Pulmonary toxicity–Pneumonitis, pulmonary fibrosis, and other forms of pulmonary toxicity leading to respiratory failure have been reported during and following treatment with cyclophosphamide, including months to years after treatment.
- Secondary malignancies– Have been reported in patients receiving cyclophosphamide. The risk of bladder cancer may be reduced by prevention of hemorrhagic cystitis.
- Veno-occlusive liver disease / hepatic sinusoidal obstruction syndrome–Has been reported in patients receiving cytoreductive regimens prior to bone marrow transplantation as well as patients receiving long-term low-dose immunosuppressive doses of cyclophosphamide.
- Alcohol content–Some cyclophosphamide products may deliver up to 0.155g/kg of ethanol
- Embryo-fetal toxicity–Exposure to cyclophosphamide during pregnancy may cause birth defects, miscarriage, fetal growth retardation, and fetotoxic effects to the newborn. 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.

continued

Adverse Reactions

Common (≥ 10%): See full prescribing information for all reported adverse events reported in clinical studies and post-marketing surveillance.

- Neutropenia
- Nausea and vomiting
- Alopecia as well as skin rash and skin/nail pigmentation changes
- Increased risk of infections
- Infertility
- Urinary complications.

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

continued

ACR/ARP Medication Guide

American College of Rheumatology
Empowering Rheumatology Professionals

Association of Rheumatology Professionals
The Interprofessional Division of the American College of Rheumatology

Intravenous Administration Pre-Infusion Checklist

- Ensure labs (CMP, CBC with differential, creatinine and urinalysis, etc.) recently updated and reviewed by provider.
- Check temperature and ask the patient if they:
  - ❑ Has a current or recent infection or illness.
  - ❑ Is taking antibiotics.
  - ❑ Has an upcoming surgery.
- Confirm contraception and negative pregnancy screening, if applicable.

If the answer is yes to any of these questions, notify the ordering provider before initiating the infusion therapy.

Intravenous Medication Preparation

- Cyclophosphamide is supplied as a 200 mg/mL multiple dose vial (500 mg/2.5 mL or 1g/5 mL) to be diluted using aseptic technique for intravenous infusion.
- For direct intravenous injection: withdraw the prescribed dose from the vial and dilute to a minimum concentration of 20 mg/mL using 0.9% NaCl, 0.45% NaCl, 5% dextrose, or a combination of 5% dextrose and 0.9% NaCl. Gently swirl to dissolve drug completely.
  - ❑ Do not use sterile water for injection because it results in a hypotonic solution and should not be injected directly.
- For intravenous infusion: Reconstitute vial using 0.9% NaCl or sterile water for injection for a cyclophosphamide concentration of 20mg/1mL. Gently swirl to dissolve drug completely. Then further dilute the reconstituted cyclophosphamide solution to a minimum concentration of 2mg/1mL using 0.9% NaCl, 0.45% NaCl, 5% dextrose, or a combination of 5% dextrose and 0.9% NaCl.
- After first use, partially used cyclophosphamide vials should be stored in the refrigerator (36 - 46°F) and used within 28 days or discarded. All diluted solutions can be stored at room temperature for up to 24 hours (if sterile water used then do not store and use immediately). If refrigerated, then diluted solutions can be stored up to 6 days if the diluent used was 0.9% NaCl or 0.45% NaCl or stored up to 36 hours if the diluent used was 5% dextrose or a combination of 5% dextrose and 0.9% NaCl.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates and discoloration are noted, the product should not be used.
- Handle and dispose of cyclophosphamide in a manner consistent with other cytotoxic drugs. Always wear gloves when handling to avoid risk of dermal exposure.

Medication Administration and Monitoring

Intravenous

- Antiemetics may be recommended to prevent nausea and vomiting due to moderate or high emetic potential.
- To minimize bladder toxicity, increase normal fluid intake during and for 1-2 days after cyclophosphamide dose. Most adult patients will require fluid intake of at least 2 L/day, and high-dose regimens should be accompanied by vigorous hydration with or without mesna therapy.
- Infuse very slowly to reduce the likelihood of rate-dependent adverse reactions (e.g. facial swelling, headache, nasal congestion, scalp burning).

Medication Administration and Monitoring *continued*

Oral

- Swallow whole; do not crush or chew; do not open capsules.
- Antiemetics may be recommended to prevent nausea and vomiting due to moderate or high emetic potential of oral cyclophosphamide.
- To minimize bladder toxicity, increase normal fluid intake. Morning administration may be preferred to ensure adequate hydration throughout the day.

Managing Infusion Reactions

- If a serious infusion-related or hypersensitivity reaction occurs, immediately interrupt the administration and initiate appropriate therapy. Notify the supervising provider of the reaction.

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