**Drug Monograph**



## A - Drug Name

# cyclophosphamide

**COMMON TRADE NAME(S):** Procytox®

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## B - Mechanism of Action and Pharmacokinetics

Cyclophosphamide is a nitrogen mustard derivative. It is transformed via hepatic and intracellular enzymes to active alkylating metabolites. Cyclophosphamide is an alkylating agent, and prevents cell division primarily by cross-linking DNA and RNA strands. It is considered to be cell cycle phase-nonspecific.

| | | |
|---|---|---|
| Absorption | Well absorbed from the gastrointestinal tract and parenterally. May also absorbed when applied topically. | |
| | Bioavailability | Oral: Yes, bioavailability 75-100%. Oral administration results in increased alkylating activity than IV. |
| Distribution | Distribution to most tissues, crosses placenta, present in breast milk and ascites | |
| | Cross blood brain barrier? | Yes, including metabolites |
| | PPB | 12-14%, metabolites 39-67% |
| Metabolism | Mainly activated by hepatic microsomal enzyme oxidation system (CYP 450). Detoxified by glutathione S transferases and alcohol dehydrogenase. | |

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| | | |
|---|---|---|
| | Active metabolites | Phosphoramide mustard / acrolein / 4-hydroxy cyclophosphamide / aldophosphamide |
| | Inactive metabolites | yes |
| Elimination | Drug and metabolites excreted by kidney, tubular reabsorption occurs. | |
| | Urine | 59-82% after 4 days (<20% unchanged) |
| | Half-life | 7 hours |

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## C - Indications and Status

**Health Canada Approvals:**

- Pediatric Acute lymphoblastic leukemia
- Acute myelogenous leukemia
- Breast cancer
- Burkitt's Lymphoma
- Chronic lymphocytic leukemia
- Chronic myelogenous leukemia
- Hodgkin lymphoma
- Lung cancer (small cell)
- Multiple myeloma
- Mycosis fungoides
- Neuroblastoma (disseminated disease)
- Non-Hodgkin lymphomas
- Retinoblastoma

**Other Uses:**

- Ewing sarcoma
- Endocrine (adrenal, thymoma)
- Gynecological cancers (small cell carcinoma, sarcoma)
- Small cell carcinomas
- Head and Neck cancer
- Wilm's Tumour
- Soft tissue sarcoma

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- Prostate cancer

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## D - Adverse Effects

**Emetogenic Potential:**
Moderate (IV doses ≤ 1500 mg/ m2)
High (IV doses > 1500 mg/ m2)
Moderate – Consider prophylaxis daily (PO doses ≥ 100 mg/ m2)
Low – No routine prophylaxis; PRN recommended (PO doses < 100 mg/ m2)

**Extravasation Potential:** None

| ORGAN SITE | SIDE EFFECT* (%) | ONSET** |
|---|---|---|
| Cardiovascular | Arrhythmia (rare) | E |
| | Arterial thromboembolism (rare) | E |
| | Cardiotoxicity (rare; including myocarditis) | E |
| | Flushing (facial, during IV administration) | I |
| | QT interval prolonged (rare) | E |
| | Venous thromboembolism (rare) | E |
| Dermatological | Alopecia (100%) (some degree; severe 5-30%) | E |
| | Hand-foot syndrome (rare) | E |
| | Nail disorder / discolouration | E |
| | Radiation recall reaction (rare) | I E |
| | Rash (rare, may be severe) | I E |
| | Skin discolouration (rare) | E |
| Gastrointestinal | Abdominal pain | E |
| | Anorexia (rare) | E |
| | Constipation (rare; sometimes severe) | E |
| | Diarrhea (rare) | E |
| | GI hemorrhage (rare) | E |
| | Mucositis (<1%) | E |
| | Nausea, vomiting (50%) (moderate to severe) | I |
| General | Delayed wound healing (rare) | E |
| | Fatigue (<10%) | E |
| | Fluid retention (including effusions) (rare) | E |

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| | | |
|---|---|---|
| Hematological | Hemolytic uremic syndrome (rare) | E D |
| | Immunosuppression (≥10%) and opportunistic infection (may be fatal, including reactivation of latent infections) | E D |
| | Myelosuppression ± infection, bleeding (≥10%) (may be severe) | E |
| Hepatobiliary | ↑ LFTs (<10%) (may be severe) | E D |
| | Pancreatitis (rare) | E |
| | Veno-occlusive disease (rare, mostly high dose, especially with busulfan; also reported with long-term low dose) | E |
| Hypersensitivity | Hypersensitivity (includes anaphylaxis; rare, may be fatal, may be cross-sensitivity with other alkylating agents) | I |
| Injection site | Injection site reaction | I |
| Metabolic / Endocrine | SIADH (rare) | E |
| | Tumor lysis syndrome (rare) | E |
| Musculoskeletal | Musculoskeletal pain | E |
| | Rhabdomyolysis (rare) | E |
| Neoplastic | Secondary malignancy (rare) | L |
| Nervous System | Dizziness (rare) | I |
| | Dysgeusia | E D |
| | Headache (rare) | I |
| | Neurotoxicity (central and peripheral) | E D |
| | RPLS / PRES (rare) | E |
| Ophthalmic | Conjunctivitis (rare) | E D |
| | Visual disorders (rare) | E |
| | Watering eyes (rare) | E |
| Renal | Nephrotoxicity (rare) | E |
| Reproductive and breast disorders | Estrogen deprivation symptoms and androgen withdrawal symptoms | E D |
| Respiratory | Pneumonitis /fibrosis (rare) | E D L |
| Urinary | Bladder fibrosis (rare; and non-hemorrhagic cystitis) | E D |
| | Hemorrhagic Cystitis (<10%) (BMT >40%) | I E D |
| Vascular | Vasculitis (rare) | E |

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

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** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for cyclophosphamide include alopecia, nausea, vomiting, immunosuppression, myelosuppression ± infection, bleeding.

**Myelosuppression** is the major dose limiting toxicity. **Immunosuppression,** opportunistic infections and reactivation of latent infections may occur, including progressive multifocal leucoencephalopathy.

Dose-related chemical **hemorrhagic cystitis** occurs due to direct contact with bladder mucosa of active and toxic metabolites which accumulate in concentrated urine. This occurs in 10% of patients (40% with high dose) and may occur during or several months after treatment. Concurrent or previous radiation therapy to the pelvis or busulfan treatment may increase the risk. Cystitis appears to result in chronic inflammation leading to fibrosis, telangiectasis of the bladder epithelium and bladder cancer. Severe cases may be fatal. **Prophylactic measures** to reduce the incidence of cystitis include diuresis and the administration of mesna, and should be implemented for patients at high risk (e.g. high dose for stem cell transplant).

**Hyperuricemia** during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (e.g., some leukemias and lymphomas), can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalinized, by addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

**Interstitial pneumonitis and pulmonary fibrosis** have been reported and may be acute or chronic. This frequently fails to respond to cyclophosphamide withdrawal and corticosteroid therapy and is often fatal. Lung biopsy is the only sure method of diagnosis. The drug should be stopped at the first hint of pulmonary toxicity; all other possible causes of pneumonitis should be ruled out. It is most frequently reported in patients with Hodgkin and non-Hodgkin lymphomas. There does not appear to be a duration, route, dose, or schedule relationship.

**Nasal stuffiness or facial discomfort** can occur with rapid injection. If troublesome for the patient, slow the infusion rate or give as an intermittent infusion rather than as an IV bolus.

**Cardiac toxicity and acute myocarditis** can occur, especially with high doses used in preparing patients for marrow transplantation (>120 mg/kg) and concomitant doxorubicin or daunorubicin therapy or with radiation to cardiac vessels or heart. Cardiac tamponade has been observed in thalassemic patients given cyclophosphamide prior to bone marrow transplant. Special caution is advised for older patients and those with pre-existing cardiac disease and prior cardiac radiation.

Cyclophosphamide has the potential to enhance radiation injury to tissues. While often called **radiation recall reactions**, the timing of the radiation may be before, concurrent with, or even after the administration of the cyclophosphamide.

**Secondary malignancies** have developed in some treated patients, often several years after administration. Neoplasms most frequently have been urinary bladder cancer, non-lymphocytic leukemia and non-Hodgkin lymphoma. Patients who develop bladder cancer usually have a history

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of hemorrhagic cystitis.

**Veno-occlusive liver disease** (VOD) may develop in patients who have received high doses (preparation for bone marrow transplantation) in combination with whole-body radiation and other cytotoxic agents. Patients with pre-existing liver dysfunction, radiation to the abdomen and low performance status may be at increased risk following high-dose cytoreductive therapy. VOD may also develop gradually with the use of long-term low-dose treatment with cyclophosphamide

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## E - Dosing

Refer to protocol by which patient is being treated.

Dosage may be reduced and/or delayed in:

- patients with bone marrow depression due to cytotoxic/radiation therapy, or
- adrenalectomized patients

Recommendations for hydration should be followed, with ample fluids and frequent voiding.

Before starting treatment:

- Exclude or correct any electrolyte imbalances
- Exclude or correct any obstructions of the urinary tract, cystitis and infections

***Adults:***

Intravenous:

- Q3W: Example - 500 mg/$m^2$ (ie. FEC regimen) to 1200mg/$m^2$ (ie. VAC regimen)

Oral:

- Q28D: Example - 100mg/$m^2$ daily for 14 days (ie. CMF PO)

Bone Marrow Transplant: much higher doses are used prior to marrow transplant than for standard treatment regimens.

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***Dosage with Toxicity:***

| Toxicity | Action* (% of previous dose) |
|---|---|
| ANC < 1.5 x $10^9$/L or platelets < 100 x $10^9$/L | Hold or manage as per protocol |
| Grade 4 ANC or platelets, febrile neutropenia or thrombocytopenic bleeding | 75% |
| Grade 3 non hematologic / organ | 75% |
| Grade 4 non hematologic /organ | Discontinue |
| Pneumonitis | Hold, investigate and if confirmed, discontinue |
| Hematuria | Hold until resolution; discontinue if severe hemorrhagic cystitis |
| * do not retreat until ANC ≥ 1.5 x $10^9$/L, platelets ≥ 100 x $10^9$/L and other toxicity recovered to ≤ grade 2 | |

***Dosage with Hepatic Impairment:***

No adjustment required, but caution should be exercised especially with oral cyclophosphamide.

| Bilirubin | Cyclophosphamide (% previous dose) |
|---|---|
| 1-2 x ULN | 100% |
| >2 x ULN | Caution |

***Dosage with Renal Impairment:***

Renal failure may lead to the reduced excretion of metabolites and increased toxicity. Significant falls in clearance (25-80%) with increased exposure have been documented in patients with renal impairment. Cyclophosphamide is hemodialysable and should be administered after hemodialysis.

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Suggested:

| Creatinine Clearance (mL/min) | Cyclophosphamide (% previous dose) |
|---|---|
| > 50 | 100% |
| 10 - 50 | May consider 75% |
| < 10 | 50%; use with caution and monitor closely |

***Dosage in the elderly:***

No dose modification routinely required, but should be used with caution.

***Children:***

Dose adjustment may be required.

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## F - Administration Guidelines

- Oral hydration is strongly encouraged; for PO cyclophosphamide: 8-10 (8oz) glasses of fluid per day; for IV cyclophosphamide: 2-3 L of fluid/day. Poorly hydrated patients may need more IV hydration. Inadequate total hydration may result in dose-related hemorrhagic cystitis.
- Patients should be encouraged to empty their bladder frequently to minimize dwell times.
- Morning administration of cyclophosphamide is recommended, to decrease the amount of drug dwelling in the bladder overnight.
- Consider usage of mesna with high dose therapy of cyclophosphamide (>1 g/$m^2$).

- Oral tablets should be administered as a single dose in the morning, with or without food.
- Patients should avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.

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- An oral preparation may be prepared by dissolving cyclophosphamide for injection in Aromatic Elixir USP (refer to product monograph).

- For direct IV injection, reconstitute with sodium chloride 0.9% injection only. Do not reconstitute with sterile water for injection, as this will result in a hypotonic solution.
- For IV infusion (recommended), may reconstitute cyclophosphamide with sodium chloride 0.9% or sterile water for injection and further dilute as follows:

| Dose | Dilution volume |
|---|---|
| ≤ 1000 mg | 100 mL sodium chloride 0.9% or dextrose 5% |
| > 1000 mg | 250 mL sodium chloride 0.9% or dextrose 5% |

Higher doses (e.g. bone marrow transplant) may need higher dilution volume (500-1000mL)

- Do not reconstitute or dilute with benzyl alcohol-containing solutions (ie. Bacteriostatic sodium chloride), since it may catalyse the decomposition of cyclophosphamide or cause toxicity in infants
- Avoid the use of aluminum-containing preparation and administration equipment, since darkening of aluminum and gas production have been reported
- Store unopened vial in the original packaging at room temperature, away from heat, light or moisture

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## G - Special Precautions

**Contraindications:**

- patients with severe hepatic or renal impairment
- patients with severe myelosuppression (leukocytes < 2.5 x $10^9$/L and/or platelets < 50 x $10^9$/L) and/or immunosuppression
- patients who have a hypersensitivity to this drug or any of its components
- patients with active infection, particularly *varicella zoster* infection
- patients with urinary outflow obstruction

**Other Warnings/Precautions:**

- Exercise caution in patients:
  - with adrenal insufficiency
  - with risk factors for cardiotoxicity or pre-existing cardiac disease
  - using cyclophosphamide in combination with neuromuscular blockers
  - with tumour infiltration in the bone marrow

- Avoid live or live-attenuated vaccines as use may result in serious or fatal infections in immunocompromised patients. Reduced immunogenicity may occur with use of inactivated vaccines.

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- Use caution when driving or operating machinery since cyclophosphamide may produce symptoms of vasomotor ataxia (e.g. dizziness, blurred vision, etc.).

**Other Drug Properties:**

- Carcinogenicity: Yes

**Pregnancy and Lactation:**

- Teratogenicity: Yes
- Mutagenicity: Yes
- Genotoxicity: Yes
- Fetotoxicity: Yes
  Cyclophosphamide is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months (**for males) and at least **12 months** (for females) after the last dose.
- Excretion into breast milk: Yes
  Breastfeeding is not recommended.
- Fertility effects: Yes
  Testicular atrophy and sterility may occur in males. Sperm-banking before treatment should be considered. Amenorrhea and ovarian failure may occur in females. Gonadal dysfunction may reverse with time, but future reproductive capacity is uncertain.

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## H - Interactions

Metabolized by CYP2B6, 2C8, 2C9, 2C19, 3A4 and 3A5.

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| alcohol | May ↑ cyclophosphamide-induced nausea and vomiting; reduced anti-tumour activity observed in animal studies | Unknown | Avoid |
| allopurinol, thiazide diuretics, ACE inhibitors | ↑ myelosuppressive effect | Unknown; additive leukopenia with ACE inhibitors | Caution; monitor |
| amiodarone | ↑ pulmonary toxicity | Additive | Caution; monitor |
| azathioprine | ↑ hepatotoxicity | Additive | Caution; monitor |
| bupropion | ↑ bupropion concentration and/or toxicity | both are CYP2D6 substrates | Caution; monitor |
| busulfan | ↑ risk of hepatic veno- | Additive; may reduce | Caution; monitor |

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|---|---|---|---|
| | occlusive disease and mucositis | cyclophosphamide clearance | |
| cardiotoxic drugs (i.e. anthracyclines, cytarabine, pentostatin, trastuzumab, prior cardiac radiation) | ↑ cardiotoxicity | Additive | Caution; monitor |
| ciprofloxacin | ↓ cyclophosphamide concentration and/or efficacy | Unknown | Caution; monitor |
| cyclosporine | ↑ risk of graft vs host disease | ↓ serum concentrations of cyclosporine | Caution; monitor |
| depolarizing muscle relaxants (i.e. succinylcholine) | prolonged post-operative apnea may occur | cyclophosphamide inhibits cholinesterase activity | Notify anesthesiologist, measure pseudo-cholinesterase levels; if decreased, consider a decrease in succinylcholine dose. |
| digoxin, verapamil | ↓ serum drug levels | ↓ intestinal absorption of digoxin, verapamil | Caution; monitor for reduced drug effect |
| drugs which induce hepatic microsomal enzymes (especially 2B6, 2C9 and 3A4) e.g. phenytoin, phenobarbital, corticosteroids, St. John's Wort, protease inhibitors | ↑ activation of cyclophosphamide, ↑ cytotoxic metabolites | induction of hepatic microsomal enzyme oxidation system | Caution; monitor |
| drugs which inhibit hepatic microsomal enzymes (e.g. chloramphenicol, grapefruit juice, itraconazole, fluconazole) | ↓ activation of cyclophosphamide | inhibition of hepatic microsomal enzyme oxidation system | Caution, monitor. Avoid grapefruit juice for 48 hours before and on day of dose. |
| etanercept | Higher incidence of non-cutaneous solid | Unknown | Avoid if possible; monitor closely if |

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|---|---|---|---|
| | malignancies | | concomitant use |
| G-CSF, GM-CSF | ↑ pulmonary toxicity | Unknown | Monitor closely |
| indomethacin | pulmonary edema | SIADH | Caution; monitor |
| lovastatin | ↑ rhabdomyolysis and renal failure | Unknown | Caution; avoid concomitant use where possible |
| methotrexate | ↑ cyclophosphamide toxicity | ↓ metabolism of cyclophosphamide | Caution; monitor |
| Nephrotoxic drugs (i.e. aminoglycosides, amphotericin B, methotrexate) | ↑ risk of nephrotoxicity | Additive | Caution; monitor renal function closely |
| paclitaxel | ↑ hematotoxicity reported when cyclophosphamide given after paclitaxel | Additive | Caution; monitor |
| prednisone | Acute respiratory failure (may be fatal) | Unknown | Monitor closely |
| metronidazole | acute encephalopathy reported | Unknown | Caution; monitor |
| ondansetron | ↓ cyclophosphamide effect (high dose) | Unknown | Caution; monitor |
| sulfonylureas | ↑ hypoglycemia | Unknown | Caution |
| tamoxifen | ↑ risk of thromboembolism | Additive | Caution; monitor |
| warfarin | increased and decreased warfarin effect reported | Unknown | Caution; monitor INR closely |

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## I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

**Recommended Clinical Monitoring**

| Monitor Type | Monitor Frequency |
|---|---|
| CBC | Baseline and before each cycle |
| Renal function tests | Baseline and before each cycle |

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|---|---|
| Liver function tests | Baseline and as clinically indicated |
| Electrolytes | Baseline and as clinically indicated |
| Urinalysis | Baseline and as clinically indicated |
| Urinalysis (RBCs) | Routine for high intravenous doses (>1000mg/m2) |
| Clinical toxicity assessment for gastrointestinal, cystitis, infection, bleeding, thromboembolism, cardiac or pulmonary adverse effects | At each visit |

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

**Suggested Clinical Monitoring**

| Monitor Type | Monitor Frequency |
|---|---|
| INR; for patients on warfarin | Baseline and as clinically indicated |
| ECGs | As clinically indicated |
| Pulmonary function tests | As clinically indicated |

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## J - Supplementary Public Funding

**ODB - General Benefit (ODB Formulary )**

- cyclophosphamide - oral tablets ()

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## K - References

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**June 2019** Updated emetic risk category

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## L - Disclaimer

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