DRUG NAME: Cyclophosphamide

SYNONYM: Cyclo, CPA, CPM, CTX, CYC, CYT

COMMON TRADE NAME: CYTOXAN®, [1] PROCYTOX®, NEOSAR® (USA)

CLASSIFICATION: Alkylating agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Cyclophosphamide is an alkylating agent of the nitrogen mustard type. [2] Cyclophosphamide requires activation to its active metabolite, phosphoramide mustard, for its alkylating action. Activation occurs mainly in the liver. Phosphoramide mustard is formed following biological transformation of aldophosphamide through oxidation by hepatic microsomal enzymes. [3] The cytotoxic effect of phosphoramide mustard is mainly due to cross-linking of strands of DNA and RNA and inhibition of DNA synthesis. [4] These actions do not appear to be cell-cycle specific.

PHARMACOKINETICS:

Interpatient variability	metabolism; clearance of cyclophosphamide and its metabolites [5]	
Oral Absorption	>75% [2]; manufacturer recommends drug be taken on an empty stomach, but states may be taken with food to decrease GI upset [6]	
	time to peak plasma concentration	1-2 h [4]
Distribution	throughout body	
	cross blood brain barrier?	to limited extent [2]
	volume of distribution	0.56 L/kg [7]
	plasma protein binding [8]	12-14% of unchanged drug; 67% of total plasma alkylating metabolites [7]
Metabolism	mainly by microsomal enzymes in the liver; [9] cytochrome P450 (CYP) primarily CYP 2B6 [10]	
	active metabolites [5]	4-hydroxycyclophosphamide, aldophosphamide, phosphoramide mustard, acrolein [11]
	inactive metabolites [5]	4-keto-cyclophosphamide, carboxyphosphamide, nornitrogen mustard
Excretion	primarily by enzymatic oxidation to active and inactive metabolites, which are mainly excreted in the urine [8]	
	urine	5-25% unchanged [2]
	feces	31-66% after oral dose
	terminal half life [8]	6.5 h (1.8-12.4 h)
	clearance [8]	1.17 mL/min/kg
Gender	no clinically important differences found	
Elderly	no clinically important differences found	
Children	terminal half life 2.4-6.5 h [8]; volume of distribution 0.67 L/kg [8]	
Ethnicity	no clinically important differences found	

Adapted from standard reference [12] unless specified otherwise.

Developed: September 1994
Limited Revision:1 June 2026

USES:

Primary uses:
*Breast cancer
Conditioning regimen for stem cell transplant
Ewing's sarcoma
*Leukemia, acute myelogenous
*Leukemia, chronic lymphocytic
*Leukemia, chronic myelogenous
*Leukemia, pediatric acute lymphoblastic
*Lung cancer
*Lymphoma, Burkitt's
*Lymphoma, Hodgkin's disease
*Lymphoma, non-Hodgkin's
Lymphoproliferative disease
*Multiple myeloma
*Mycosis fungoides
*Neuroblastoma
*Ovarian cancer
*Retinoblastoma
Rhabdomyosarcoma

Other uses:
Bladder cancer [13]
Brain cancer [13]
Cervical cancer [13]
Endometrial cancer [12]
Gestational trophoblastic neoplasia [13]
Leukemia, acute lymphocytic [13]
Lymphoma, cutaneous T-cell [12]
Osteosarcoma [13]
Soft tissue sarcoma [13]
Testicular cancer [13]
Thymoma [13]
Waldenstrom's macroglobulinemia [13]
Wilm's tumour [12]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- hypersensitivity reaction to cyclophosphamide [2]; cross-sensitivity with other alkylating agents is possible [1]

Caution:
- risk of ***cardiotoxicity*** may be increased in patients with pre-existing cardiac disease or following high dose cyclophosphamide in patients with advanced age, previous chest radiation, and/or treatment with other cardiotoxic agents [3]
- cyclophosphamide may ***suppress positive reactions to skin test antigens*** (such as tuberculin purified protein derivative, trichophyton, candida) [3]
- ***false positive results*** may be reported for Papanicolaou ***(PAP)*** tests [3]

Carcinogenicity: Secondary malignancies have been reported in patients treated with cyclophosphamide, alone and in combination regimens, and may develop several years after cyclophosphamide has been discontinued. Reported malignancies include urinary tract cancers, myelodysplastic alterations progressing to acute leukemias, lymphoma, thyroid cancer, and sarcomas. Urinary tract malignancies have usually occurred in patients who previously had hemorrhagic cystitis. Malignancy has also been reported after *in utero* exposure to cyclophosphamide. [3]

Mutagenicity: Cyclophosphamide is both genotoxic and mutagenic in animals. [3]

Fertility: Cyclophosphamide is genotoxic and mutagenic in somatic cells and male and female germ cells. Cyclophosphamide may cause sterility in both sexes because it interferes with oogenesis and spermatogenesis. Cyclophosphamide-induced sterility may be irreversible and appears to depend on the dose of cyclophosphamide, duration of therapy, and the state of gonadal function at the time of treatment. Amenorrhea develops in a significant proportion of women and is associated with decreased estrogen and increased gonadotropin secretion. Amenorrhea may be transient or permanent, but it is more likely to be permanent in older women. Oligomenorrhea has also been reported. The exact duration of follicular development in humans is not known, but may be longer than 12 months,

Developed: September 1994
Limited Revision:1 June 2026

so this effect should be considered if patient is considering an intended pregnancy after cyclophosphamide treatment has ended. [3] The rate of permanent ovarian failure also differs with combination regimen used. For example, the rate is lower with combination regimens of doxorubicin and cyclophosphamide compared with regimens of cyclophosphamide, methotrexate and fluorouracil. Treatment with cyclophosphamide, methotrexate and fluorouracil for six months causes permanent ovarian failure in 70 percent of women over 40 years of age versus 40 percent of younger women. Also, the median time to onset of ovarian failure is shorter in older women than in younger women (2-4 months vs 6-16 months), and it is less likely to be reversible in older women (reversible in about 10 percent vs up to 50 percent in younger women). [2,14] Females treated with cyclophosphamide during prepubescence who have retained ovarian function after completing treatment are at increased risk of developing premature menopause (i.e., cessation of menses before age 40 years). Male patients may develop oligospermia or azoospermia, associated with increased gonadotropin and normal testosterone secretion. Males treated during prepubescence may develop normal secondary sexual characteristics, but have oligospermia or azoospermia. Azoospermia is reversible in some patients, but reversal may not occur for several years after treatment has ended. Some degree of testicular atrophy can also occur. [3]

Pregnancy: Because cyclophosphamide is genotoxic and mutagenic in somatic cells and male and female germ cells, cyclophosphamide should not be used during pregnancy and male patients should not father children during treatment or for at least 6 months after treatment has ended. Cyclophosphamide crosses the placental barrier. Exposure to cyclophosphamide *in utero* may cause miscarriage, fetal growth retardation, and fetotoxic effects in the newborn, including leukopenia, anemia, pancytopenia, severe bone marrow hypoplasia, and gastroenteritis. Malformations have been reported in babies born to mothers treated with cyclophosphamide in the first trimester. In animal studies, exposure of oocytes to cyclophosphamide during follicular development resulted in decreased implantations and viable pregnancies, and an increased risk of malformations. Based on animal data, the increased risk of failed pregnancy and malformations may persist after cyclophosphamide is discontinued. Male and female patients of reproductive potential should use contraception during treatment. [3]

Breastfeeding is not recommended as this drug is excreted in breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhea have been reported in children breastfed by women treated with cyclophosphamide. [3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. [15]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	anaphylactic reaction [16]
	nasal congestion [16](1-10%); see paragraph after **Side Effects** table
blood/bone marrow/ febrile neutropenia	anemia
	methemoglobinemia with bone marrow transplant (BMT) doses [16]
	myelosuppression; WBC nadir 8-15 days, platelet nadir 10-15 days, recovery 17-28 days
	thrombocytopenia
cardiovascular	***cardiac dysfunction in high-dose*** (<1%) [16]; see paragraph after **Side Effects** table
coagulation	hypoprothrombinemia, risk of bleeding (very rare)
constitutional symptoms	asthenia or sweating (<1%)
	dizziness [16] (<1%)

Developed: September 1994
Limited Revision:1 June 2026

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
dermatology/skin	*extravasation hazard:* none [17]
	alopecia [8,16] (40-60%); begins 3-6 weeks after start of therapy
	facial flushing following IV administration [2,16] (1-10%)
	hyperpigmentation (skin and nails) [2,16] (<1%)
	rash, hives, or itching [2,16] (1-5%)
	redness, swelling, or pain at injection site [2,16]
	toxic epidermal necrolysis [16] (<1%)
endocrine	hyperglycemia [2]
gastrointestinal	*emetogenic potential:* (dose-related) >1g high moderate; <1g low moderate [18]
	anorexia (33%)
	diarrhea [16] (>10%)
	hemorrhagic colitis [16] (<1%)
	mucositis [16] (>10%)
	myxedema or sore lips [2] (<11%)
	nausea and vomiting [16] (dose related: >90% for doses >1500 mg/m^2, 60-90% for doses 750-1500 mg/m^2, 30-60% for doses ≤750 mg/m2 or oral); usually beginning 6-10 hours after administration
	stomatitis [2,16] (>10%)
hepatic	hepatotoxicity [16] (<1%)
	jaundice [16] (<1%)
metabolic/laboratory	hyperkalemia, usually in context of tumour lysis [16] (<1%)
	hyperuricemia with high-dose and/or long-term therapy [16] (<1%)
	syndrome of inappropriate antidiuretic hormone (SIADH) [2,16] (1-5%); see paragraph after **Side Effects** table
pain	headache [2,16] (1-10%)
pulmonary	interstitial pulmonary fibrosis, with high-dose and/or long-term therapy [16] (<1%)
	pneumonitis, with high-dose and/or long-term therapy [16] (<1%)
renal/genitourinary	non-hemorrhagic cystitis [7]
	hemorrhagic cystitis (up to 40%) [16]; see paragraph after **Side Effects** table
	renal tubular necrosis [16] (1-5%)
	hemorrhagic ureteritis (<1%)
secondary malignancy	urinary bladder, myeloproliferative, or lymphoproliferative malignancies [16] (<1%)
sexual/reproductive function	interferes with oogenesis and spermatogenesis [16] (>10%); may be irreversible in some patients
	gonadal suppression (amenorrhea) [2]

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Developed: September 1994
Limited Revision:1 June 2026

Cardiac toxicity may occur in patients receiving high-dose cyclophosphamide (e.g., 60 mg/kg daily or 120-270 mg/kg over a few days). [12] Cardiac toxicity has ranged from minor, transient ECG changes and asymptomatic elevation of cardiac enzymes at total doses of 100 mg/kg to fatal myocarditis and myocardial necrosis at total doses ranging upwards from 144 mg/kg delivered over 4 days. [5] Patients may experience heart failure, arrhythmias, irreversible cardiomyopathy, pericarditis, or death as a result of cardiotoxicity. Clinical signs include dyspnea, tachypnea, fluid retention, increased systemic venous pressure and shock. [19] Risk factors for cardiac toxicity include previous chest or mediastinal radiotherapy, anthracycline administration, concomitant administration of chemotherapy drugs which are not normally considered cardiotoxic, especially carmustine, cytarabine, and 6-thioguanine, [5] and by the presence of left ventricular dysfunction (ejection fraction less than 50%). [20] The mechanism may involve direct injury to the endothelium by phosphoramide mustard, an active metabolite of cyclophosphamide. [20,21] In contrast to anthracycline-induced cardiomyopathy which occurs months to years after cumulative doses of anthracyclines, cyclophosphamide-induced cardiotoxicity occurs much earlier and does not appear to be cumulative. [5,20-22] Treatment is supportive. [5]

Hemorrhagic cystitis has been reported in up to 40% of patients (especially children) on long term or high dose cyclophosphamide therapy. [7,12] Risk factors for developing hemorrhagic cystitis include the rate of the cyclophosphamide infusion and the rate of metabolism of cyclophosphamide, as well as the hydration status of the patient, their urine output and frequency of urination, plus concurrent exposure to other urotoxic drugs or genitourinary radiotherapy. [23] The mechanism may involve direct injury to the urothelium by acrolein, an active metabolite of cyclophosphamide. [11] Hemorrhagic cystitis can develop within a few hours or be delayed several weeks. [2] Clinical diagnosis is made based on non-specific symptoms such as hematuria, dysuria, urgency, and increased frequency of urination and can be confirmed using cystoscopy. [23] Severe hemorrhagic cystitis can lead to constriction of the bladder, anemia, recurrent urinary tract infection, bladder perforation, renal failure and death. [23] Longterm complications include bladder fibrosis and contraction, urinary reflux and transitional cell bladder tumours. Non-hemorrhagic cystitis, edema of the bladder and suburethral bleeding can also occur. [7]

Recommended *prophylactic measures* include encouraging patients to avoid taking the drug at night, to drink plenty of fluids during therapy and to void frequently. Administer cyclophosphamide as early in the day as possible to decrease the amount of drug remaining in the bladder overnight. Patients should also be well hydrated before treatment and for 24-72 hours following treatment (most adults will require at least 2 L of fluid per day). With large IV doses of cyclophosphamide, intravenous hydration is usually recommended. The use of mesna and/or continuous bladder irrigation is rarely needed for doses <2 g/m^2. However, mesna has been used in patients receiving cyclophosphamide for immunologically-mediated disorders (e.g., Wegener's granulomatosis, systemic lupus erythematosus, dermatomyositis, polyarteritis). Further measures to reduce the incidence of cystitis include catheter bladder drainage, bladder irrigation, and intravenous hydration with diuresis. Hyperhydration is generally not recommended as it places the patient at risk for fluid overload and electrolyte imbalance, particularly given the antidiuretic effect of cyclophosphamide. Diuretics may be indicated if urine production declines to <100 mL/m^2/h. Mesna and hyperhydration appear to be equally effective in preventing cyclophosphamide-induced cystitis in the BMT population. [2,12,16,23]

Treatment of hemorrhagic cystitis begins with discontinuation of cyclophosphamide. Increase fluid intake and maintain the platelet count at 50 x 10^9/L or higher to minimize the extent of bleeding. Several treatment options are currently advocated, depending on the severity of bleeding. [12,23]

Treatment of early cystitis:

- *First line:* Administer hyperhydration. Standard hyperhydration may consist of NS or ½NS at a rate of 3.0 L/m^2 per 24-hour period. Depending on the patient's electrolyte status, KCl and MgS04 are generally added to the fluid at concentrations of 20-40 mEq/L and 2-4 g/L respectively. Patients who have visible clots in the urine, or have bladder spasms should receive continuous bladder irrigation. Treatment is generally continued for 48 hours after the urine returns to normal colour and symptoms have resolved. [24]
- *Second line:* Initiate a bladder irrigation with alum (aluminum potassium sulphate) which is prepared by pharmacy as a 1% solution for intravesical administration. This is instilled at a rate of 300-1000 mL/hour and the rate is adjusted to maintain clear pink drainage. Responses to alum are improved following removal of clots in the bladder using either cystoscopy or irrigation prior to therapy. As alum contains significant amounts of aluminum, aluminum levels should be taken in patients with renal impairment or requiring prolonged therapy. [24]

Developed: September 1994
Limited Revision:1 June 2026

- *Third line:* Administer prostaglandin (CARBOPROST®) which is thought to stimulate platelet aggregation and cause local vasoconstriction. The dose is generally 400-500 mcg (0.8-1.0 mg/dL in 50 mL NS) instilled into the bladder. Clamp catheter and allow solution to dwell for 60 minutes. Repeat every six hours until response. Like alum, this therapy works best when the bladder is evacuated of clots before starting. Patients who respond will do so by 5-7 days. CARBOPROST® can cause intense bladder spasm and this can be a major problem. Therapy with oxybutynin, belladonna and opium suppositories, or systemic narcotic analgesics may be necessary to manage bladder spasm.
- In rare cases, hemorrhagic cystitis is resistant to the above treatments and bladder fulguration with formalin or other chemicals is needed. [24]

Treatment of late onset cystitis:
Many cases of late onset cystitis are due to secondary viral infection or bacterial infection of the injured mucosa. Before starting therapy, culture for bacterial pathogens, cytomegalovirus (CMV) and adenovirus. Primary therapy is hyperhydration, possibly with bladder irrigation plus anti-infective treatment if a pathogen is found. [24]

Hyperuricemia may result from cell lysis by cyclophosphamide and may lead to electrolyte disturbances or acute renal failure. [25] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients [26]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 mL/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH >7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine. [27] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate. [28]

Nasal stuffiness or facial discomfort may occur. Patients experience runny eyes, rhinorrhea, sinus congestion, and sneezing immediately after infusion. This nasopharyngeal discomfort or "wasabi nose" may be associated with rapid injection of cyclophosphamide. [16] The reaction may be caused by a mucosal inflammatory response or possibly a cholinergic mechanism. If troublesome for the patient, several interventions have been used such as slowing the rate of infusion, analgesics, decongestants, antihistamines, intranasal beclomethasone, or intranasal ipratropium. [29-32]

Pulmonary toxicity, including ***pneumonitis, pulmonary fibrosis,*** pulmonary veno-occlusive disease, acute respiratory distress syndrome, and respiratory failure have been reported during and following treatment with cyclophosphamide. Pneumonitis may develop years after treatment has ended, although acute pulmonary toxicity has also been reported after a single dose of cyclophosphamide. Late onset pneumonitis, occurring greater than 6 months after the start of cyclophosphamide, appears to be associated with a particularly high mortality. [3] Risk of interstitial pulmonary fibrosis may be higher in patients receiving high doses of cyclophosphamide over prolonged periods or who have been exposed to other drugs with pulmonary toxicities and/or pulmonary radiotherapy. The mechanism for pulmonary toxicity may involve direct injury to the pulmonary epithelium by cyclophosphamide metabolites. In some cases, discontinuation of the drug and initiating corticosteroid therapy fails to reverse the condition, which can be fatal. Signs and symptoms typically include tachycardia, dyspnea, fever, non-productive cough, basilar crepitant rales, interstitial bilateral infiltrates on chest x-ray, hypoxemia, and ventilation/perfusion dysfunction. Discontinue cyclophosphamide at the first sign of pulmonary toxicity and exclude all other possible causes of pneumonitis. [12,33]

Cyclophosphamide has the potential to enhance ***radiation injury*** to tissues. This is a rare side effect. While often called radiation recall reactions, the timing of the radiation may be before, concurrent with, or even after the administration of the cyclophosphamide. Recurrent injury to a previously radiated site may occur weeks to months following the radiation. [2]

Developed: September 1994
Limited Revision:1 June 2026

Secondary malignancies have developed in some patients, often several years after administration. The most frequently reported neoplasms are urinary bladder cancer, non-lymphocytic leukemia and non-Hodgkin's lymphoma. Urinary bladder malignancies generally have occurred in patients who previously had hemorrhagic cystitis. [1,7]

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may occur in patients receiving cyclophosphamide, resulting in hyponatremia, dizziness, confusion or agitation, unusual tiredness or weakness. This syndrome is more common with cyclophosphamide doses 50 mg/kg or higher and may be aggravated by the administration of large volumes of fluids to prevent hemorrhagic cystitis. The condition is self-limiting. Diuretic therapy may be helpful in the situation when the patient has stopped urinating (especially if this occurs during the first 24 hours of cyclophosphamide therapy). Susceptible patients should be monitored for cardiac decompensation. If weight gain is excessive (e.g., 1.5-2 kg) during hydration, the volume of IV fluid should be reduced. [1,9]

Administration of cyclophosphamide in doses higher than 30-40 mg/kg has been associated with ***water retention and dilutional hyponatremia***. Children may be especially susceptible. The mechanism is related to direct injury to the distal renal tubules and collecting ducts by cyclophosphamide metabolites. Symptoms include decreased urine flow, decreased serum osmolarity and sodium, and increased urine osmolarity. Symptoms can occur 4 to 12 hours after cyclophosphamide and generally resolve within 20 to 24 hours after therapy. [9,12]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
allopurinol [34]	38% increase in toxic cyclophosphamide metabolites; 2-fold increase in half-life of cyclophosphamide; up to 3-fold increase in bone marrow suppressant effects due to cyclophosphamide [34]	unknown; may be related to allopurinol's effects on hepatic metabolism or renal excretion of cyclophosphamide metabolites [34]	monitor for cyclophosphamide toxicity [34]
digoxin [34,35]	digoxin AUC reduced by 45.6% when digoxin tablets were administered within 5 days of high dose cyclophosphamide and total body irradiation [35]	reduced absorption of digoxin tablets possibly caused by the temporary slowing of cell division induced by cyclophosphamide and resulting diminished epithelial mass in the gastrointestinal tract [35]	check digoxin levels and monitor for reduced digoxin efficacy
grapefruit juice [36]	decreased or delayed activation of cyclophosphamide, which may impair efficacy	moderate inhibition of CYP 3A4 metabolism in the intestinal wall [16,37] by grapefruit juice	avoid grapefruit juice for 48 hours before starting oral cyclophosphamide and on day of dose
phenobarbital [3,34,38]	may increase rate of conversion to active and inactive cyclophosphamide metabolites	strong induction of CYP 2B6 by phenobarbital [16,38]	monitor for increased cyclophosphamide toxicity[3]
phenytoin [3,10,34]	may increase rate of conversion to active and inactive cyclophosphamide metabolites	strong induction of CYP 2B6 by phenytoin [16,38]	monitor for increased cyclophosphamide toxicity[3]

Developed: September 1994
Limited Revision:1 June 2026

AGENT	EFFECT	MECHANISM	MANAGEMENT
rifampin [3,34,38]	may increase rate of conversion to active and inactive cyclophosphamide metabolites	strong induction of CYP 2B6 by rifampin [16,38]	monitor for increased cyclophosphamide toxicity[3]
succinylcholine [34,39]	increased serum concentration of succinylcholine [34]; prolonged neuromuscular blockade produced by succinylcholine is probable	cyclophosphamide inhibition of plasma cholinesterase resulting in decreased metabolism of succinylcholine	monitor for succinylcholine toxicity [34]; consider succinylcholine dose reduction based on measured plasma cholinesterase levels
warfarin [3,34,39]	increased and decreased warfarin effects have been reported [3]	unknown [34]; may inhibit warfarin metabolism or clotting factor synthesis [39]	monitor coagulation parameters; adjust warfarin dose as needed

Adapted from standard reference unless specified otherwise.

SUPPLY AND STORAGE:

Oral *:* Baxter Corporation supplies cyclophosphamide as 50 mg sugar-coated tablets. Tablets contain lactose. Store at room temperature. Protect from direct light. [36,40]

Injection :
Andone Pharmaceutical Inc. supplies cyclophosphamide as 1000 mg and 2000 mg single-use (preservative free) vials of crystalline powder for reconstitution. Store at room temperature. Protect from direct light. Do not use vials with melted content. [41]

Baxter Corporation supplies cyclophosphamide as 500 mg, 1000 mg, and 2000 mg single-use (preservative free) vials of crystalline powder for reconstitution. Store at room temperature. Protect from direct light. Do not use vials with melted content. [36,40]

Marcan Pharmaceuticals Inc. supplies cyclophosphamide as 500 mg, 1000 mg, and 2000 mg single-use (preservative free) vials of crystalline powder for reconstitution. Store at room temperature. Protect from direct light. Do not use vials with melted content. [42]

SteriMax Inc. supplies cyclophosphamide as 500 mg, 1000 mg, and 2000 mg single-use (preservative free) vials of crystalline powder for reconstitution. Store at room temperature. Protect from direct light. Do not use vials with melted content.[3]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility: consult detailed reference

Additional information: Cyclophosphamide ***oral suspension*** may be prepared using the intravenous formulation. Reconstitute vials with normal saline to a concentration of 20 mg/mL. Withdraw vial contents and dilute 1:1 with suspending vehicle (simple syrup or ORA-PLUS®). Prepared suspensions in either suspending vehicle are stable 2

Developed: September 1994
Limited Revision:1 June 2026

months in the refrigerator. When stored at room temperature, simple syrup preparations are stable 3 days and ORA-PLUS® preparations are stable 8 days. [43]

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	has been used
Direct intravenous	***each 100 mg or fraction thereof over at least 1 minute***
Intermittent infusion	***over 20-60 minutes***
Continuous infusion	***the dose can be administered in a convenient volume***
Intraperitoneal	has been used but not recommended due to need for metabolic activation [12]
Intrapleural	has been used but not recommended due to need for metabolic activation [12]
Intrathecal	no information found; metabolic activation required [12]
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count. Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Oral:	4 weeks [44,45]	***100 mg/m²*** (range 75-100 mg/m²) ***PO once daily for 14 consecutive days*** (total dose per cycle 1400 mg/m²)
	3-4 weeks [45]:	***300 mg/m²*** (range 200-450 mg/m²) ***PO once daily for 5 consecutive days*** (total dose per cycle 1500 mg/m² [range 1000-2250 mg/m²]) Round dose to the nearest 50 mg. The manufacturer recommends that the drug be taken on an empty stomach, but states it may be taken with food to decrease GI upset. [6]
Intravenous:	3 weeks [46-49]	***600 mg/m²*** (range 500-1000 mg/m²) ***IV for one dose on day 1***
	4 weeks [50]:	***1000 mg/m² IV for one dose on day 1***
	6 weeks [51]:	***1200 mg/m² IV for one dose on day 1***

Developed: September 1994
Limited Revision:1 June 2026

BC Cancer usual dose noted in ***bold, italics***

Cycle Length:

4 weeks [44]: ***525 mg/m² IV for one dose on day 1 and day 15***
(total dose per cycle 1050 mg/m²)

4 weeks [52]: ***1200 mg/m² IV for one dose on day 1 and day 8***
(total dose per cycle 2400 mg/m²)

11 weeks [48]: ***1000 mg/m² IV for one dose on day 1 and day 56***
(total dose per cycle 2000 mg/m²)

High dose protocols with or without bone marrow transplant:
note: ideal body weight is often used.

60 mg/kg IV for one dose on day -3 and day -2 [53]
(total dose 120 mg/kg over 2 days)

50 mg/kg IV for one dose on day -6, day -5 and day -4 [54]
(total dose 150 mg/kg over 3 days)

2700 mg/m² IV for one dose on day 1 and day 2 [55]
(total dose 5400 mg/m² over 2 days)

2500 mg/m² IV for one dose on day 1

1800 mg/m² once daily IV for five consecutive days starting on day -5 [56]
(total dose 7200 mg/m² over 4 days)

1800 mg/m² IV for one dose on day -6, day -5, day -4 and day -3 [57,58]
(total dose 7200 mg/m²over 4 days)

2000 mg/m² IV for one dose on day 3, day 4 and day 5 [59]
(total dose 6000 mg/m²over 3 days)

1000 mg/m² IV for one dose on day 1 and day 2 [60]
(total dose 2000 mg/m²over 2 days)

Concurrent radiation: infrequently radiation is given during treatment [51,61] ; more often given following chemotherapy [44,62-68]

Dosage in myelosuppression: modify according to protocol by which patient is being treated

Dosage in renal failure: Suggested dose modifications [69]:

Creatinine clearance (mL/min)	Cyclophosphamide dose
≥10	100%
<10	75%

Calculated creatinine clearance = $\frac{\text{N* x (140 - Age) x weight}}{\text{serum creatinine in micromol/L}}$

* For males N = 1.23; for females N = 1.04

Developed: September 1994
Limited Revision:1 June 2026

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Dosage in hepatic failure:	no information found; however, severe hepatic impairment may result in decreased activation of cyclophosphamide and reduce its efficacy [3]	
Dosage in dialysis:	dialyzable with a high extraction efficiency [8]	
	hemodialysis: ½ dose has been suggested [69] Case reports: there have been 2 case reports giving high-dose cyclophosphamide with continuous bladder irrigation +/- mesna [70,71]; hemodialysis (duration 6 h) was performed 6 h [70] and 14 h [71] after cyclophosphamide infusion Dialysis should not be started sooner then 12 h after cyclophosphamide infusion [72]	
	chronic ambulatory peritoneal dialysis (CAPD): dose as for GFR <10 mL/min/1.73m^2 (i.e., administer 75% of dose) [73]	
	continuous arteriovenous or venovenous hemofiltration (CAVH): dose as for GFR 10-50 mL/min/1.73m^2 (i.e., administer 100% dose) [69]	

Children:

	Cycle Length:	
Oral:	daily	50-300 mg/m^2 PO daily
Intravenous:	3-4 weeks [74]:	250-1800 mg/m^2 IV for one dose for 4 consecutive days, on days 1 to 4
	3-4 weeks [75]:	up to 2000-3000 mg/m^2 IV for one dose on day 1

REFERENCES:

1. Bristol-Myers Squibb Canada. Cyclophosphamide product monograph. Montreal, Canada; April, 2004.
2. CyclophosphamideUSP DI. Volume 1. Drug information for the health care professional. 20th ed. Englewood, Colorado: Micromedex, Inc.; 2002.
3. SteriMax Inc. Cyclophosphamide for injection product monograph. Ontario, Canada; May 14, 2024.
4. Crom WR, Glynn-Barnhart AM, Rodman JH, et al. Pharmacokinetics of Anticancer Drugs in Children. Clinical Pharmacokinetics ; 1987;12:179–182
5. Perry MC. The Chemotherapy Source Book. Baltimore: Williams & Wilkins; 1992. p. 286–289
6. Kinda Karra. Associate, Medical Information and Drug Safety, Bristol-Myers Squibb Canada. Personal Communication. 2005.
7. Repchinsky C, BSP. Compendium of Pharmaceuticals and Specialties. 2004. p. 1610–1613
8. Balis F, Holcenberg JS, Bleyer WA. Clinical Pharmacokinetics of Commonly Used Anticancer Drugs. Clinical Pharmacokinetics ; 1983;8: 202-232
9. Dorr RT, Von-Hoff DD. Drug monographs. Cancer chemotherapy handbook. 2nd ed. Norwalk, Connecticut: Appleton and Lange; 1994. p. 319–332
10. de Jonge ME, Huitema ADR, van Dam SM, et al. Significant induction of cyclophosphamide and thiotepa metabolism by phenytoin. Cancer Chemother Pharmacol ; 2004;55:507–510
11. Miller LJ, Chandler SW, Ippoliti CM. Treatment of cyclophosphamide-induced hemorrhagic cystitis with prostaglandins. Annals of Pharmacotherapy. ; 1994;28(5):590–4

Developed: September 1994
Limited Revision:1 June 2026

12. McEvoy GK. AHFS 2004 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 2004. p. 948–952
13. CyclophosphamideUSP DI. Volume 1. Drug information for the health care professional. 20th ed. Englewood, Colorado: Micromedex, Inc.; 2000. p. 1155–1161
14. Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. NEJM ; 2001;344(26):1997–2008
15. Tamara Shenkier. Medical Oncologist, BC Cancer Agency Vancouver Centre. Personal communication. 2005.
16. Rose BD editor. Cyclophosphamide: Drug Information. www.uptodate.com ed. : UpToDate; 2005.
17. BC Cancer Agency Provincial Systemic Therapy Program. Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 February , 2004.
18. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; May , 1999.
19. Angelucci E, Mariotti E, Lucarelli G, et al. Sudden cardiac tamponade after chemotherapy for marrow transplantation in thalassaemia. Lancet. ; 1992;339(8788):287–9
20. Taniguch I. Clinical Significance of Cyclophosphamide-induced Cardiotoxicity. Internal Medicine ; 2005;44(No. 2):89–90
21. Kamezaki K, Fukuda T, Makino S, et al. Cyclophosphamide-induced Cardiomyopathy in a Patient with Seminoma and a History of Mediastinal Irradiation. Internal Medicine ; 2005;44(No 2):120–123
22. Chanan-Khan A, Srinivasan S, Czuczman M. Prevention and Management of Cardiotoxicity from Antineoplastic Therapy. J Support Oncol ; 2004;2:251–266
23. West NJ. Prevention and treatment of hemorrhagic cystitis. Pharmacotherapy. ; 1997;17(4):696–706
24. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2003. p. 76–77
25. DeVita VT, Hellman S, Rosenberg SA. Cancer Principles & Practice of Oncology. 6th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2001. p. 2640
26. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. 4th ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2003. p. 27
27. Sanofi-Synthelabo. FASTURTEC® product information. Markham, Ontario; 2004.
28. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. E-Edition ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2010. p. 93–94
29. Kosirog-Glowacki JL, Bressler LR. Cyclophosphamide-induced facial discomfort. Ann Pharmacother ; 1994;28(2):197–199
30. Arena PJ. Oropharyngeal sensation associated with rapid intravenous administration of cyclophosphamide (NSC-26271). Cancer Chemotherapy Reports - Part 1. ; 1972;56(6):779–80
31. Silberstein PT, Vercellotti GM. Facial burning from cyclophosphamide. Cancer Treatment Reports. ; 1984;68(7-8):1057
32. Lo K, Aulakh AK, Gingerich KS, et al. Cyclophosphamide-induced nasopharyngeal discomfort (wasabi nose): a report of two cases. 2002;J Oncol Pharm Practice(8):131–134
33. Segura A, Yuste A, Cercos A, et al. Pulmonary fibrosis induced by cyclophosphamide. Annals of Pharmacotherapy. ; 2001;35(7-8):894–7
34. UpToDate Lexi-Drugs® Interaction Checking (database on the Internet). Cyclophosphamide. UpToDate® Inc.; Accessed January 15, 2025. Updated December 23, 2024. Available at: http://online.lexi.com
35. Bjornsson TD, Huang AT, Roth P, et al. Effects of high-dose cancer chemotherapy on the absorption of digoxin in two different formulations. Clin Pharmacol Ther ; 1986;39(1):25–28
36. Baxter Corporation. PROCYTOX® product monograph. Mississauga, Ontario; 7 September, 2012.
37. Rose BD. CYP3A4 Substrates/CYP3A4 Inhibitors (Moderate). UpToDate; Accessed 25 August, 2005. Available at: https://www.uptodate.com
38. Rose BD. CYP2B6 Substrates/CYP2B6 Inducers (Strong). UpToDate; Accessed 25 August, 2005. Available at: https://www.uptodate.com
39. Tatro DS editor. Drug Interactions Facts on Disc. St. Louis: Facts and Comparisons; 2004.
40. Baxter Corporation. Important Product Discontinuation Notice: Discontinuation of PROCYTOX 25 mg Tablets (DIN 02241795) and PROCYTOX 200mg/200 mL Vial (DIN 02241797). August 13, 2025.
41. Andone Pharmaceutical Inc. Cyclophosphamide for injection product monograph. Oakville, Ontario; March 28, 2024.
42. Marcan Pharmaceuticals Inc. Cyclophosphamide for injection product monograph. Ottawa, Ontario; August 18, 2025.
43. Kennedy R, Groepper D, Tagen M, et al. Stability of cyclophosphamide in extemporaneous oral suspensions. Ann Pharmacother ; February 1, 2010;44(2):295–301DOI: https:10.1345/aph.1M578
44. BC Cancer Agency Breast Tumour Group. BCCA protocol summary for adjuvant thearpy for breast cancer using cyclophosphamide, epirubicin and fluorouracil (BRAJCEF). Vancouver: BC Cancer Agency; 2002.
45. BC Cancer Agency Lymphoma Tumour Group. BCCA Protocol Summary for lymphoma palliative chemotherapy (LYPALL). Vancouver, British Columbia: BC Cancer Agency; 1 Nov , 2002.
46. BC Cancer Agency Breast Tumour Group. BCCA Protocol summary for adjuvant therapy for breast cancer using cyclophosphamide, doxorubicin and fluorouracil (BRAJCAF). Vancouver: BC Cancer Agency; 2001.
47. BC Cancer Agency Breast Tumour Group. BCCA Protocol summary for adjuvant therapy for breast cancer using doxorubicin and cyclophosphamide (BRAJAC). Vancouver: BC Cancer Agency; 2001.
48. BC Cancer Agency Lung Tumour Group. BCCA Protocol summary for treatment of extensive small cell lung cancer (SCLC) with cyclophosphamide, doxorubicin and vincristine (CAV) (LUCAV). Vancouver: BC Cancer Agency; 2002.
49. BC Cancer Agency Breast Tumour Group. BCCA Protocol summary for adjuvant therapy for premenopausal high risk breast cancer using cyclophosphamide, methotrexate and fluorouracil (BRAJCMF). Vancouver: BC Cancer Agency; 1999.

Developed: September 1994
Limited Revision:1 June 2026

50. BC Cancer Agency Lymphoma Tumour Group. BCCA protocol summary for advanced indolent lymphoma using cyclophosphamide, vincristine, prednisone (LYCVP). Vancouver: BC Cancer Agency; 2002.
51. BC Cancer Agency Sarcoma Tumour Group. BCCA protocol summary for adjuvant therapy for patients with newly diagnosed Ewing's sarcoma/peripheral neuroectodermal tumour (PNET) or rhabdomyosarcoma using vincristine, doxorubicin and cyclophosphamide (SAVAC). Vancouver: BC Cancer Agency; 2002.
52. BC Cancer Agency Lymphoma Tumour Group. BCCA protocol summary for the treatment of Hodgkin's lymphoma using cyclophosphamide, vincristine and prednisone (LYCCOP). Vancouver: BC Cancer Agency; 2002.
53. Leukemia/Bone Marrow Transplant Program of British Columbia. Intensive therapy and autography for Leukemia or Non-Hodgkin's lymphoma (BMT IV BUCY). BC Cancer Agency, ; 2003
54. Leukemia/Bone Marrow Transplant Program of British Columbia. Intensive multimodal therapy and autologous BMT for non-Hodgkin's lymphoma (BMT LY 98-01). BC Cancer Agency, ; 2003
55. BC Cancer Agency Lymphoma Tumour Group. BCCA protocol summary for the consolidation for lymphoma using etoposide, cyclophosphamide and vincristine (LYECV). Vancouver: BC Cancer Agency; 2002.
56. Leukemia/Bone Marrow Transplant Program of British Columbia. High-dose chemotherapy with autologous HSCT for high-risk nonseminomatous germ cell tumours (BMT 00-04). BC Cancer Agency, ; 2003
57. Leukemia/Bone Marrow Transplant Program of British Columbia. Intensive multimodal therapy and hematopoietic progenitor cell transplantation for progressive Hodgkin's disease (BMT 88-01). BC Cancer Agency, ; 2000
58. Leukemia/Bone Marrow Transplant Program of British Columbia. Intensive multimodal therapy and autography for progressive Hodgkin's disease (HD-CBV 00-01). BC Cancer Agency, ; 2004
59. Leukemia/Bone Marrow Transplant Program of British Columbia. High dose etoposide and cyclophosphamide salvage therapy for refractory acute leukemia (AL 91-02). BC Cancer Agency, ; 2004
60. Leukemia/Bone Marrow Transplant Program of British Columbia. Treatment of Lymphoblastic lymphoma (NHL 98-01). BC Cancer Agency, ; 2004
61. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for treatment of limited stage small cell lung cancer (SCLC) alternating cyclophosphamide, doxorubicin and vincristine (CAV) with etoposide and cisplatin (EP) plus early thoracic irradiation (LUALTL). Vancouver: BC Cancer Agency; 2002.
62. BC Cancer Agency Breast Tumour Group. BCCA Protocol summary for Palliative Therapy for metastatic Breast Cancer using Doxorubicin and Cyclophosphamide (BRAVAC). Vancouver: BC Cancer Agency; 1999.
63. BC Cancer Agency Breast Tumour Group. BCCA Protocol summary for Inflammatory Breast Cancer using cyclophosphamide, doxorubicin and fluorouracil. (BRINFCAF). Vancouver: BC Cancer Agency; 2004.
64. BC Cancer Agency Breast Tumour Group. BCCA Protocol summary for Inflammatory Breast Cancer using cyclophosphamide, epirubicin and fluorouracil. (BRINFCEF). Vancouver: BC Cancer Agency; 2005.
65. BC Cancer Agency Breast Tumour Group. BCCA Protocol summary for Locally Advanced Breast Cancer using cyclophosphamide, doxorubicin and fluorouracil. (BRLA2). Vancouver: BC Cancer Agency; 2004.
66. BC Cancer Agency Lymphoma Tumour Group. BCCA protocol summary for the treatment of Lymphoma with doxorubicin, cyclophosphamide, vincristine and prednisone.(LYCHOP). Vancouver: BC Cancer Agency; 2005.
67. BC Cancer Agency Lymphoma Tumour Group. BCCA protocol summary for the treatment of Lymphoma with doxorubicin, cyclophosphamide, vincristine, prednisone and rituximab.(LYCHOP-R). Vancouver: BC Cancer Agency; 2005.
68. BC Cancer Agency Sarcoma Tumour Group. (SAVAC+M) BCCA Protocol Summary for Vincristine, Adriamycin and Cyclophosphamide combination for patients with newly diagnosed Ewing's sarcoma/peripheral neuroectodermal tumour (PNET) and rhabdomyosarcoma with pelvic primaries or chemotherapy induced hematuria. SAVAC (r SAVAC+M is alternated with SAIME). Vancouver, British Columbia: BC Cancer Agency; 1 April , 2003.
69. Aronoff GR, Berns JS, Brier ME, Golper TA, et al. Drug Prescribing in Renal Failure. 4th ed. 1999. p. 72–73
70. Bischoff ME, Blau W, Wagner T, et al. Total body irradiation and cyclophosphamide in a conditioning regimen for unrelated bone marrow transplantation in a patient with chronic myelogenous leukemia and renal failure on hemodialysis. Bone Marrow Transplantation ; 1998;22:591–593
71. Perry JJ, Fleming RA, Rocco MV, et al. Administration and pharmacokinetics of high-dose cyclophosphamide with hemodialysis in acute leukemia and end-stage renal disease. Bone Marrow Transplantation ; 1999;23:839–842
72. Haubitz M, Bohnenstengel F, Brunkhorst R, et al. Cyclophosphamide pharmacokinetics and dose requirements in patients with renal insufficiency. Kidney International ; 2002;61:1495–1501
73. Aronoff GR, Bennett WM, Berns JS, Brier ME, et al. Drug Prescribing in Renal Failure: Dosing guidelines for adults and children. 5th ed. Philadelphia, Pennsylvania: American College of Physicians; 2007. p. 98
74. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology. Fourth ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 246
75. Pochedly C, editor. Neoplastic Diseases of Childhood. 1st ed. Chur, Switzerland: Harwood Academic Publishers; 1994. p. 218–220

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Limited Revision:1 June 2026