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] An activated form of cyclophosphamide, phosphoramide mustard, alkylates, or binds, to DNA. Its cytotoxic effect is mainly due to cross-linking of strands of DNA and RNA, and to inhibition of protein synthesis.[3] These actions do not appear to be cell-cycle specific.

PHARMACOKINETICS:

Interpatient variability	metabolism; clearance of cyclophosphamide and its metabolites[4]	
Oral Absorption	>75%[2]; manufacturer recommends drug be taken on an empty stomach, but states may be taken with food to decrease GI upset[5]	
	time to peak plasma concentration	1-2 h[3]
Distribution	throughout body	
	cross blood brain barrier?	to limited extent[2]
	volume of distribution	0.56 L/kg[6]
	plasma protein binding[7]	12-14% of unchanged drug; 67% of total plasma alkylating metabolites[6]
Metabolism	mainly by microsomal enzymes in the liver;[8] cytochrome P450 (CYP) primarily CYP 2B6[9]	
	active metabolites[4]	4-hydroxycyclophosphamide, aldophosphamide, phosphoramide mustard, acrolein[10]
	inactive metabolites[4]	4-keto-cyclophosphamide, carboxyphosphamide, nornitrogen mustard
Excretion	primarily by enzymatic oxidation to active and inactive metabolites, which are mainly excreted in the urine[7]	
	urine	5-25% unchanged[2]
	feces	31-66% after oral dose
	terminal half life[7]	6.5 h (1.8-12.4 h)
	clearance[7]	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[7]; volume of distribution 0.67 L/kg[7]	
Ethnicity	no clinically important differences found	

Adapted from standard reference[11] unless specified otherwise.

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

*Health Canada approved indication

Other uses:
Bladder cancer[12]
Brain cancer[12]
Cervical cancer[12]
Endometrial cancer[11]
Gestational trophoblastic neoplasia[12]
Leukemia, acute lymphocytic[12]
Lymphoma, cutaneous T-cell[11]
Osteosarcoma[12]
Soft tissue sarcoma[12]
Testicular cancer[12]
Thymoma[12]
Waldenstrom's macroglobulinemia[12]
Wilm's tumour[11]

SPECIAL PRECAUTIONS:

Contraindicated in patients who have a history of hypersensitivity reaction to cyclophosphamide.[2] There is possible cross-sensitivity with other alkylating agents.[1]

Carcinogenicity: Secondary malignancies have developed in patients treated with cyclophosphamide alone or in combination with other antineoplastics. Occurring most frequently are bladder, myeloproliferative and lymphoproliferative malignancies. Secondary malignancies are most common in patients treated initially for myeloproliferative or lymphoproliferative diseases or for non-malignant conditions with immune pathology. Urinary bladder malignancies are most common in patients who experienced hemorrhagic cystitis.

Mutagenicity: Because of the mutagenic potential of cyclophosphamide, adequate methods of contraception should be used by patients (both male and female) during and at least four months after treatment.[1]

Fertility: Gonadal suppression may occur and sterility can be irreversible in some patients.[2] Age and duration of chemotherapy are the main factors contributing to ovarian failure.[13] For example, treatment with cyclophosphamide, methotrexate and fluorouracil for six months results in permanent ovarian failure in 70 percent of women over 40 years of age and in 40 percent of younger women. 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 ovarian failure is less likely to be reversible in older women (in about 10 percent vs. up to 50 percent). The rate of permanent ovarian failure is lower with regimens of doxorubicin and cyclophosphamide than with cyclophosphamide, methotrexate and fluorouracil.

Heart disease: Caution should be used when treating patients with cyclophosphamide who have pre-existing heart disease.[6]

Pregnancy: FDA Pregnancy Category D.[2] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding should be terminated prior to initiating cyclophosphamide therapy as this drug is excreted in breast milk.[1]

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.[14]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	anaphylactic reaction[15]
	nasal congestion when IV doses are administered too rapidly (large doses via 30-60 minute infusion);[15] patients experience runny eyes, rhinorrhea, sinus congestion, and sneezing immediately after infusion[15] (1-10%)
blood/bone marrow/ febrile neutropenia	anemia
	methemoglobinemia with bone marrow transplant (BMT) doses[15]
	myelosuppression; WBC nadir 8-15 days, platelet nadir 10-15 days, recovery 17-28 days
	thrombocytopenia
cardiovascular	***cardiac dysfunction in high-dose*** (<1%);[15] high-dose can be defined as 60 mg/kg daily or 120-270 mg/kg over a few days;[11] manifests as CHF; cardiac necrosis or hemorrhagic myocarditis; pericardial tamponade (BMT doses)[15]
coagulation	hypoprothrombinemia, risk of bleeding (very rare)
constitutional symptoms	asthenia or sweating (0.1-1%)
	dizziness[15] (<1%)
dermatology/skin	*extravasation hazard: none*[16]
	alopecia[7,15] (40-60%); begins 3-6 weeks after start of therapy
	facial flushing following IV administration[2,15] (1-10%)
	hyperpigmentation (skin and nails)[2,15] (<1%)
	rash, hives, or itching[2,15] (1-5%)
	redness, swelling, or pain at injection site[2,15]
	toxic epidermal necrolysis[15] (<1%)
endocrine	hyperglycemia[2]
gastrointestinal	***emetogenic potential: >1g high moderate; <1g low moderate***[17]
	anorexia (33%)
	diarrhea[15] (>10%)
	hemorrhagic colitis[15] (<1%)
	mucositis[15] (>10%)
	myxedema or sore lips[2] (0.1-11%)
	nausea and vomiting are dose-related[15]: > 90% for >1500 mg/m^2, 60-90% for 750-1500 mg/m2, 30-60% for ≤ 750 mg/m2 or oral; usually beginning 6-10 hours after administration
	stomatitis[2,15] (>10%)
hepatic	hepatotoxicity[15] (<1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	jaundice[15] (<1%)
metabolic/laboratory	hyperkalemia, usually in context of tumour lysis[15] (<1%)
	hyperuricemia with high-dose and/or long-term therapy[15] (<1%)
	syndrome of inappropriate antidiuretic hormone (SIADH) causing hyponatremia
pain	headache[2,15] (1-10%)
pulmonary	interstitial pulmonary fibrosis, with high-dose and/or long-term therapy[15] (<1%)
	pneumonitis, with high-dose and/or long-term therapy[15] (<1%)
renal/genitourinary	non-hemorrhagic cystitis[6]
	hemorrhagic cystitis (up to 40%)[15]; with high-dose and/or long term therapy[2]; severe, potentially fatal
	renal tubular necrosis[15] (1-5%)
	hemorrhagic ureteritis (<1%)
secondary malignancy	urinary bladder, myeloproliferative, or lymphoproliferative malignancies[15] (<1%)
sexual/reproductive function	interferes with oogenesis and spermatogenesis[15] (>10%); may be irreversible in some patients; gonadal suppression (amenorrhea)[2]
syndromes	syndrome of inappropriate antidiuretic hormone (SIADH) secretion with high-dose and/or long-term therapy[2,15] (1-5%)

Adapted from standard reference[1,11] unless specified otherwise.

Cardiac toxicity may occur in patients receiving high-dose cyclophosphamide. High-dose can be defined as 60 mg/kg daily or 120-270 mg/kg over a few days.[11] Other risk factors for developing 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,[4] and by the presence of left ventricular dysfunction (ejection fraction less than 50%).[18] The mechanism may involve direct injury to the endothelium by phosphoramide mustard, an active metabolite of cyclophosphamide.[18,19] Unlike anthracyclines, cyclophosphamide-induced cardiotoxicity does not appear to be cumulative.[4,18,20] In contrast to anthracycline-induced cardiomyopathy which occurs months to years after cumulative doses of anthracyclines, cyclophosphamide-induced cardiotoxicity occurs much earlier.[19] Toxicity has ranged from minor, transient ECG changes and asymptomatic elevation of cardiac enzymes at a total dose of 100 mg/kg to fatal myocarditis and myocardial necrosis at total doses ranging upwards from 144 mg/kg delivered over 4 days.[4] Clinical signs include dyspnea, tachypnea, fluid retention, increased systemic venous pressure and shock.[21] Patients may experience heart failure, arrhythmias, irreversible cardiomyopathy, pericarditis, or death as a result of cardiotoxicity.[21] Treatment is supportive.[4]

Hemorrhagic cystitis may occur in up to 40% of patients (especially children) on long term or high dose cyclophosphamide therapy.[6,11] Other risk factors for developing hemorrhagic cystitis include rate of infusion, and rate of metabolism of cyclophosphamide, as well as the hydration status, urine output, frequency of urination, and concurrent exposure to other urotoxic drugs or genitourinary radiotherapy.[22] The mechanism may involve direct injury to the urothelium by acrolein, an active metabolite of cyclophosphamide.[10] Hemorrhagic cystitis can develop within a few hours or be delayed several weeks.[2] Clinical diagnosis includes non-specific symptoms such as hematuria, dysuria, urgency and increased frequency of urination and can be confirmed using cystoscopy.[22] Severe hemorrhagic cystitis can lead to constriction of the bladder, anemia, recurrent urinary tract infection, bladder perforation, renal failure and death.[22] 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.[6]

Prophylactic measures include encouraging patients to drink plenty of fluids during therapy (most adults will require at least 2 L/day), to void frequently, and to avoid taking the drug at night.[15] Patients should be well hydrated before and for 24-72 hours following treatment.[22] As well, cyclophosphamide should be administered as early in the day as possible to decrease the amount of drug remaining in the bladder overnight.[2] With large IV doses, IV hydration is usually recommended.[15] The use of mesna and/or continuous bladder irrigation is rarely needed for doses <2g/m^2.[15] However, mesna has been used in patients receiving cyclophosphamide for immunologically mediated disorders (e.g., Wegener's granulomatosis, systemic lupus erythromatosus, dermatomyositis, polyarteritis).[11] Further measures to reduce the incidence of cystitis include catheter bladder drainage, bladder irrigation, intravenous hydration with diuresis, hyperhydration, and the administration of mesna. 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.[22] Diuretics may be indicated if urine production declines to <100 mL/m^2/h. It appears that mesna and hyperhydration are equally effective in preventing cyclophosphamide-induced cystitis in the BMT population.

Treatment of hemorrhagic cystitis[11,22] begins with discontinuation of cyclophosphamide. Fluid intake should be increased and the platelet count should be maintained at >50 000/mm^3 to minimize the extent of bleeding. There are several treatment options currently advocated, depending on the severity of bleeding.

Treatment of early cystitis[23]:

- *The first line therapy* is to administer hyperhydration. Standard hyperhydration may consist of NS or 1/2 NS 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 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 the symptoms have resolved.
- *The second line therapy* is to 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 in patients requiring prolonged therapy.
- *The third line therapy* is with prostaglandin (carboprost) which is thought to stimulate platelet aggregation and cause local vasoconstriction. The dose is generally 0.8-1.0 mg/dL in 50 mL NS (400-500 mcg) instilled into the bladder; clamp catheter and allow solution to dwell for 60 minutes; repeat every six hours until response.[23] 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 oxybutinin, Belladonna and opium suppositories, or systemic narcotic analgesics may be necessary. In rare cases, hemorrhagic cystitis is resistant to the above treatments and bladder fulguration with formalin or other chemicals is needed.

Treatment of late onset cystitis[23]:
Many of these cases are due to secondary viral infection or bacterial infection of the injured mucosa. Culture for bacterial pathogens, cytomegalovirus (CMV) and adenovirus should be done before starting therapy. Primary therapy is hyperhydration, possibly with bladder irrigation. Patients may be need to be treated if pathogen is found (i.e., ganciclovir or foscarnet for CMV, ribavirin for adenovirus, antibiotics for bacterial infections).

Immunogenicity: Positive reactions to skin test antigens (e.g., tuberculin purified protein derivative, trichophyton, candida) are frequently suppressed in patients receiving cyclophosphamide.[11]

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[24] 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[25]:

- 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.[26] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminium hydroxide (AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminium hydroxide has been added, discontinue sodium bicarbonate.[27]

Interstitial pulmonary fibrosis[11,28] may occur in patients receiving high doses of cyclophosphamide over prolonged periods. Other risk factors include exposure to other drugs with pulmonary toxicities and pulmonary radiotherapy. The mechanism may involve direct injury to the pulmonary epithelium by cyclophosphamide metabolites.[28] In some cases discontinuation of the drug and initiating corticosteroid therapy fails to reverse this 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. Interstitial pneumonitis has also been reported in patients receiving cyclophosphamide. The drug should be stopped at the first sign of pulmonary toxicity; all other possible causes of pneumonitis should be ruled out.

Nasal stuffiness or facial discomfort may occur. This nasopharyngeal discomfort "wasabi nose" may be associated with rapid injection of cyclophosphamide.[29-31] This reaction may be caused by a mucosal inflammatory response or possibly a cholinergic mechanism.[32] If troublesome for the patient, several interventions have been used[32]: the slowing down of the infusion rate or giving as an intermittent infusion rather than as an IV bolus, the use of analgesics, decongestants, antihistamines, intranasal beclomethasone, or intranasal ipratropium.

Radiation recall reactions[2]***:*** 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.

SIADH (syndrome of inappropriate secretion of ADH)[1] may occur in patients receiving cyclophosphamide, resulting in hyponatremia, dizziness, confusion or agitation, unusual tiredness or weakness. This syndrome is more common with doses >50 mg/kg and may be aggravated by administration of large volumes of fluids to prevent hemorrhagic cystitis.[8] The condition is self-limiting although 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 (1.5-2 kg) during hydration, the volume of IV fluid should be reduced.

Secondary malignancies[1] 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.[6]

Water retention and dilutional hyponatremia: Administration of cyclophosphamide in doses higher than 30-40 mg/kg has been associated with water retention and dilutional hyponatremia.[8,11] 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. These can occur 4 to 12 hours after cyclophosphamide and resolve within 20 to 24 hours after therapy.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
allopurinol	delayed, moderate; increased myelosuppressive effects of cyclophosphamide is possible	unknown	frequent monitoring with a complete blood count may be required

AGENT	EFFECT	MECHANISM	MANAGEMENT
amiodarone[33]	increased risk of pulmonary fibrosis	unknown, possibly additive effect	avoid combination if possible; otherwise increase monitoring
chloramphenicol	delayed, moderate; decrease or delay in activation of cyclophosphamide	inhibition (weak) of the CYP2C8/9 and CYP3A4 enzymes by chloramphenicol[33,34]	standard monitoring procedures for both drugs
ciprofloxacin[35]	delayed, moderate; decreased antimicrobial effect of quinolone antibiotics is possible	decreased quinolone absorption by altering the intestinal mucosa	ciprofloxacin can be used as a prophylactic antibiotic in cyclophosphamide based regimens.[36] consider monitoring ciprofloxacin therapy.
corticosteroids	decreased or increased effect of cyclophosphamide	induction (weak) of the CYP3A4 enzyme by corticosteroids[15,37-39]	clinical significance of this interaction is unlikely based on evidence available; observe for altered effect of cyclophosphamide.
digoxin	delayed, moderate; reduced serum levels of digoxin is suspected	drug-induced alterations of the intestinal mucosa may be involved	monitoring for reduced digoxin effect
grapefruit juice[40]	delayed, moderate; decreased or delayed activation of cyclophosphamide	inhibition (moderate) of the CYP3A4 enzyme[15,41] by grapefruit juice	avoid grapefruit juice for 48 hours before and on day of dose
hydrochlorothiazide[42,43]	myelosuppressive effects of cyclophosphamide may be increased	unknown	monitor for myelosuppression; consider alternative antihypertensive therapy
indapamide	delayed, moderate; prolonged leucopenia is possible	unknown	avoid concurrent use; consider alternative antihypertensive therapy
indomethacin[6]	4 cases of severe pulmonary edema and acute life-threatening water intoxication	unknown	avoid concurrent use
phenytoin[9], phenobarbital, rifampin and other drugs which induce CYP2B6[44]	increased rate at which cyclophosphamide is converted to active and toxic metabolites and possibly to inactive metabolites	induction (strong) of the CYP2B6 enyzme[15,44] by phenytoin, phenobarbital and rifampin.	clinical significance of this interaction is unknown; observe for altered effect of cyclophosphamide
succinylcholine	rapid, moderate; prolonged neuromuscular blockade produced by succinylcholine is probable	cyclophosphamide inhibits plasma cholinesterase resulting in decreased metabolism of succinylcholine	consider reducing succinylcholine based on measured plasma cholinesterase levels
warfarin	delayed, moderate; increased anticoagulant effect of warfarin suspected	inhibition of warfarin metabolism, or clotting factor synthesis	monitoring coagulation parameters during and after chemotherapy; adjust warfarin dose as needed

Adapted from standard reference[35] unless specified otherwise.

SUPPLY AND STORAGE:

Oral[6]*:* Store at room temperature.
CYTOXAN® available as 25 mg and 50 mg white tablets with blue flecks.
PROCYTOX® available as 25 mg and 50 mg white to off-white, sugar-coated tablet.

Injection[6]***:*** Store at room temperature.
CYTOXAN® available as a non-lyophilized formulation manufactured by Bristol-Myers Squibb;[1] available in single-use vials of 1000 mg and 2000 mg. Contains no preservative. Protect from light.
PROCYTOX® available as a non-lyophilized formulation[45] manufactured by Baxter; available in 200 mg, 500 mg, 1000 mg and 2000 mg vials. Contains no preservative. Protect from light.

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

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, 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 months in the refrigerator. When stored at room temperature, simple syrup preparations are stable 3 days and ORA-PLUS® preparations are stable 8 days.[46]

PARENTERAL ADMINISTRATION:

BCCA 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	***in 50-100 mL of compatible IV solution 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[11]
Intrapleural	has been used but not recommended due to need for metabolic activation[11]
Intrathecal	no information found; metabolic activation required[11]
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:

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Oral:	4 weeks[36,47]	***100 mg/m^2 (range 75-100 mg/m^2) once daily for 14 consecutive days (total dose per cycle 1400 mg/m^2)***
	3-4 weeks[47]:	***300 mg/m^2 (range 200-450 mg/m^2) once daily for 5 consecutive days. (total dose per cycle 1500 mg/m^2 [range 1000-2250 mg/m^2])***

Round dose to the nearest 25 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.[5]

Intravenous:	3 weeks[48-51]	***600 mg/m^2 (range 500-1000 mg/m^2) for one dose on day 1***
	4 weeks[52]:	***1000 mg/m^2 for one dose on day 1***
	6 weeks[53]:	***1200 mg/m^2 for one dose on day 1***
	4 weeks[36]:	***525 mg/m^2 for one dose on day 1 and day 15 (total dose per cycle 1050 mg/m^2)***
	4 weeks[54]:	***1200 mg/m^2 for one dose on day 1 and day 8 (total dose per cycle 2400 mg/m^2)***
	11 weeks[50]:	***1000 mg/m^2 for one dose on day 1 and day 56 (total dose per cycle 2000 mg/m^2)***
High dose protocols with or without bone marrow transplant: note: ideal body weight is often used.		**60 mg/kg for one dose on day -3 and day -2[55] (total dose 120 mg/kg over 2 days)**
		50 mg/kg for one dose on day -6, day -5 and day -4[56] (total dose 150 mg/kg over 3 days)
		2700 mg/m^2 for one dose on day 1 and day 2[57] **(total dose 5400 mg/m^2 over 2 days)**
		2500 mg/m^2 for one dose on day 1
		1800 mg/m^2 once daily for five consecutive days starting on day -5[58] (total dose 7200 mg/m^2 over 4 days)
		1800 mg/m^2 for one dose on day -6, day -5, day -4 and day -3[59,60] (total dose 7200 mg/m^{2}over 4 days)
		2000 mg/m^2 for one dose on day 3, day 4 and day 5[61] (total dose 6000 mg/m^{2}over 3 days)
		1000 mg/m^{2}for one dose on day 1 and day 2[62] (total dose 2000 mg/m^{2}over 2 days)

Concurrent radiation: infrequently radiation is given during treatment[53,63] ; more often given following chemotherapy[36,64-70]

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure: Suggested dose modifications[71]:

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

Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times weight}{\text{Serum Creatinine in } \mu mol/L}$

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

Dosage in hepatic failure: no adjustment required

Dosage in dialysis: dialyzable with a high extraction efficiency[7]

hemodialysis: ½ dose has been suggested[71]
there have been 2 case reports of giving high-dose cyclophosphamide with continuous bladder irrigation +/- mesna.[72,73] Hemodialysis (duration 6 h) was performed 6 h[72] and 14 h[73] after cyclophosphamide infusion. Dialysis should not be started sooner then 12 h after cyclophosphamide infusion.[74]

chronic ambulatory peritoneal dialysis (CAPD): dose as for GFR < 10 mL/min/1.73m^2 (i.e., administer 75% of dose)[75]

continuous arteriovenous or venovenous hemofiltration (CAVH): dose as for GFR 10-50 mL/min/1.73m^2 (i.e., administer 100% dose)[71]

Children[76,77]***:***

	Cycle Length:	
Oral:	daily:	50-300 mg/m^2
Intravenous:	3-4 weeks[76]	250-1800 mg/m^2 for one dose on day 1, day 2, day 3 and day 4
	3-4 weeks[77]:	up to 2000-3000 mg/m^2 for one dose on day 1

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