

DRUG NAME: Cyclosporine**SYNONYM(S):** ciclosporin,¹ cyclosporin,¹ cyclosporin A,¹ CsA,² CyA³**COMMON TRADE NAME(S):** NEORAL®, SANDIMMUNE® I.V., SANDOZ CYCLOSPORINE®, APO-CYCLOSPORINE®, GENGRAF® (USA)**CLASSIFICATION:** miscellaneous*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Cyclosporine is a metabolite extracted from the fungus *Tolypocladium*⁴ It is a potent suppressor of the immune system, particularly T-lymphocytes.² Cyclosporine binds to the intracellular receptor cyclophilin, subsequently inhibiting cytokine production, including interleukin-2 and 4, tumour necrosis factor alpha, and interferon gamma, which leads to impairment of normal lymphoid cell activation.^{2,3} Other mechanisms may contribute to immunosuppression.⁴ Cyclosporine is cell cycle phase-specific; lymphocytes in the G0 or G1 phase of the cell cycle are specifically and reversibly inhibited.² Direct cytotoxic effects on T- and B-lymphocytes have also been demonstrated.^{3,5} Cyclosporine is an immunosuppressive agent.⁴

PHARMACOKINETICS:

Oral Absorption	significant inter- and intra-patient variability	
Distribution	highly lipophilic; high concentrations in body fat, with accumulation in liver, pancreas, lungs, kidneys, adrenal glands, spleen and lymph nodes; exhibits multicompartment behaviour with eventual saturation of peripheral compartment	
	cross blood brain barrier?	yes; very low levels detected in brain and cerebrospinal fluid
	volume of distribution	3.5-9 L/kg
	plasma protein binding	90-98%, mostly to lipoproteins and erythrocytes ^{4,6}
Metabolism	extensively biotransformed by cytochrome P450; no single major metabolic pathway	
	active metabolite(s) ⁶	AM1, AM9, AM4N
	inactive metabolite(s)	no information found
Excretion	primarily biliary; renal excretion is a minor pathway	
	urine	6%; 0.1% as unchanged drug
	feces	metabolites (44%) and unchanged drug (<1%) in bile
	terminal half life	highly variable; approximately 18 h (range 7.7-26.9 h)
	clearance ^{4,6}	5-7 mL/min/kg; highly variable; impaired in liver disease
Elderly	more likely to have serum creatinine ≥50% higher than baseline after treatment for 3-4 months; may be more likely to develop systolic hypertension ⁶	
Children	may require more frequent and larger doses to achieve therapeutic blood levels ⁴ ; higher clearance than adults, variable by age ⁶	

Adapted from standard reference⁴ unless specified otherwise.**USES:****Primary uses:**Cytopenia associated with large granular lymphocyte leukemia^{2,5,7-10}**Other uses:**

*Health Canada approved indication

SPECIAL PRECAUTIONS:**Contraindications:**

- history of hypersensitivity reaction to cyclosporine or polyoxyethylated castor oil which is present in the intravenous formulation⁴

Caution:

- **immunosuppression** induced by cyclosporine may aggravate pre-existing localized and generalized bacterial, fungal, parasitic and viral infections and may predispose patients to their development.⁴
- **renal function** can be impaired by cyclosporine. Cyclosporine treatment is not recommended in patients with abnormal renal function. Special caution is advised in patients over 65 years, due to the natural decline in renal function with age.⁴ Nephrotoxic effects may be additive, therefore concurrent therapy with other potentially nephrotoxic drug should be avoided where possible.⁶ If use is necessary, dosing should be guided by monitoring cyclosporine blood levels.¹¹
- **hypertension** may develop. Cyclosporine treatment is not recommended in patients with uncontrolled hypertension.⁴
- risk of **hyperkalemia** may be increased, especially in patients with renal dysfunction.⁴
- **hyperlipidemia** has been reported with treatment. Perform lipid profile before treatment and after the first month of therapy. Restriction of dietary fat should be considered if lipids increase. Caution is advised in patients receiving concurrent HMG-CoA reductase inhibitors (i.e., lovastatin) due to a risk of myocyte necrosis.⁴ See Drug Interaction table.
- **hyperuricemia** is commonly reported, particularly in patients receiving concurrent diuretics, and may result from decreased renal clearance of uric acid. Gout may occur in some patients.^{4,6}
- **vaccination** may be less effective due to diminished immune response. Live attenuated vaccines should be avoided to reduce risk of infection from the vaccine.⁴
- **anaphylactoid reactions** have been reported due to the presence of polyoxyethylated castor oil in the intravenous formulation. Special caution is necessary for patients who have previously received preparations containing polyoxyethylated castor oil or are otherwise pre-disposed to allergic reaction. Patients receiving SANDIMMUNE I.V.® should be under continuous observation for at least the first 30 minutes following the start of the infusion, and at frequent intervals thereafter. Infusion should be discontinued if anaphylaxis develops. Prophylactic administration of antihistamines (H1 and H2 blockers) have been used to prevent or reduce the severity of anaphylactoid reactions. Oral formulations (NEORAL®) do not contain polyoxyethylated castor oil.⁴
- **potential drug interactions** are numerous. If combined therapy is unavoidable, careful monitoring of blood cyclosporine concentration and appropriate dosage modification is suggested.⁴ See **Drug Interaction** table.

Carcinogenicity: Increased risk of secondary malignancies, most commonly skin cancer and non-Hodgkin's lymphoma, is a known complication of cyclosporine treatment, alone or in combination. Risk may be greater during concurrent therapy with multiple immunosuppressive agents.⁶

Mutagenicity: Not mutagenic in Ames test or mammalian *in vitro* mutation test. Cyclosporine is clastogenic in human lymphocytes *in vitro* but not in other mammalian *in vitro* and *in vivo* chromosome tests.^{4,6}

Fertility: Impaired fertility has not been demonstrated in mammalian studies.⁶

Pregnancy: FDA Pregnancy Category C.¹² Animal studies have shown fetal risks and there are no controlled studies in women. In humans, cyclosporine crosses the placenta.^{6,12} Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding is not recommended due to the potential secretion into breast milk.^{4,6}

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.¹¹

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	allergic reactions , including anaphylaxis ⁶ (1-3%)
	anaphylactoid reactions , due to polyoxyethylated castor oil in IV formulation; see paragraph following Side Effects table
	angioedema ⁶ (1-3%)
auditory/hearing	hearing loss ⁶ (1-3%)
	tinnitus ⁶ (1-3%)
	vestibular disorder ⁶ (1-3%)
blood/bone marrow/ febrile neutropenia	anemia ⁶ (1-3%)
	leukopenia ⁶ (1-3%)
	thrombocytopenia ⁶ (1-3%)
cardiovascular (arrhythmia)	abnormal heart sounds ⁶ (1-3%)
	arrhythmia ⁶ (5%)
cardiovascular (general)	cardiac failure ⁶ (1-3%)
	hypertension (26-50%) ⁶ ; see paragraph following Side Effects table
	myocardial infarction ⁶ (1-3%)
	peripheral ischemia ⁶ (1-3%)
coagulation	bleeding ⁶ (1-3%)
	clotting disorders ⁶ (1-3%)
	nose bleed ⁶ (1-3%)
constitutional symptoms	fatigue (1-10%)
	fever ⁶ (1-3%)
	influenza-like symptoms ⁶ (6-10%)
	weight changes ⁶ (1-3%)
dermatology/skin	<i>extravasation hazard</i> : none
	abnormal pigmentation ⁶ (1-3%)
	acne (1-3%) ⁶
	alopecia ⁶ (4%)
	brittle nails, abnormal nail growth ⁶ (1-3%)
	dermatitis ⁶ (1-3%)
	dry skin ⁶ (1-3%)
	flushing ⁶ (1-5%)
	folliculitis ⁶ (1-3%)
	hirsutism ⁶ (21-45%); see paragraph following Side Effects table
	hypertrichosis (1-19%) ^{4,6}
	keratosis ⁶ (1-3%)
	pruritus ⁶ (1-3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	rash ⁶ (1-12%)
	urticaria ⁶ (1-3%)
endocrine	hot flushes ⁶ (1-3%)
gastrointestinal (see paragraph following Side Effects table)	<i>emetogenic potential: low</i> ¹³
	abdominal distention ⁶ (1-3%)
	anorexia (1-10%)
	appetite increase ⁶ (1-3%)
	belching ⁶ (1-3%)
	constipation ⁶ (1-3%)
	diarrhea (1-13%) ^{4,6}
	dysphagia ⁶ (1-3%)
	dyspepsia ⁶ (2-12%)
	esophagitis ⁶ (1-3%)
	flatulence ⁶ (5%)
	gastritis, gastroenteritis ⁶ (1-3%)
	gingival bleeding (1-3%) ⁶
	gingival hyperplasia (1-35%) ^{4,6,14} ; see paragraph following Side Effects table
	gingivitis ⁶ (4%)
	glossitis ⁶ (1-3%)
	nausea (1-23%) ^{4,6}
	salivary gland enlargement ⁶ (1-3%)
	stomatitis ⁶ (7%)
	ulcer ⁶ ; gastric (1-3%), peptic (1-3%)
vomiting (1-10%)	
hemorrhage	rectal hemorrhage ⁶ (3%)
	uterine hemorrhage ⁶ (1-3%)
hepatobiliary/pancreas	hepatic dysfunction (1-10%) ^{4,6}
infection (see paragraph following Side Effects table)	pneumonia ⁶ (1%)
	respiratory infection, unspecified ⁶ (1-9%)
	sinusitis ⁶ (3-4%)
	upper respiratory infection ⁶ (14%)
	urinary tract infection ⁶ (3%)
lymphatics	edema, unspecified ⁶ (14%)
metabolic/laboratory	hyperbilirubinemia (1-3%) ⁶ : dose dependent, reversible; may require dose reduction ⁴
	hyperglycemia ⁶ (1-3%)
	hyperkalemia (1-10%); see paragraph following Side Effects table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
	<i>hyperlipidemia</i> (>10%); serum triglycerides elevation (15%), serum cholesterol elevation ⁶ (≤3%); usually reversible after dose reduction or treatment cessation
	hyperuricemia (1-10%)
	hypomagnesemia (1-10%); see paragraph following Side Effects table
	liver enzyme elevation, reversible (≤1%); indicates toxicity ⁶ ; may require dose reduction ⁴
	nonprotein nitrogen elevation ⁶ (19%)
	<i>serum creatinine, urea elevation</i> ; dose dependent, reversible; may respond to dose reduction
musculoskeletal	arthropathy ⁶ (5%)
	gout ⁶
	<i>muscle cramps, myalgia</i> (1-12%) ^{4,6} ; see paragraph following Side Effects table
	muscle contractions, involuntary ⁶ (12%)
neurology	anxiety ⁶ (1-3%)
	confusion ⁶ (1-3%)
	depression ⁶ (6%)
	dizziness ⁶ (1-8%)
	emotional lability ⁶ (1-3%)
	flat affect ⁶ (≤1%)
	hypoesthesia ⁶ (1-3%)
	impaired concentration ⁶ (1-3%)
	insomnia ⁶ (1-4%)
	migraine ⁶ (3%)
	nervousness ⁶ (1-3%)
	neuropathy ⁶ (1-3%)
	paresthesia (1-11%) ^{4,6}
	seizures ⁶ ; particularly with high dose corticosteroids
	somnolence ⁶ (1-3%)
	<i>tremor</i> (10-55%) ^{4,6}
	vertigo ⁶ (1-3%)
ocular/visual	abnormal vision ⁶ (1-3%)
	cataract ⁶ (1-3%)
	conjunctivitis ⁶ (1-3%)
pain	<i>abdominal pain</i> (1-15%) ^{4,6}
	arthralgia ⁶ (1-6%)
	breast pain ⁶ (1-3%)
	chest pain ⁶ (1-6%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	headache (10-25%) ^{4,6}
	myalgia ⁶ (1-3%)
	pain, unspecified ⁶ (4-13%)
pulmonary	bronchitis, bronchospasm ⁶ (1-5%)
	cough ⁶ (5%)
	dyspnea ⁶ (5%)
	pharyngitis ⁶ (5%)
	rhinitis ⁶ (3-5%)
renal/genitourinary	dysuria ⁶ (≤1%)
	incontinence ⁶ (1-3%)
	micturition frequency, polyuria, nocturia ⁶ (1-4%)
	pyelonephritis ⁶ (1-3%)
	renal dysfunction (>10%); see paragraph following Side Effects table
secondary malignancy	lymphoma; see paragraph following Side Effects table
	skin malignancy; see paragraph following Side Effects table
sexual/reproductive function	breast fibroadenosis ⁶ (1-3%)
	gynecomastia ⁶ (3%)
	menstrual disorders ⁶ (3%)
	increased or decreased libido ⁶ (1-3%)

Adapted from standard reference⁴ unless specified otherwise.

Anaphylactoid reactions, including facial flushing, flushing of the upper thorax, non-cardiogenic pulmonary edema, blood pressure changes, tachycardia and wheezing, have been reported with SANDIMMUNE I.V.® due to the presence of polyoxyethylated castor oil in the formulation. If anaphylaxis develops, infusion should be discontinued.^{4,6}

Many adverse **gastrointestinal effects** are reported. Symptoms of diarrhea, nausea, vomiting, anorexia, and abdominal discomfort occur more frequently. Reports of gastritis, hiccoughs, and peptic ulcer are less frequent; and constipation, difficulty swallowing, and upper GI bleeds are rare.⁶

Gingival hyperplasia induced by cyclosporine is clinically similar to that induced by phenytoin. It may appear more frequently in children. Risk is reduced by the maintenance of good oral hygiene. Onset is rapid, taking 1-2 weeks to develop.¹⁴ Resolution generally occurs 1-2 months after treatment cessation, although gingivectomy may be required in severe cases.⁶ Metronidazole and azithromycin have been used to treat gingival hyperplasia in some patients.¹⁴⁻¹⁶

Hirsutism occurs frequently and mainly involves the face, arms, eyebrows, and back. It is usually mild, although severe cases have been reported. In transplant patients, it usually develops within 2-4 weeks. Some improvement may be seen with dose reductions, although it is not typically dose-related. Cosmetic solutions may be necessary.⁶

Hypertension is reported in 26-50% patients, usually developing within a few weeks of treatment initiation. Incidence is variable, depending on treatment indication. Both systolic and diastolic blood pressure are affected. The mechanism is not clearly defined but renal vasoconstriction is proposed. Regular monitoring of blood pressure is required. Hypertension may respond to dosage reduction and/or antihypertensive therapy; treatment with diuretics is

not recommended. Blood pressure typically returns to normal within 3 months of treatment cessation.^{4,6} **Other cardiovascular effects**, including myocardial infarction, arrhythmia, abnormal heart sounds, cardiac failure, and peripheral ischemia, have also been reported with treatment.⁶

Infectious complications occur frequently with treatment, although rates are comparable with similar therapies. In some studies, infections are reported in up to 25% of patients. Local and systemic bacterial, viral, and fungal infections are described, including influenza-like symptoms (6-10%), upper respiratory infections (8-14%), urinary tract infection (3%), pneumonia (1%), and other respiratory infections (1-3%). As well, abscesses, cellulitis, herpes infections, monilliasis, renal abscess, fungal infection, and viral infection each reportedly occur in 1-3% of patients.⁶

Magnesium clearance is enhanced by cyclosporine, possibly leading to symptomatic hypomagnesemia. Monitor magnesium levels and supplement as required. **Hyperkalemia** sometimes occurs. Monitor potassium levels and use caution with potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, potassium containing drugs, and potassium rich diets.⁴

Adverse **musculoskeletal** events occur in approximately 13% of patients. Arthralgia is reported in 6%.⁶ **Myotoxicity**, including muscle pain and weakness, myositis, and rhabdomyolysis have been reported with concomitant administration with lovastatin, simvastatin, atorvastatin, pravastatin, and rarely, fluvastatin. Statin therapy should be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or at risk of severe renal injury secondary to rhabdomyolysis.⁴ See **Drug Interaction** table.

Nervous system effects are numerous and may be associated with high cyclosporine blood concentrations, concurrent high-dose corticosteroids, hypertension, and/or hypomagnesemia. Reported effects include tremor, seizures, headache, paresthesia, psychiatric disorders, dizziness and migraine. Cyclosporine-induced tremor is usually mild in severity and may manifest as a fine hand tremor. Tremor may improve despite continued treatment or may be alleviated by dose reduction. Headache may occur in up to 25%. Psychiatric disorders, reported in up to 5%, include anxiety, impaired concentration, confusion, emotional lability, flat affect, depression, changes in libido, nervousness, and somnolence. A syndrome of severe neurotoxicity, manifesting as cortical blindness, quadriplegia, seizures, and/or coma accompanied by white-matter changes, has also been documented.⁶

Secondary malignancies, especially of the skin, and lymphoproliferative disorders have developed with treatment. Malignancy frequency is increased with the intensity and duration of treatment. Screening for malignancies is recommended; caution is advised for patients with malignant or premalignant conditions of the skin. Lesions should be biopsied and appropriately treated prior to cyclosporine treatment and cyclosporine discontinued if malignancy occurs. Excess ultraviolet light exposure should be avoided. Female patients should also have a cervical exam within the first 6 months of therapy and periodically thereafter to rule out malignancy.⁴

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice ⁴	may increase cyclosporine blood level	may inhibit CYP 3A4 metabolism of cyclosporine in the intestinal wall	avoid grapefruit and grapefruit juice
allopurinol ^{4,17}	increased cyclosporine blood level; increased renal toxicity	unknown	monitor cyclosporine level and renal function; adjust dose as needed
amiodarone ^{4,18}	increased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
barbiturates ⁴	decreased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed

AGENT	EFFECT	MECHANISM	MANAGEMENT
bosentan ^{4,17}	decreased cyclosporine blood level; increased bosentan plasma levels and toxicity	unknown	avoid concurrent use; monitor for bosentan toxicity; monitor cyclosporine level; adjust cyclosporine dose as needed
calcium channel blockers ^{4,17}	increased cyclosporine blood level and pharmacologic effect; possible renal impairment	unknown	monitor cyclosporine level and renal function; adjust dose as needed
carbamazepine ^{4,18}	decreased cyclosporine blood level; possibly decreased immunosuppressive effect	induction of CYP 3A4 by carbamazepine	monitor cyclosporine level; adjust dose as needed
cholic acid derivatives ⁴	increased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
colchicine ^{4,18}	increased colchicine and cyclosporine blood levels; enhanced myopathy and neuropathy, especially in renal dysfunction	reduced colchicine clearance via inhibition of P-glycoprotein by cyclosporine; other mechanisms unknown	monitor cyclosporine level; monitor for colchicine toxicity; colchicine dose reduction or withdrawal may be required; caution in renal or hepatic impairment
corticosteroids ⁴	increased cyclosporine blood level	unknown	reduce cyclosporine dose to 3-6 mg/kg/day orally; monitor cyclosporine level; adjust dose as needed
danazol ⁴	increased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
digoxin ^{4,18}	digitalis toxicity (characterized by GI and neuropsychiatric symptoms, and cardiac arrhythmias)	reduced digoxin clearance	monitor for digitalis toxicity; dose reduction or withdrawal may be required.
etoposide ⁴	increased therapeutic effect and toxicity of etoposide	reduced etoposide clearance	monitor for etoposide toxicity; adjust dose as needed, consider reducing etoposide dose by 50% ¹⁸
fenofibrate ⁴	reversible renal impairment and increased serum creatinine	unknown	monitor kidney function; withdraw fenofibrate if impairment significant.
fluconazole, itraconazole, ketoconazole, voriconazole ⁴	increased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
HIV protease inhibitors ^{4,18}	increased blood levels of both	mutual inhibition of CYP 3A isoenzymes	monitor cyclosporine level; adjust doses as needed
imatinib ⁴	increased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
imipenem ⁴	increased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed

AGENT	EFFECT	MECHANISM	MANAGEMENT
macrolide antibiotics ^{4,18}	increased cyclosporine blood level; possible renal and hepatic toxicity	increased oral absorption of cyclosporine and inhibition of CYP 3A4 by macrolide	monitor cyclosporine level; monitor renal and hepatic function; adjust dose as needed
methylprednisolone ⁴	increased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
metoclopramide ⁴	increased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
octreotide ⁴	decreased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
oral contraceptives ⁴	increased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
orlistat ⁴	decreased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
oxcarbazepine ⁴	decreased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
phenytoin ^{4,18}	decreased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
prednisolone ⁴	Cushingoid symptoms	reduced prednisolone clearance	monitor for toxicity due to either drug; monitor cyclosporine level; adjust dose as needed
red wine ¹⁹	decreased cyclosporine blood level	50% increase in cyclosporine clearance	avoid combination; effect not studied in all formulations
repaglinide ^{4,18}	increased repaglinide plasma level; increased risk of hypoglycemia	inhibition of hepatic uptake and CYP 3A4 metabolism by cyclosporine	monitor blood glucose; adjust repaglinide dose as needed
rifampin ^{4,18}	decreased cyclosporine blood level	increased clearance and reduced oral bioavailability of cyclosporine	monitor cyclosporine level; adjust dose as needed
St. John's Wort (Hypericum perforatum) ^{4,17}	decreased cyclosporine blood level	induction of hepatic and prehepatic CYP 3A4 by St. John's Wort	monitor cyclosporine level; adjust dose as needed
sirolimus ⁴	significant increase in sirolimus blood level; increased serum creatinine	unknown	reversible with cyclosporine dose reduction; monitor serum creatinine
statins (HMG-CoA reductase inhibitors; i.e., lovastatin, simvastatin, atorvastatin, pravastatin, and fluvastatin) ⁴	reports of myotoxicity, may precipitate acute renal failure; see paragraph following Side Effects table	decreased statin clearance	reduce statin dose as per manufacturer; monitor for myotoxicity; statin withdrawal may be required.
sulfapyrazone ⁴	decreased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
terbinafine ⁴	decreased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed
ticlodipine ⁴	decreased cyclosporine blood level	unknown	monitor cyclosporine level; adjust dose as needed

AGENT	EFFECT	MECHANISM	MANAGEMENT
vaccines ^{4,6}	diminished response to vaccination	decreased immune response	vaccinate prior to treatment or delay vaccination if possible
vaccines, live ⁴	increased risk of infection from vaccine	decreased immune response	avoid vaccination with live vaccines during treatment

Inhibitors or inducers of CYP 3A4 may increase or decrease plasma or whole blood cyclosporine levels.⁴

Cyclosporine is an inhibitor of CYP 3A4. Plasma levels of substrates of this enzyme may be increased.⁴

Cyclosporine is an inhibitor of transporter P-glycoprotein. Plasma levels of substrates of this transporter may be increased.⁴

SUPPLY AND STORAGE:

Oral:

Novartis Pharmaceuticals Canada Inc. supplies cyclosporine as 10, 25, 50, and 100 mg soft gelatin capsules and 100 mg/mL oral solution in a microemulsion formula. Non-medicinal ingredients: ethanol, hydrogenated castor oil, maize oil, and propylene glycol. Store at room temperature. Do not freeze. Do not remove from original packaging until required for use. A noticeable characteristic odour is normal when blisters are opened. Swallow capsules whole. Oral solutions should be used within 2 months of opening.⁴

Sandoz Canada Inc. supplies cyclosporine as 25, 50, and 100 mg soft gelatin capsules in a microemulsion formula. Non-medicinal ingredients: ethanol, polyethylene glycol. Store at room temperature. Do not remove from original packaging until required for use. A noticeable characteristic odour is normal when blisters are opened. Swallow capsules whole.²⁰

Apotex Inc. supplies cyclosporine as 100 mg/mL oral solution. Non-medicinal ingredients: benzyl alcohol, polyethylene glycol, and polyoxyl 40 hydrogenated castor oil. Store at room temperature. Do not freeze. Do not remove from original packaging until required for use. Oral solutions should be used within 2 months of opening.²¹

Additional information: A reversible jelly-like formation of the oral solution may occur at temperatures below 20°C. Minor flakes or slight sediment may remain which will not effect the efficacy and safety of the product.^{4,21}

Injection:

Novartis Pharmaceuticals Canada Inc. supplies cyclosporine as 50 and 250 mg ampoules at a concentration of 50 mg/mL injection in a polyoxyethylated castor oil/ethanol vehicle. Store at room temperature. Do not freeze.⁴

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.

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:BCCA administration guideline noted in ***bold, italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	<ul style="list-style-type: none"> • over two to six hours⁴ • glass containers should be used if available; do NOT use PVC containers or containers containing silicone oil or fatty substances⁴ • administer through non-PVC tubing²²
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
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 (ANC). 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******Oral:***^{4,20,21,23}

lymphoma:
100 mg PO twice daily to start. Adjust dose as necessary to maintain target blood cell count. Maximum dose = 400 mg/day.

Oral doses should always be given in two divided doses. Oral preparations (with a microemulsion formulation) may be taken without regard to meals.^{4,20,21} Capsules should be swallowed whole. Oral solutions should be diluted (preferably with orange juice or apple juice; soft drinks or others may be used according to individual taste). Do NOT mix with grapefruit juice. Stir well immediately before administration.⁴

Higher doses may be required in the presence of gastrointestinal disturbances which may decrease drug absorption.

Intravenous:^{4,6}

reserve for patients unable to tolerate oral formulations; patients unable to tolerate oral treatment may be treated with IV infusion at one-third the oral dose.

Concurrent radiation:

no information found

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

<i>Dosage in myelosuppression:</i>	no information found
<i>Dosage in renal failure:</i>	dose at 100%; <i>reduce dose as needed to keep serum creatinine below 125% of normal</i> ; suggest decrease by 25-50% with each adjustment and discontinue treatment if adjustment does not reverse increased serum creatinine after 2 adjustments. ^{7,12,24} Cyclosporine blood levels can be used to guide dosing. ¹¹
<i>Dosage in hepatic failure:</i> ^{6,12}	no information found; adjustment probably necessary; monitor LFTs and cyclosporine levels closely.
<i>Dosage in dialysis:</i> ^{12,24}	supplemental doses not required

Children: no information found

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