

DRUG NAME: Methotrexate

SYNONYM(S): amethopterin,¹ MTX

COMMON TRADE NAME(S):

CLASSIFICATION: antimetabolite

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

MECHANISM OF ACTION:

Methotrexate is a folate antagonist.² Tetrahydrofolate is the active form of folic acid required for purine and thymidylate synthesis. Folic acid is reduced to tetrahydrofolate by dihydrofolate reductase (DHFR). The cytotoxicity of methotrexate results from three actions: inhibition of DHFR, inhibition of thymidylate, and alteration of the transport of reduced folates.³ Inhibition of DHFR results in a deficiency of thymidylate and purines and therefore a decrease in DNA synthesis, repair and cellular replication.³ The affinity of DHFR to methotrexate is far greater than its affinity for folic acid or dihydrofolic acid, therefore large doses of folic acid given simultaneously will not reverse the effects of methotrexate.² However, leucovorin calcium, a derivative of tetrahydrofolic acid, may block the effects of methotrexate if given shortly after the methotrexate since it does not require DHFR for activation.² Moderate ($\geq 100 \text{ mg/m}^2$) to high-dose methotrexate ($\geq 1000 \text{ mg/m}^2$)⁴ plus leucovorin rescue is routinely used therapeutically in cancer treatment.³ Methotrexate is most active against rapidly multiplying cells because the cytotoxic effects occur primarily during the S phase of the cell cycle.³ Methotrexate also has immunosuppressive activity, possibly due to inhibition of lymphocyte multiplication.⁵

PHARMACOKINETICS:

Interpatient variability	significant differences in time to peak concentration	
Oral Absorption	highly variable and dose dependent ⁵ ; 60% for doses up to 30 mg/m ² ; significantly less for doses >80mg/m ²	
	food delays absorption and reduces peak concentration	
	time to peak plasma concentration	1-2 h
Distribution	actively transported across cell membranes at serum concentrations < 0.1 µmol/mL, mainly passive diffusion at higher concentration ⁵ ; widely distributed with highest concentration in kidneys, gallbladder, spleen, liver, and skin ⁵ ; also distributes into third space fluids ⁵	
	cross blood brain barrier?	a ratio of 10-30:1 for CNS concentrations of methotrexate ⁶ ; higher CNS concentrations noted in patients with recent cranial irradiation and in patients with primary CNS lymphoma due to disruption of the blood-brain barrier
	volume of distribution	0.4-0.8 L/kg
	plasma protein binding	50%
Metabolism	<10%; hepatic and intracellular	
	active metabolite	methotrexate polyglutamates ⁵ and 7-hydroxy-methotrexate ⁷
	inactive metabolite	4-amino-4-deoxy-N ¹⁰ -methylpteroic acid (DAMPA) ⁸
Excretion	primarily renal via glomerular filtration and active tubular secretion	
	urine	80-90%

	feces	10% biliary
	terminal half life	3-10 h for doses < 30 mg/m ² ; 8-15 h for higher doses ⁵
	clearance	decreased at higher doses
Children ⁸	more rapid elimination in urine; greater volume of distribution	

Adapted from standard reference² unless specified otherwise.

USES:

Primary uses:

- *Bladder cancer
- *Breast cancer
- *Gastric cancer
- *Choriocarcinoma
- Gestational trophoblastic cancer¹¹
- *Head and neck cancer
- *Leptomeningeal cancer
- *Leukemia, acute lymphoblastic
- *Lymphoma, Burkitt's
- *Lymphoma, childhood
- *Lymphoma, cutaneous T-cell (mycosis fungoides)
- *Lymphoma, non-Hodgkin's
- *Sarcoma, osteogenic
- Urothelial cancer¹²

Other uses:

- Leukemia, acute lymphocytic⁹
- Leukemia, acute promyelocytic⁹
- Sarcoma, soft tissue⁹
- Lymphoma, intraocular¹⁰

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- **Pleural effusions or ascites**³: Methotrexate exits slowly from third space compartments resulting in prolonged half-life and unexpected toxicity. In patients with significant third space accumulation, the fluid should be removed prior to treatment and methotrexate levels should be monitored.³ If the fluid cannot be drained prior to therapy, a dose reduction is appropriate.¹³

Special populations: Elderly patients may be at increased risk for toxicity due to decreased hepatic and renal function, as well as decreased folate stores.³ A dose reduction as well as monitoring for early signs of toxicities should be considered.³

Carcinogenicity: There are no controlled studies in humans. Evidence regarding increased risk of tumours is conflicting, complicating the assessment of carcinogenic potential. Malignant lymphomas have been reported in patients receiving low-dose methotrexate, but in some patients, they may regress without treatment following methotrexate withdrawal. Animal studies have been inconclusive. However, there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells; clinical significance is unknown.¹⁴

Mutagenicity: Clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.⁵

Fertility: Methotrexate therapy may result in impairment of fertility, oligospermia, and menstrual dysfunction in humans, during and for a short period after cessation of therapy.^{14,15}

Pregnancy: Methotrexate can cause fetal death, embryotoxicity, abortion, and teratogenic effects in humans. The optimal time interval between cessation of methotrexate treatment of either partner and pregnancy has not been established. Published intervals vary from 3 months to 1 year after treatment has ended.^{14,15}

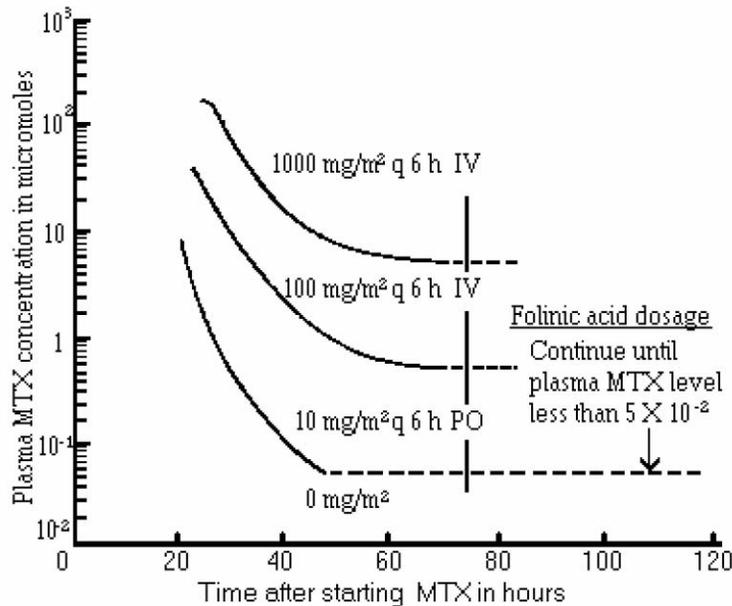
Breastfeeding is contraindicated as methotrexate has been detected in human breast milk.^{14,15}

Leucovorin rescue⁴ is required in some methotrexate regimens.

Methotrexate dose:

- >500 mg/m² requires leucovorin rescue.
- 100-500 mg/m² may require leucovorin rescue.

Bleyer Nomogram:



Reference: Bleyer WA. The clinical pharmacology of methotrexate – new applications of an old drug. *Cancer* 1978;41(1):36-51

Note: 0.05 micromol/L = 5 x 10⁻² micromoles/L

Leucovorin dose PO/IV/IM (see Bleyer nomogram):

- 10-25 mg/m² every 6 hours for approximately 8 to 10 doses, starting 24 hours after the start of methotrexate infusion.^{4,16-20} (note: for leucovorin doses >25 mg administer IV).²¹
- Leucovorin dose modifications begin on day 3, if required, based on methotrexate levels taken that morning (i.e., level taken 36-48 hours following the start of the methotrexate infusion). Methotrexate levels are repeated every morning and leucovorin adjusted based on the graph to follow.¹⁶⁻¹⁸
- Continue until the methotrexate level is <0.05 to 0.1 micromol/L.^{22,23} The change in threshold concentration from 0.05 microl/L (as per Bleyer nomogram) to 0.1 micromol/L is a result of worldwide changes in the immunoassay used to measure methotrexate serum levels. New laboratory methods have a higher limit of detection than previous methods and inaccuracies have been reported with methotrexate levels below 0.1 micromol/L.²⁴

Note: Leucovorin doses >25 mg should be given IV²¹

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.²⁵ When placebo-controlled trials are available, adverse events are included if the incidence is \geq 5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
allergy/immunology	anaphylaxis (<1%)
	vasculitis (1-10%)
auditory/hearing	tinnitus
blood/bone marrow/ febrile neutropenia	anemia
	<i>neutropenia</i> : 1 st nadir 4-7 days with recovery in 7-13 days; 2 nd nadir 12-21 days with recovery in 15-20 days ²⁶
	<i>thrombocytopenia</i> : nadir 5-12 days with recovery in 15-27 days ²⁶
cardiovascular (general)	hypotension
	pericardial effusion
	pericarditis
constitutional symptoms	chills and fever (frequent) ²⁶
	fatigue (frequent) ²⁶
	malaise (1-10%)
	mood alteration; with low-dose methotrexate
dermatology/skin	<i>extravasation hazard</i> : none ²⁷
	acne
	alopecia (1-10%); usually reversible but may require several months ²⁶
	dermatitis
	erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, toxic epidermis necrolysis ³
	folliculitis
	furunculosis
	photosensitivity (1-10%)
	pigmentary changes (1-10%)
	pruritus
	rash (1-10%); on extremities ²⁶
	reddening of skin (>10%)
	skin necrosis ³
	telangiectasia
urticaria	
endocrine	diabetes (1-10%)
gastrointestinal	<i>emetogenic potential</i> ²⁸ : dose-related: moderate (high-moderate for >1000 mg/m ² ; low-moderate for 250-1000 mg/m ²); low for \leq 250 mg/m ² to >50 mg/m ² ; rare for \leq 50 mg/m ²
	abdominal discomfort

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
	anorexia (>10%)
	diarrhea (>10%)
	gingivitis (>10%)
	glossitis (>10%)
	nausea; dose-related
	perforation (>10%) ⁴
	pharyngitis
	<i>stomatitis</i> (>10%)
	<i>vomiting</i> ; dose-related
hemorrhage	ecchymoses, petechiae
	hematemesis ⁵
	hematuria
	melena ⁵
hepatobiliary/pancreas	pancreatitis
hepatic	<i>hepatotoxicity</i> (1-10%)
metabolic/laboratory	<i>azotemia</i> ; more common with high-dose methotrexate than with low-dose ²⁵
	hyperuricemia (>10%)
	liver function tests, elevated ⁵ ; usually transient, asymptomatic and return to normal within 10 to 14 days ²⁵
musculoskeletal	arthralgia/myalgia (1-10%)
	hemiparesis
	osteoporosis, fractures; with high-dose methotrexate ²⁶
	osteonecrosis
	soft tissue necrosis
neurology	<i>neurotoxicities</i> (>10%); with intrathecal administration or high-dose methotrexate
	cognitive dysfunction, mild transient (<1%); with low-dose methotrexate ²⁶
	cranial sensations; with low-dose methotrexate
	dizziness (1-10%)
	seizure (1-10%)
ocular/visual	blurred vision (1-10%)
	conjunctivitis
	eye discomfort
	severe visual changes
pain	headache ²⁶

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
pulmonary	pulmonary toxicity (2-8%) ²⁹ ; can occur with all doses of methotrexate, although more often with chronic low-dose ²⁵
renal/genitourinary	renal dysfunction (1-10%); with high-dose methotrexate
secondary malignancy	lymphomas; may regress following withdrawal of methotrexate ³
sexual/reproductive function	abortifacient, fetal defects ²⁶
	gynecomastia
	loss of libido/impotence
	menstrual dysfunction
	oogenesis, interference with
	spermatogenesis, interference with
syndromes	acute neurologic syndrome (<1%); with high-dose methotrexate
	tumour lysis syndrome ; especially when given for systemic Burkitt's lymphoma ²⁵
vascular	cerebral thrombosis
	deep vein thrombosis
	pulmonary embolism
	retinal vein thrombosis

Adapted from standard references^{2,30} unless specified otherwise.

Glucarpidase (*carboxypeptidase-G2*, CPDG2, VORAXAZE®^{31,32}) is a recombinant bacterial enzyme that inactivates extracellular methotrexate to 2,4-diamino-N¹⁰-methylpteroic acid [DAMPA].³¹ Glucarpidase can rapidly lower serum methotrexate levels by >95% within 15 minutes of administration.³³ Cellular uptake of glucarpidase is increased when it is given with leucovorin. However, leucovorin is a weak substrate for glucarpidase and may compete with methotrexate for binding. Therefore, administration time of leucovorin and glucarpidase should be separated.³¹ Also, leucovorin should be continued after administration of glucarpidase, which may deactivate the active metabolite of leucovorin^{34,35}. Glucarpidase can be used to treat patients at risk for methotrexate toxicity secondary to delayed elimination³¹ and is available through the Health Canada Special Access Programme:

- Glucarpidase 50 units/kg IV over 5 minutes³¹
 - For methotrexate level >100 micromol/L, may give second dose of glucarpidase 48 hours after administration of first dose.³⁶
- High-dose leucovorin (eg, 1000 mg/m² IV every 6 hours) should be given prior to the receipt and administration of glucarpidase.³⁶
 - Leucovorin should be given at least 2-4 hours before or after administration of glucarpidase.³¹
 - After administration of glucarpidase, leucovorin should be continued at a high dose of 250 mg/m² IV every 6 hours for a total of 48 hours; after that time, leucovorin rescue should be modified based on methotrexate levels and clinical signs of toxicity.³⁶
 - Note that following glucarpidase administration, methotrexate level based on standard clinical immunoassay methods may be artificially high due to interference from high levels of DAMPA.³¹

Methotrexate-induced **hepatotoxicity** can be seen with both high and low-dose methotrexate, and can be life-threatening.²⁶ Increased serum aminotransferases (14%) and less commonly hyperbilirubinemia is seen more often in high-dose methotrexate.⁸ The liver enzymes can increase with each cycle, and usually return to pre-treatment levels once methotrexate has been discontinued for 1 month.³⁷ Cirrhosis and fibrosis are more often seen with

chronic low-dose methotrexate.^{8,37} See Dosing guidelines for hepatic failure. Patients should be warned to avoid alcohol, prescription medications or herbal supplements that may increase risk of hepatotoxicity.²⁵

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.³⁸ 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 pre-existing renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients³⁹:

- 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 greater than 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.⁴⁰ 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 aluminium hydroxide has been added, discontinue sodium bicarbonate.⁴¹

Neurologic complications³⁰: Methotrexate-induced neurotoxicities can be seen with intrathecal injection of methotrexate and with high-dose methotrexate.⁴ The neurotoxicities may be due to the accumulation of adenosine resulting from the inhibition of purine synthesis.²⁶

For Intrathecal (IT) administration

- Aseptic meningitis³⁰: This is the most common toxicity seen with IT administration (10%); includes headache, neck rigidity, back pain, nausea, vomiting, fever, and lethargy. Aseptic meningitis can begin 2-4 hours after the drug is injected, and can last 12-72 hours. There is usually no treatment required; the risk of developing this can be decreased by the administration of IT hydrocortisone, or oral corticosteroids. Patients may be rechallenged.
- Transverse myelopathy³⁰: This is much less common³⁰; includes isolated spinal cord dysfunction over hours or days. Transverse myelopathy can begin between 30 minutes and 48 hours after treatment. This is more common with concurrent radiotherapy or frequent IT injections of methotrexate. Recovery from this condition is variable. Patients are not rechallenged.
- Leukoencephalopathy³⁰: This can be a delayed complication and is more common in patients receiving whole brain radiotherapy or previous IV methotrexate. Symptoms include confusion, irritability, somnolence, ataxia, dementia, and occasionally seizures and coma.⁵
- Encephalopathy, seizures, neurologic deficits, lumbosacral radiculopathy, neurogenic pulmonary edema, and sudden death can rarely occur.³⁰

For high-dose methotrexate (≥ 1000 mg/m²)

- Acute neurotoxicity³⁰: includes somnolence, confusion, and seizures within 24 hours of treatment. These usually resolve spontaneously; rechallenge is possible.
- Subacute neurotoxicity³⁰: seen with weekly or every two week administration. “Stroke-like” syndrome, including transient neurologic deficits, confusion, and seizures. Occurring about 6 days after drug administration, lasting from 15 minutes to 72 hours and then resolving. Rechallenge is possible.

Leukoencephalopathy: refer to “for IT administration” above.

Methotrexate-induced **pulmonary toxicity** can be seen with both high and low-dose methotrexate, and can be life-threatening.²⁶ Pulmonary toxicity can be either symptomatic or asymptomatic and can be caused by inflammation, infection or neoplasia.²⁶

- Inflammatory lung disease: most common here is hypersensitivity pneumonitis.²⁹
 - Pulmonary infections: opportunistic infections due to compromised immune system.²⁹
 - Pulmonary lymphoma: Non-Hodgkin’s (B cell) lymphoma which regresses after discontinuation of methotrexate.²⁹
- Methotrexate-induced pulmonary toxicity can be acute, subacute, or chronic.²⁹ Patients who experience pulmonary toxicity will often develop this within the first year of methotrexate therapy, but it can occur much earlier or much later.²⁹ Subacute toxicity is the most common and includes dyspnea, non-productive cough, fever, crackles, cyanosis, pulmonary fibrosis, pleural effusions.²⁹ Treatment includes discontinuing methotrexate and initiating

corticosteroid therapy.²⁹ Improvement can occur within days of stopping methotrexate; rechallenging with the drug is not recommended.²⁹

High-dose methotrexate-induced **renal failure** is a medical emergency because methotrexate is mainly eliminated by the kidneys.⁴² Renal damage is due to precipitation of methotrexate in the tubules and to tubule injury. Drug precipitation can often be prevented by hydration and alkalization of the urine.⁸ Hydration produces a high urine output and lowers the concentration of methotrexate in the tubular fluid; alkalization of the urine increases the solubility of methotrexate. During the recovery period sustained methotrexate levels may result in substantial bone marrow and gastrointestinal toxicity.²⁵ Management should include continued monitoring of methotrexate levels, administration of leucovorin (see leucovorin rescue) and alkalized intravenous fluids until plasma levels fall below 0.05 micromol/L.²⁵

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
acitretin ^{4,43}	delayed, major, suspected; increased methotrexate hepatic toxicity	unknown	avoid concurrent use
alcohol ⁴	enhanced hepatotoxicity	additive	limit or avoid alcohol intake during therapy
aminoglycosides, oral ⁴³	delayed, moderate, possible; decreased methotrexate levels	decreased GI absorption of methotrexate	consider parenteral use of methotrexate
amiodarone ⁴³	delayed, major, possible; increased methotrexate levels	unknown	consider monitoring for methotrexate toxicity
asparaginase ⁴⁴	decreased effect of methotrexate when asparaginase is given immediately prior to or with methotrexate; enhanced effect of methotrexate when asparaginase is given after methotrexate	suppression of asparagine concentrations	give asparaginase 9-10 days before methotrexate or shortly after methotrexate
azathioprine ⁴³	delayed, moderate, possible; increased azathioprine levels	decreased metabolism of azathioprine	primarily a concern with high-dose methotrexate; dose reduction may be considered for azathioprine
bile acid sequestrants (e.g., cholestyramine, colestipol) ⁴⁵	may decrease methotrexate levels	decreased absorption of methotrexate ⁴⁵	separate the administration of these drugs by 2 or more hours
caffeine ⁴³	delayed, moderate, possible; decreased methotrexate antirheumatic effect	unknown	monitor clinical response; consider reduction in caffeine intake if needed
carboxypeptidase G2 (CPDG2) ⁴⁶	decreased toxicity of methotrexate	rapidly metabolizes methotrexate	may be used to rapidly lower serum methotrexate
chloroquine ⁴³	delayed, minor, possible; decreased methotrexate antirheumatic effect	unknown	monitor clinical response; consider increase in methotrexate dose

AGENT	EFFECT	MECHANISM	MANAGEMENT
corticosteroids ⁴	may decrease methotrexate levels in leukemia cells	may decrease the uptake of methotrexate into leukemia cells	separate the administration of these drugs by 12 hours; note that dexamethasone does not appear to affect methotrexate uptake into cells
cyclosporine ⁴	may increase both methotrexate and cyclosporine toxicity	unknown ⁴⁷	monitor for both cyclosporine and methotrexate toxicity ⁴⁷
cytarabine ⁴	methotrexate, when administered prior to cytarabine, may enhance the efficacy and toxicity of cytarabine	unknown	some protocols are designed to take advantage of this effect; monitor toxicity
digoxin ⁴³	delayed, moderate, suspected; decreased digoxin levels	decreased GI absorption of digoxin	monitor for digoxin pharmacologic effects
doxycycline ⁴³	delayed, major, possible; increased methotrexate levels	unknown	monitor for methotrexate toxicity
haloperidol ⁴³	delayed, moderate, possible; increased methotrexate dermatological toxicity	unknown	monitor for methotrexate toxicity
hydroxychloroquine ⁴³	delayed, minor, possible; decreased methotrexate antirheumatic effect	unknown	monitor clinical response; consider increase in methotrexate dose
leucovorin	decreased toxicity of methotrexate	leucovorin "rescues" normal cells from toxic effects of methotrexate	administer leucovorin after methotrexate if required
mercaptopurine ^{4,43}	delayed, moderate, possible; increased mercaptopurine levels	decreased metabolism of mercaptopurine	primarily a concern with high-dose methotrexate; dose reduction may be considered for mercaptopurine
NSAIDs (e.g., diclofenac, ibuprofen, naproxen) ^{4,43}	delayed, major, suspected; increased methotrexate levels	reduced renal clearance of methotrexate	primarily a concern with high-dose methotrexate; monitor methotrexate levels i.e., longer leucovorin rescue; note that risk may be lower with selective COX-2 inhibitors (e.g., celecoxib)
omeprazole, pantoprazole, esomeprazole, other proton pump inhibitors (PPI) ^{7,48-51}	increased methotrexate and 7-hydroxy-methotrexate levels, leading to increased methotrexate toxicity	mechanism unclear; possibly reduced renal clearance of methotrexate and 7-hydroxy-methotrexate	monitor for methotrexate toxicity; for high-dose methotrexate, consider discontinuing PPI one day prior to methotrexate; consider an H2 antagonist (e.g., ranitidine) instead of PPI

AGENT	EFFECT	MECHANISM	MANAGEMENT
penicillins (e.g., amoxicillin, piperacillin, ticarcillin) ^{4,43}	delayed, major, suspected; increased methotrexate levels	competitive inhibition of renal tubular secretion of methotrexate	primarily a concern with high doses of penicillins and high-dose methotrexate; monitor for methotrexate toxicity longer leucovorin rescue
phenytoin ⁴³	delayed, moderate, suspected; decrease phenytoin levels	decreased absorption or increased metabolism of phenytoin	monitor for phenytoin levels
probenecid ^{4,43}	rapid, major, probable; increased methotrexate levels	decreased renal excretion of methotrexate.	primarily a concern with high-dose methotrexate; monitor methotrexate levels i.e., longer leucovorin rescue
procarbazine ⁴³	delayed, major, possible; increased methotrexate renal toxicity	unknown	consider allowing an interval of ≥ 72 h between the administration of the final dose of procarbazine and the initiation of a high-dose methotrexate infusion
salicylates (e.g., ASA) ^{4,43,52,53}	rapid, major, suspected; increased methotrexate levels	decreased renal clearance and plasma protein binding of methotrexate	salicylate doses used for prophylaxis of cardiovascular events are not likely to be a concern; consider monitoring methotrexate levels
sulfonamides (e.g., co-trimoxazole, sulfamethoxazole, sulfisoxazole) ^{4,43,52,53}	delayed, major, suspected; increased methotrexate levels	decreased protein binding and renal clearance of methotrexate; methotrexate may induce folate deficiency, which can develop into acute megaloblastic anemia upon administration of timethoprin-sulfamethoxazole	primarily a concern with high-dose methotrexate; monitor methotrexate levels i.e., longer leucovorin rescue
tetracycline ⁴³	delayed, major, possible; increased methotrexate levels	unknown	monitor for methotrexate toxicity
theophylline ⁴	methotrexate may increase theophylline levels	decreased clearance of theophylline ⁵	monitor for theophylline levels ⁵
thiazides ⁴³	delayed, moderate, possible; increased methotrexate induced myelosuppression	unknown	consider alternative antihypertensive therapy
trimethoprim ⁴³	delayed, major, suspected; increased methotrexate toxicities	both drugs are folate antagonists and may have synergistic effect on folate metabolism	monitor for methotrexate toxicity

AGENT	EFFECT	MECHANISM	MANAGEMENT
urine alkalinizers (e.g., potassium acetate, potassium citrate, sodium acetate, sodium bicarbonate, sodium citrate, sodium lactate)	rapid, minor, possible; decreased methotrexate levels	increased renal excretion of methotrexate	no clinical intervention required

SUPPLY AND STORAGE:

Oral:

Accord Healthcare Inc.,⁵⁴ Apotex Inc.,⁵⁵ and Pharmascience Inc.⁵⁶ supplies methotrexate as 2.5 mg tablets. Tablets contain lactose. Store at room temperature and protect from light.

Pfizer Canada ULC supplies methotrexate as 10 mg tablets. Tablets contain lactose. Store at room temperature and protect from light.⁵⁷

Injection:

Pfizer Canada ULC supplies methotrexate as 20 mg/2 mL and 50 mg/2 mL ready-to-use, single use (preservative free) vials; as 500 mg/20 mL, 1 g/40 mL, and 2.5 g/100 mL ready-to-use, multi-dose (preservative free) vials; and as 50 mg/2 mL and 500 mg/20 mL ready-to-use, multi-dose (with preservative) vials. Store at room temperature. Protect from light.¹⁴

Accord Healthcare Inc. supplies methotrexate as 50 mg/2 mL, 500 mg/20 mL, and 1 g/40 mL ready-to-use, single use (preservative free) vials and 50 mg/2 mL and 500 mg/20 mL ready-to-use, multi-dose (with preservative) vials. Store at room temperature. Protect from light.¹⁵

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.

Additional information:

- methotrexate is sparingly soluble in acidic conditions and precipitation may occur²
- for intraocular use (i.e., intravitreal injection), preservative free methotrexate is preferred⁵⁸

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	can be used ⁸
<i>Intramuscular</i>	<i>inject into a suitable muscle</i> ^{11,14,59,60}
<i>Direct intravenous</i>	IV push ^{48,61}
<i>Intermittent infusion*</i>	<i>over 20 min to 24 h</i> ³⁰
<i>Continuous infusion*</i>	<i>over 24-42 h</i> ³⁰
Intraperitoneal	no information found

BC Cancer administration guideline noted in bold, italics	
Intrapleural	no information found
Intrathecal†	dilute in small volume (5-10 mL)⁶² preservative-free NS to a concentration of 1-2 mg/mL^{5,63} ; some clinicians use higher concentrations ⁶³
Intra-arterial	can be used ²
Intravesical	no information found
Intraocular ^{10,64,65}	has been used; give 0.1 mL as intravitreal injection in the affected eye

*High-dose methotrexate requires preservative-free methotrexate and leucovorin rescue.⁶⁶

†Intrathecal methotrexate requires preservative-free methotrexate. See [BC Cancer Policy III-50 Administration of High Alert Medications by the Intrathecal Route via Lumbar Puncture or Ommaya Reservoir](#).

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:

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

Oral:	Cycle Length: 1 week⁶⁷:	15-25 mg/m² PO for one dose on day 1 and then day 3 or 4 (total dose per cycle 30-50 mg/m ²)
	4 weeks⁶⁸⁻⁷¹	2.5 mg PO once or twice a day for 2 consecutive days starting on day 1 and 2 of each week* (total dose per cycle 20-40 mg) (*two non-consecutive days of the week have also been used for metronomic or low-dose dosing) ^{71,72}
Intravenous:	1 week⁶⁷:	40 mg/m² IV for one dose on day 1 (total dose per cycle 40 mg/m ²)
	1-3 weeks⁷³:	30-60 mg/m² IV for one dose on day 1 (total dose per cycle 30-60 mg/m ²)
	1-4 weeks^{74,75}:	1000-12000 mg/m² IV over 4 hours for one dose on day 1 (total dose per cycle 1000-12000 mg/m ²) requires leucovorin rescue (see <i>Special Precautions</i>)
	2 weeks^{59,60}:	0.4 mg/kg/day IV for one dose on days 1 to 5 max 25 mg/day (total dose per cycle 2 mg/kg; max 250 mg)
	2 weeks⁷⁶:	25 mg/m² IV for one dose on day 1 (total dose per cycle 25 mg/m ²)

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

	Cycle Length:	
	2 weeks ^{12,77,78:}	30 mg/m² IV for one dose on day 1 (total dose per cycle 30 mg/m ²)
	2 weeks ^{20:}	100 mg/m² IV for one dose and 300 mg/m² IV over 4 hours for one dose both on day 1 (total dose per cycle 400 mg/m ²) requires leucovorin rescue (see <i>Special Precautions</i>)
	2 weeks ^{19:}	100 mg/m² IV for one dose and 300 mg/m² IV over 4 hours for one dose both on day 8 (total dose per cycle 400 mg/m ²) requires leucovorin rescue (see <i>Special Precautions</i>)
	2 weeks ^{19:}	1000 mg/m² IV over 24 hours for one dose on day 8 (total dose per cycle 1000 mg/m ²) requires leucovorin rescue (see <i>Special Precautions</i>)
	3 weeks ^{18:}	3000 mg/m² IV over 4 hours for one dose on day 10 (total dose per cycle 3000 mg/m ²) requires leucovorin rescue (see <i>Special Precautions</i>)
	4 weeks ^{79,80:}	40 mg/m² IV for one dose on days 1 and 8 (total dose per cycle 80 mg/m ²)
	4 weeks ^{81:}	30 mg/m² IV for one dose on days 1 and 15 and 22 (total dose per cycle 90 mg/m ²)
<i>Intramuscular:</i>	2 weeks ^{11,59,60:}	50 mg IM for one dose on days 1, 3, 5, and 7 OR days 1, 3, 5, and 8 (total dose per cycle 200 mg)
	2 weeks ^{60:}	1 mg/kg IM for one dose on days 1, 3, 5, and 7 OR days 1, 3, 5, and 8 (total dose per cycle 4 mg/kg)
	weekly ^{14:}	15-30 mg IM for one dose on days 1-5 (total dose per cycle 75-150 mg)
	weekly ^{14:}	50 mg IM for one dose on day 1 OR 25 mg IM for one dose twice weekly (total dose per cycle 50 mg)
<i>Intrathecal:</i>	n/a	12 mg IT for one dose once or twice weekly ^{82,83} (maximum two IT injections per week)
	n/a	12-12.5 mg IT as part of combination therapy once weekly ^{18,19}

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

Intraocular: Cycle Length: **2-4 weeks**^{10,64,65;} **400 mcg/0.1 mL by intravitreal injection in the affected eye for one dose**

Concurrent radiation: increased risk of soft tissue necrosis and osteonecrosis²

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

Dosage in renal failure:

Suggested dose modifications^{84:}

Creatinine clearance (mL/min)	Methotrexate dose
61-80	75%
51-60	70%
10-50	30-50%
<10	avoid

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

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

OR alternately, for creatinine clearance less than 100 mL/min, reduce methotrexate dose proportionately to the reduction in creatinine clearance:^{16,17,85,86}

e.g., CrCl ≥100 mL/min, give 100% of dose

CrCl = 85 mL/min, give 85% of dose

CrCl = 60 mL/min, give 60% of dose

Metronomic or low-dose dosing:

Suggested dose modifications:^{68,69,72}

Creatinine clearance (mL/min)	Methotrexate dose
>30	100%
15-30	50%
<15	avoid

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

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

Dosage in hepatic failure:

Suggested dose modifications^{84,87}

Bilirubin (micromol/L)	or	AST (units/L)	Dose
50-85		3 x ULN	75 %
>85		-	avoid

Dosage in dialysis^{88:}

hemodialysis: 50% dose

chronic ambulatory peritoneal dialysis (CAPD): no information found

continuous renal replacement therapy (CRRT): 30-50% dose

Children:

	Cycle Length:	
<i>Oral, Intramuscular, Subcutaneous</i> ⁸ :	1-2 weeks:	7.5-30 mg/m ²
<i>Intravenous</i> ⁸ : <i>bolus or continuous infusion (6-24 h)</i>	n/a	10-33,000 mg/m ² *
		*Doses above 100 to 300 mg/m ² , which are usually administered by continuous infusion, must be followed by leucovorin rescue. ⁸
<i>Intrathecal</i> ⁸ :	n/a	6 mg (age <1 yr) 8 mg (age 1 yr) 10 mg (age 2 yr) 12 mg (age ≥3 yr)

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