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 mg/m^2) to high-dose methotrexate ($\geq$ 1000 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 reference[2] unless specified otherwise.

USES:

Primary uses:
*Bladder cancer
*Breast cancer
*Gastric cancer
*Choriocarcinoma
*Head and neck cancer
*Leptomeningeal cancer
*Leukemia, acute meningeal
*Leukemia, acute lymphoblastic
*Leukemia, acute lymphocytic
*Lymphoma, Burkitt's
*Lymphoma, childhood
*Lymphoma, non-Hodgkin's
*Mycosis fungoides
*Primary unknown cancer
*Sarcoma, lymphatic
*Sarcoma, osteogenic

*Health Canada approved indication

Other uses:
Esophageal cancer[4]
Lung cancer[4]
Testicular cancer[4]

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.[9]

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]

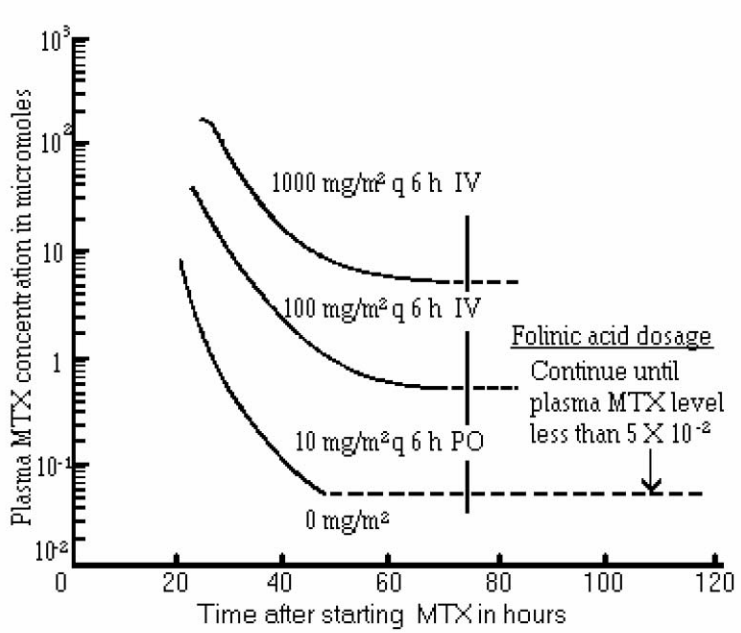
Carcinogenicity: Not yet studied.[5]

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

Fertility[2]: Methotrexate can induce a spontaneous abortion in pregnant women especially if given in the first trimester. Methotrexate therapy may result in impairment of fertility, oligospermia, and menstrual dysfunction in humans, during and for a short period after cessation of therapy. Pregnancy should be avoided if either partner is receiving methotrexate.
- Males: during and for a minimum of three months after therapy.
- Females: during and for at least one ovulatory cycle after therapy.

Pregnancy: FDA Pregnancy Category D. 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 is contraindicated as methotrexate is detected in human breast milk.[2]
Leucovorin rescue[4]: is required in some methotrexate regimens.
Methotrexate dose:
- >500 mg/m^2 requires leucovorin rescue.
- 100-500 mg/m^2 may require leucovorin rescue.



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

Note: 0.05 micromol/L = 5 x 10^{-2} micromoles/L

Leucovorin dose PO/IV/IM (see Bleyer nomogram):
- 10-25 mg/m^2 every 6 hours for approximately 8 to 10 doses, starting 24 hours after the start of methotrexate infusion.[4,10-14] (note: for leucovorin doses >25 mg administer IV).[15]
- 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.[10-12]
- Continue until the methotrexate level is <0.05 to 0.1 micromol/L.[16,17] 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.[18]

Note: Leucovorin doses >25 mg should be given IV[15]

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.[19] 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 ***bold, italics***	
allergy/immunology	anaphylaxis (<1%)
	vasculitis (1-10%)
auditory/hearing	tinnitus
blood/bone marrow/ febrile neutropenia	anemia
	neutropenia: WBC 1st nadir 4-7 days with recovery in 7-13 days; 2nd nadir 12-21 days with recovery in 15-20 days[20]
	thrombocytopenia: platelet nadir 5-12 days with recovery in 15-27 days[20]
cardiovascular (general)	hypotension
	pericardial effusion
	pericarditis
constitutional symptoms	chills and fever (frequent)[20]
	fatigue (frequent)[20]
	malaise (1-10%)
	mood alteration; with low-dose methotrexate
dermatology/skin	*extravasation hazard:* none[21]
	acne
	alopecia (1-10%); usually reversible but may require several months[20]
	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[20]
	reddening of skin (>10%)
	skin necrosis[3]
	telangiectasia
	urticaria
endocrine	diabetes (1-10%)
gastrointestinal	*emetogenic potential*[22]*:* dose-related: 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
	anorexia (>10%)
	diarrhea (>10%)
	gingivitis (>10%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	glossitis (>10%)
	nausea; dose-related
	perforation (>10%)[4]
	pharyngitis
	stomatitis (>10%)
	vomiting; dose-related
hemorrhage	ecchymoses, petechiae
	hematemesis[5]
	hematuria
	melena[5]
hepatobiliary/pancreas	pancreatitis
hepatic	***hepatoxicity*** (1-10%)
metabolic/laboratory	***azotemia***; more common with high-dose methotrexate than with low-dose[19]
	hyperuricemia (>10%)
	liver function tests, elevated[5]; usually transient, asymptomatic and return to normal within 10 to 14 days[19]
musculoskeletal	arthralgia/myalgia (1-10%)
	hemiparesis
	osteoporosis, fractures; with high-dose methotrexate[20]
	osteonecrosis
	soft tissue necrosis
neurology	***neurotoxicities*** (>10%); with intrathecal administration or high-dose methotrexate
	cognitive dysfunction, mild transient (<1%); with low-dose methotrexate[20]
	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[20]
pulmonary	***pulmonary toxicity*** (2-8%)[23]; can occur with all doses of methotrexate, although more often with chronic low-dose[19]
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***[20]
	gynecomastia

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	loss of libido/impotence
	menstrual dysfunction
	oogenesis, interference with
	spermatogenesis, interference with
	vaginal discharge
syndromes	***acute neurologic syndrome*** (<1%); with high-dose methotrexate
	tumour lysis syndrome; especially when given for systemic Burkitt's lymphoma[19]
vascular	cerebral thrombosis
	deep vein thrombosis
	pulmonary embolism
	retinal vein thrombosis

Adapted from standard references[2,24] unless specified otherwise.

Hepatotoxicity: Methotrexate-induced hepatotoxicity can be seen with both high and low-dose methotrexate, and can be life-threatening.[20] 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.[25] Cirrhosis and fibrosis are more often seen with chronic low-dose methotrexate.[8,25] See Dosing guidelines for hepatic failure. Patients should be warned to avoid alcohol, prescription medications or herbal supplements that may increase risk of hepatotoxicity.[19]

Pulmonary toxicity: Methotrexate-induced pulmonary toxicity can be seen with both high and low-dose methotrexate, and can be life-threatening.[20] Pulmonary toxicity can be either symptomatic or asymptomatic and can be caused by inflammation, infection or neoplasia.[20]

- Inflammatory lung disease: most common here is hypersensitivity pneumonitis.[23]
- Pulmonary infections: opportunistic infections due to compromised immune system.[23]
- Pulmonary lymphoma: Non-Hodgkin's (B cell) lymphoma which regresses after discontinuation of methotrexate.[23]

Methotrexate-induced pulmonary toxicity can be acute, subacute, or chronic.[23] 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.[23] Subacute toxicity is the most common and includes dyspnea, non-productive cough, fever, crackles, cyanosis, pulmonary fibrosis, pleural effusions.[23] Treatment includes discontinuing methotrexate and initiating corticosteroid therapy.[23] Improvement can occur within days of stopping methotrexate; rechallenging with the drug is not recommended.[23]

Acute renal failure: High-dose methotrexate-induced renal failure is a medical emergency because methotrexate is mainly eliminated by the kidneys.[26] 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.[19] Management should include continued monitoring of methotrexate levels, administration of leucovorin (see leucovorin rescue) and alkalinized intravenous fluids until plasma levels fall below 0.05 micromol/L.[19]

Glucarpidase *(carboxypeptidase-G2,* CPDG2, VORAXAZE®[27,28]) is a recombinant bacterial enzyme that inactivates extracellular methotrexate to 2,4-diamino-N^{10}–methylpteroic acid [DAMPA].[27] Glucarpidase can rapidly lower serum methotrexate levels by >95% within 15 minutes of administration.[29] 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.[27] Also, leucovorin should be continued after administration of glucarpidase, which may deactivate the active metabolite of leucovorin[3031] (see below).

Glucarpidase can be used to treat patients at risk for methotrexate toxicity secondary to delayed elimination[27] and is available through the Health Canada Special Access Programme:

- Glucarpidase 50 units/kg IV over 5 minutes[27]
  - For methotrexate level > 100 micromol/L, may give second dose of glucarpidase 48 hours after administration of first dose.[32]
- High-dose leucovorin (eg, 1000 mg/m2 IV every 6 hours) should be given prior to the receipt and administration of glucarpidase.[32]
  - Leucovorin should be given at least 2-4 hours before or after administration of glucarpidase.[27]
  - 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.[32]
  - 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.[27]

Neurologic complications[24]: 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.[20]

For Intrathecal (IT) administration

- Aseptic meningitis[24]: 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 myelopathy[24]: This is much less common[24]; 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.
- Leukoencephalopathy[24]: 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.[24]

For high-dose methotrexate ($\geq$ 1000 mg/m^2)

- Acute neurotoxicity[24]: includes somnolence, confusion, and seizures within 24 hours of treatment. These usually resolve spontaneously; rechallenge is possible.
- Subacute neurotoxicity[24]: 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, see above.

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[33] 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[34]:

- 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.[35] It may be used for treatment or

prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminium hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminium hydroxide has been added, discontinue sodium bicarbonate.[36]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
acitretin[4,37]	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[37]	delayed, moderate, possible; decreased methotrexate levels	decreased GI absorption of methotrexate	consider parenteral use of methotrexate
amiodarone[37]	delayed, major, possible; increased methotrexate levels	unknown	consider monitoring for methotrexate toxicity
asparaginase[38]	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[37]	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)[39]	may decrease methotrexate levels	decreased absorption of methotrexate[39]	separate the administration of these drugs by 2 or more hours
caffeine[37]	delayed, moderate, possible; decreased methotrexate antirheumatic effect	unknown	monitor clinical response; consider reduction in caffeine intake if needed
carboxypeptidase G2 (CPDG2)[40]	decreased toxicity of methotrexate	rapidly metabolizes methotrexate	may be used to rapidly lower serum methotrexate
chloroquine[37]	delayed, minor, possible; decreased methotrexate antirheumatic effect	unknown	monitor clinical response; consider increase in methotrexate dose
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

AGENT	EFFECT	MECHANISM	MANAGEMENT
cyclosporine[4]	may increase both methotrexate and cyclosporine toxicity	unknown[41]	monitor for both cyclosporine and methotrexate toxicity[41]
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[37]	delayed, moderate, suspected; decreased digoxin levels	decreased GI absorption of digoxin	monitor for digoxin pharmacologic effects
doxycycline[37]	delayed, major, possible; increased methotrexate levels	unknown	monitor for methotrexate toxicity
haloperidol[37]	delayed, moderate, possible; increased methotrexate dermatological toxicity	unknown	monitor for methotrexate toxicity
hydroxychloroquine[37]	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[4,37]	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)[4,37]	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)[7,42-45]	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
penicillins (e.g., amoxicillin, piperacillin, ticarcillin)[4,37]	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

AGENT	EFFECT	MECHANISM	MANAGEMENT
phenytoin[37]	delayed, moderate, suspected; decrease phenytoin levels	decreased absorption or increased metabolism of phenytoin	monitor for phenytoin levels
probenecid[4,37]	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[37]	delayed, major, possible; increased methotrexate renal toxicity	unknown	consider allowing an interval of $\geq$ 72 h between the administration of the final dose of procarbazine and the initiation of a high-dose methotrexate infusion
salicylates (e.g., ASA)[4,37,46,47]	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)[4,37,46,47]	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[37]	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[37]	delayed, moderate, possible; increased methotrexate induced myelosuppression	unknown	consider alternative antihypertensive therapy
trimethoprim[37]	delayed, major, suspected; increased methotrexate toxicities	both drugs are folate antagonists and may have synergistic effect on folate metabolism	monitor for methotrexate toxicity
urine alkalizers (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:
Apotex supplies methotrexate as a 2.5 mg tablet.[48] Selected non-medicinal ingredients: lactose.[48] Store at room temperature and protect from light.[48]

Wyeth supplies methotrexate as a 2.5 mg tablet.[49] Selected non-medicinal ingredients: lactose. Store at room temperature and protect from light.[49]

Injection:
Hospira Healthcare Corporation supplies methotrexate as 20 mg/2 mL and 50 mg/2 mL single-use vials of sterile solution without preservative, and 50 mg/2 mL and 500mg/20 mL vials of sterile solution with preservative. In addition, Hospira Healthcare Corporation supplies methotrexate as 500 mg/20 mL, 1g/40 mL, and 2.5g/100 mL bulk vials of sterile solution without preservative for pharmacy use only. Store at room temperature. Protect from light.[50]

Novopharm Limited supplies methotrexate as 50 mg/2 mL, 100 mg/4 mL, and 200 mg/8 mL vials of sterile solution without preservative. Store at room temperature. Protect from light.[51]

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[2]: Methotrexate is sparingly soluble in acidic conditions and precipitation may occur.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	can be used[8]
Intramuscular	can be used[2]
Direct intravenous	IV push[42,52]
Intermittent infusion*	***in a suitable volume of compatible IV solution and administer over 20 min to 24 h***
Continuous infusion*	***in a suitable volume of compatible IV solution and administer over 24-42 h[24]***
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal†	***dilute in small volume (5-10 mL)[53] preservative-free NS to a concentration of 1-2mg/mL[5,54];*** some clinicians use higher concentrations[54]
Intra-arterial	can be used[2]
Intravesical	no information found

*High-dose methotrexate requires preservative-free methotrexate and leucovorin rescue.[55]

†Intrathecal methotrexate requires preservative-free methotrexate. See *BC Cancer Agency Policy III-50 Administration of Cytotoxic Drugs by the Intrathecal Route via Lumbar Puncture or Ommaya Reservoir* in Appendix.

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***

	Cycle Length:	
Oral:	1 week[56]:	***15-25 mg/m^2 PO for one dose on day 1 and then day 3 or 4 (total dose per cycle 30-50 mg/m^2)***
	4 weeks[57-60]	***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)[60,61]
Intravenous:	1 week[56]:	***40 mg/m^2 IV for one dose on day 1 (total dose per cycle 40 mg/m^2)***
	1-3 weeks[62]:	***30-60 mg/m^2 IV for one dose on day 1 (total dose per cycle 30-60 mg/m^2)***
	1-4 weeks[63,64]:	***1000-12000 mg/m^2 IV over 4 hours for one dose on day 1 (total dose per cycle 1000-12000 mg/m^2) requires leucovorin rescue (see special precautions)***
	2 weeks[65]:	***25 mg/m^2 IV for one dose on day 1 (total dose per cycle 25 mg/m^2)***
	2 weeks[14]:	***100 mg/m^2 IV for one dose and 300 mg/m^2 IV over 4 hours for one dose both on day 1 (total dose per cycle 400 mg/m^2) requires leucovorin rescue (see special precautions)***
	2 weeks[13]:	***100 mg/m^2 IV for one dose and 300 mg/m^2 IV over 4 hours for one dose both on day 8 (total dose per cycle 400 mg/m^2) requires leucovorin rescue (see special precautions)***
	2 weeks[13]:	***1000 mg/m^2 IV over 24 hours for one dose on day 8 (total dose per cycle 1000 mg/m^2) requires leucovorin rescue (see special precautions)***
	3 weeks[12]***:***	***3000 mg/m^2 IV over 4 hours for one dose on day 10 (total dose per cycle 3000 mg/m^2) requires leucovorin rescue (see special precautions)***
	4 weeks[66,67]:	***40 mg/m^2 IV for one dose on days 1 and 8***

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

	Cycle Length:	
		(total dose per cycle 80 mg/m^2)
	4 weeks[68]:	***30 mg/m^2 IV for one dose on days 1 and 15 and 22 (total dose per cycle 90 mg/m^2)***
Intrathecal:	n/a	***12 mg IT for one dose once or twice weekly[69,70] (maximum two IT injections per week)***
	n/a	***12-12.5 mg as part of combination therapy once weekly[12,13]***

Concurrent radiation: increased risk of soft tissue necrosis and osteonecrosis[2]

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)	Methotrexate dose
61-80	75%
51-60	70%
10-50	30-50%
< 10	avoid

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

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

OR alternately, for creatinine clearance <100 mL/min, reduce methotrexate dose proportionately to the reduction in creatinine clearance:[10,11,72,73]
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:[57,58,61]

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

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

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

Dosage in hepatic failure: Suggested dose modifications[71,74]

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

Dosage in dialysis[75]: hemodialysis: 50% dose
chronic ambulatory peritoneal dialysis (CAPD): no information found
continuous renal replacement therapy (CRRT): 30-50% dose

Children:

	Cycle Length:	
Oral, Intramuscular, Subcutaneous[8]:	1-2 weeks:	7.5-30 mg/m^2
Intravenous[8]: bolus or continuous infusion (6-24 h)	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]

Intrathecal[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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