Drug Monograph

A - Drug Name

methotrexate

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B - Mechanism of Action and Pharmacokinetics

Methotrexate and its active metabolites compete for the folate binding site of the enzyme dihydrofolate reductase. Folic acid must be reduced to tetrahydrofolic acid by this enzyme for DNA synthesis and cellular replication to occur. Competitive inhibition of the enzyme leads to blockage of tetrahydrofolate synthesis, depletion of nucleotide precursors, and inhibition of DNA, RNA and protein synthesis. Methotrexate also inhibits thymidylate synthase and the transport of reduced folates into the cell. Methotrexate is cell cycle phase-specific (S phase).

Absorption	Peak serum levels are achieved in 1-2 h (PO) and 30-60 min (IM).	
	Bioavailability	oral: 60% bioavailability at doses <30 mg/m^2 in most patients. Significantly less bioavailability at > 80 mg/m^2. Bioavailability decreased by food and milk.
Distribution	Highest levels in kidney, gallbladder, spleen, liver and skin, retained in kidney and liver for prolonged periods. Methotrexate crosses the placenta, is found in breast milk and malignant effusions. Some accumulation may occur with repeated daily dosing, especially in liver.	
	Cross blood brain barrier?	poorly
	PPB	50 %

Metabolism	Methotrexate is partially metabolized by intestinal flora after oral administration. Low dose methotrexate does not appear to undergo significant metabolism. Following high dose treatment, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms that can be converted back to methotrexate by hydrolases. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of polyglutamates may remain in tissues for extended periods. Methotrexate also undergoes minor metabolism into 7-hydroxymethotrexate (with lower solubility); accumulation may become significant after high dose methotrexate. Active metabolites: Polyglutamates Inactive metabolites: Yes, including 7-hydroxy-methotrexate
Elimination	Excreted principally by the kidney (80-90%) by glomerular filtration and active tubular secretion; biliary excretion is < 10%, significant inter- and intrapatient variability. Clearance is delayed in the presence of a third compartment fluid collection (i.e. pleural effusion, ascites). Enterohepatic recirculation of methotrexate may occur. Clearance relates inversely with dose. Urine: 80-90% excreted unchanged Half-life: 3-10 hours (low dose, < 30mg/m^2) 8-15 hours (high dose)

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C - Indications and Status

Health Canada Approvals:

- Breast cancer
- Bladder cancer
- Choriocarcinoma
- Gastric cancer
- Head and neck cancer
- Osteogenic sarcoma
- Non-Hodgkin lymphoma (intermediate and high grade, Burkitt)
- Advanced stages of childhood lymphoma (III and IV, St. Jude's Childrens' Research Hospital Staging System)
- Acute lymphoblastic leukemia

- Advanced stages of mycosis fungoides (cutaneous T-cell lymphoma)
- Metastasis of unknown primary
- Leptomeningeal spread of malignancies (carcinomatosis/leukemia/lymphoma)

Refer to the product monograph for a full list and details of approved indications.

Other Uses:

- Gestational Trophoblastic Disease
- Desmoid and Giant Cell tumour sarcoma
- Hematological malignancies (acute myeloid leukemia, acute promyelocytic leukemia, myeloma, T-cell lymphoma, low grade Non-Hodgkin lymphoma)

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D - Adverse Effects

Emetogenic Potential: Moderate (IV doses ≥ 250 mg/m2)
Low (IV doses > 30 and < 250 mg/m2)
Minimal (IV doses ≤ 30mg/m2 or PO doses)

Extravasation Potential: Minimal

The incidence and severity of side effects vary depending on the dose, frequency of administration and the duration of exposure to significant blood methotrexate levels to the target organs. Side effects, including severe or life-threatening adverse effects and post-marketing, are listed in the table below.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (rare)	E
	Hypotension (rare)	E
	Pericarditis , pericardial effusion (rare)	E
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (occasional)	E
	Erythema multiforme (rare)	E
	Photosensitivity (rare)	E
	Radiation recall reaction	I E
	Rash (1 to <10%; may rarely be severe)	I E
	Skin hyperpigmentation (rare)	E
	Skin hypopigmentation	E

	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Anorexia (≥10%)	E
	Diarrhea (1 to <10%; especially 24-48h after administration)	E
	Dyspepsia (≥10%)	E
	GI perforation (rare)	E
	Mucositis (≥10%) (may be severe)	E
	Nausea, vomiting (10%) (dose-dependent)	I
General	Fatigue (1 to <10%)	E
Hematological	↓ Immunoglobulins (rare)	E
	Myelosuppression ± infection, bleeding (1 to <10%)	E
	Other - Aplastic anemia (rare)	E
Hepatobiliary	↓ albumin (rare)	E
	Cirrhosis (or hepatic fibrosis; with long-term, low-dose use) (<1%)	L
	↑ LFTs (15%) (transient)	E
	Pancreatitis (rare)	E
Hypersensitivity	DRESS syndrome (rare)	E
	Hypersensitivity (rare)	I
Infection	Opportunistic infection or viral reactivation (rare)	E
Metabolic / Endocrine	Diabetes mellitus (rare)	E
	Tumor lysis syndrome (rare)	I
Musculoskeletal	Fracture (rare)	D
	Musculoskeletal pain (rare)	E
	Osteoporosis (rare)	D
	Other - osteonecrosis (rare, secondary to lymphoproliferative disorders)	E D
Neoplastic	Lymphoma (secondary) (low-grade; rare)	L
Nervous System	Cognitive disturbance (rare)	E
	Dizziness (rare)	E
	Headache (1 to <10%)	E
	Leukoencephalopathy (rare; acute or chronic)	L
	Seizure (rare)	E
Ophthalmic	Blurred vision (rare; transient visual changes)	E

	Conjunctivitis (rare)	E
Renal	Nephrotoxicity (especially with high doses; rare)	E
	Proteinuria (rare)	E
Reproductive and breast disorders	Infertility (rare)	E D
	Irregular menstruation (rare)	E D
	Oligospermia (rare)	E D
Respiratory	Other - Alveolar hemorrhage (rare)	E
	Pneumonitis (1%)	E
Vascular	Vasculitis (rare; including allergic)	I E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common adverse effects are **stomatitis, myelosuppression and gastrointestinal** effects such as **nausea.** Toxicity is increased with prolonged duration of exposure as well as increased dose, and exacerbated by renal failure, NSAID usage, 3rd space collections and dehydration. Consider monitoring serum levels with any dose in such circumstances.

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (e.g., some leukemias and lymphomas), can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalinized, by addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

Risk factors for **stomatitis** include renal impairment, irradiation to the head and neck area and prolonged infusion. Administration of leucovorin decreases the risk of toxicity to the gastrointestinal tract.

Severe skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis have been reported and may be fatal. These reactions are not dose-dependent and may occur within days of administration of oral, IM or IV methotrexate. Recovery has been reported with treatment discontinuation.

Skin cancer has been reported in psoriasis or mycosis fungoides patients, who received concomitant methotrexate and psoralen plus ultraviolet light therapy (PUVA).

Renal toxicity may be related to precipitation of methotrexate and 7-OH methotrexate (less soluble than methotrexate) in the renal tubules and collecting ducts. Methotrexate was found to be 10 times less soluble in acidic urine than urine at pH 7. The risk of renal failure due to high-dose methotrexate (>1 g/m^2) can be minimized by brisk diuresis, alkalinization of the urine (adjust urinary pH with IV sodium bicarbonate to maintain pH > 7), and monitoring of creatinine and serum methotrexate

levels.

Acute elevation of hepatic enzymes is usually transient and asymptomatic. Decrease in serum albumin or persistent liver abnormalities may indicate serious liver toxicity. This occurs more frequently in patients receiving moderate to high methotrexate doses. Chronic hepatotoxicity (fibrosis or cirrhosis) is more common in patients receiving long term (usually more than 2 years) and after a cumulative dose of at least 1.5g, and may be fatal. Reactivation or worsening of hepatitis B and C infections, including fatal cases, have been observed with methotrexate. Some cases occurred after treatment discontinuation.

Clearance of methotrexate is delayed in the presence of **fluid in the third space (e.g., pleural effusions, ascites)**, and toxicity may be enhanced. It is recommended that such effusions be evacuated before treatment with methotrexate.

Myelosuppression may develop with any dosage schedule, but is more severe with high doses, daily administration of lower doses, in malnourished patients, in patients with decreased renal function and in patients with effusions, ascites or significant edema. Administration of leucovorin decreases the risk of myelosuppression when given with high-dose methotrexate. The nadir of leukocytes, neutrophils and platelets usually occurs between 4 to 13 days after an IV bolus, followed by recovery 2-4 weeks after the dose. Occasionally, the decrease in leukocytes and neutrophils may present as 2 nadirs; the first after 4-7 days and the second after 12-21 days, followed by recovery.

Methotrexate has the ability to enhance radiation injury to tissues. While often called **radiation recall reactions**, the timing of the radiation may be before, concurrent with or even after the administration of the methotrexate. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

Chemical meningitis may occur with intrathecal methotrexate, beginning within 12 hours after injection, and may persist for ≥ 1 week. This is characterized by stiff neck, headache, back pain, nausea and vomiting, fever and lethargy. Administration at intervals of less than 1 week may result in increased subacute toxicity. The syndrome may be subacute (paraplegias/paresthesia) or chronic (leukoencephalopathy), and transient or permanent. Risk factors include advanced age, methotrexate dose used, presence of overt meningeal leukemia, or concurrent cranial radiation.

Other CNS toxicities include an **acute or subacute encephalopathy** consisting of behavioural abnormalities, focal sensorimotor signs, abnormal reflexes or hemiparesis, occasionally with seizures, in patients receiving high-dose methotrexate. The exact cause is unknown. It has occurred within 2-4 weeks of high-dose methotrexate treatment, and is usually transient.

Delayed neurotoxicity, occurring months to years after methotrexate, can be severe and even fatal. This syndrome, a progressive **leukoencephalopathy**, is rare and usually associated with some combination of cranial irradiation, systemic methotrexate and intrathecal methotrexate. Clinical signs are those of progressive neurologic deterioration and include confusion, ataxia, dementia, limb spasticity, coma, seizures and death. Prognosis with leukoencephalopathy is variable; most patients have continued neurological deficits. The syndrome may be partially reversible if methotrexate is discontinued. The risk of leukoencephalopathy is increased with increasing cumulative doses of methotrexate (may also occur with low oral doses), by concurrent cranial radiation and when methotrexate IT is used to treat meningeal tumour rather than for prophylaxis.

Pulmonary toxicity can be immediate or delayed. It is not always fully reversible and may be fatal. The immediate toxicity is associated with pneumonitis, acute pleuritic chest pain and chronic non-productive cough. Pulmonary toxicity does not appear to be dose-related. It appears to be schedule-dependent, since daily or weekly administration schedules are more toxic than every 2-4 week administration schedules, but there does not appear to be a threshold. Corticosteroids may hasten recovery.

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E - Dosing

Evaluate any pre-existing hepatitis B and C before starting treatment.

Methotrexate is frequently administered in combination with other drugs. Hydration, urine alkalinization, leucovorin rescue and monitoring of levels may be required depending on the dose used.

Risk factors for elevated or prolonged methotrexate levels include third space fluid accumulation, GI obstruction, previous cisplatin therapy, dehydration, aciduria and impaired renal function.

Table 1:

	100-500 mg/m^2	500-1000 mg/m^2	≥ 1000mg/m^2
Hydration and alkalinization of urine	Consider*	Yes	Yes
Leucovorin rescue	Consider*	Yes	Yes
Methotrexate levels		Consider*	Yes
* especially if risk factors			

Adults:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy.

Some examples include:

Oral (for administration of low doses):

- Q 2-3 w: 10-30 mg/day for 5 days
- Q4w: 40 mg/m^2 days 1 and 8

Intravenous (low doses may be given as IM depending on the protocol):

- Q4w: 40 mg/m^2 day 1 and 8;
- Q4w: 30 mg/m^2 days, 1, 15, 22
- Q3w: 30 mg/m^2 days 1 and 8
- Weekly: 30 – 60 mg/m^2
- Q3-4w: 120 mg/m^2 - 1.5 g/m^2 (also refer to table 1)
- Depend on protocol: 3.5 g/m^2 – 12 g/m^2 (also refer to table 1)

Intrathecal:

- Q2-7d: 12 mg in preservative-free NS
- Dose is the same whether given intrathecally or into an Ommaya (intraventricular) reservoir. Elderly patients may require a reduced dose.

Dosage with Toxicity:

Toxicity	Action
Grade 4 neutropenia or thrombocytopenia, febrile neutropenia or thrombocytopenic bleeding	Hold until recovery * and then reduce by 25%
Grade 3 non-hematologic/organ	Hold until recovery * and then reduce by 25%
Grade 4 non-hematologic/organ	Discontinue
Suspected pneumonitis	Hold, investigate appropriately and discontinue if confirmed
Leukoencephalopathy, hepatic fibrosis, viral reactivation	Discontinue
* until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and other toxicity ≤ grade 2	

Overdose or Severe Toxicity: Can be treated with prompt leucovorin rescue. Acute, intermittent dialysis with a high-flux dialyzer has also been used. Hydration and urinary alkalinization may prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. There have been case reports of intravenous carboxypeptidase G2 use in cases of overdose to hydrolyze methotrexate to inactive metabolites and hasten clearance.

Dosage with Hepatic Impairment:

Bilirubin (µmol/L)		Transaminases	% usual dose
2.5 - 4 x ULN	or	> 3 x ULN	75%
> 4 x ULN			DISCONTINUE

Dosage with Renal Impairment:

Methotrexate is **contraindicated** in patients with severe renal impairment. The following are recommended starting doses in patients with renal impairment. May require further dose adjustment due to wide inter-subject variability in pharmacokinetics.

Creatinine clearance (mL/min)	Starting dose (% usual dose)
>80	100%
80	75%
60*	60%
50*	55%
<50	Use alternative therapy
*High-dose methotrexate treatment should be given only if Clcr > 60 mL/min.	

Dosage in the elderly:

Methotrexate has not been well studied in the elderly. It should be used with extreme caution because of likely renal and hepatic impairment and reduced folate stores in the elderly. Monitor closely. Consider lower doses with intrathecal usage.

Children:

Refer to protocols being used. Methotrexate solutions containing benzyl alcohol should not be used in neonates (less than 1 month of age).

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F - Administration Guidelines

- Preservative-free methotrexate must be used for intrathecal, intracerebroventricular, high dose administration, or in neonates (less than one month of age).
- Do not admix with 5FU, prednisolone, KCl or other drugs unless compatibility data are available.
- Avoid contact with acidic solutions since methotrexate precipitation may occur.
- May be given IM or by IV push, depending on the dose and regimen.
- May also be admixed in Normal Saline or 5% dextrose; the manufacturer recommends dilution to a concentration of 0.4 to 2 mg/mL. Infuse IV over 30 minutes to 24 hours, depending on the regimen.
- Store unopened vials between 15 to 25ºC. Protect from light.

Methotrexate (High dose >1g/m^2) - The following steps are **MANDATORY**:

- Preservative-free methotrexate formulation must be used
- Alkalinization and hydration (example):
  - Hydrate with 1000 mL/m^2 of IV fluid over 6 hours before starting methotrexate infusion. Continue hydration at 125mL/m^2/h (3L/m^2/day) during the methotrexate infusion, and for 2 days after the infusion is completed.
  - Alkalinize urine, starting 6-12 hours before Methotrexate, with IV or PO Sodium Bicarbonate; ensure urine pH > 7 before starting methotrexate. Maintain urine pH > 7.
- Continue hydration and alkalinization during methotrexate infusion and for 48h after completion of Methotrexate infusion
- Leucovorin rescue to start 24-36 hours after start of Methotrexate; continue until serum levels drop below 0.1 micromolar (toxic range depends on local policy and methotrexate assays used). Refer to Leucovorin monograph).

Intrathecal Methotrexate:

- Preservative-free formulation must be used
- Mix with preservative-free diluent using strict aseptic technique.

Oral Methotrexate:

- Avoid taking methotrexate tablets with food or milk, as absorption may be reduced.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to methotrexate or any components of the formulation or container
- Patients with severe renal impairment including end stage renal disease with and without dialysis
- Women of childbearing potential until pregnancy is excluded
- Breastfeeding women
- Concomitant use with nitrous oxide anesthesia
- Formulations containing benzyl alcohol are contraindicated for use in intrathecal, intracerebroventricular, high-dose therapy, or neonates (less than one month of age)

Refer to the product monograph for contraindications related to the treatment of psoriasis or rheumatoid arthritis.

Other Warnings/Precautions:

- Use with extreme caution in patients with a history of peptic ulceration or ulcerative colitis and in patients with poor performance status, with active infection, impaired bone marrow function, prior or current wide field radiation, chronic liver disease, cirrhosis or with mild or moderate renal impairment.
- Avoid the use of live vaccines.
- Immunization may be ineffective when given during methotrexate treatment.
- Rare hypogammaglobulinemia has been reported.
- Not recommended in patients with active or chronic hepatitis B or C infection.
- Use caution with administration of packed red blood cells and methotrexate. Increased toxicity, probably due to prolonged high methotrexate concentrations, have been observed in patients

receiving 24-hour methotrexate infusion and subsequent transfusion.

- Folate deficiency states may increase methotrexate toxicity.
- Methotrexate tablets containing lactose should not be used in patients with hereditary lactose/galactose/lactase disorders.
- Patients with relevant third space fluid collections have prolonged excretion of methotrexate levels and a resulting increase in toxicity. Evacuation of fluid collections and close monitoring of serum levels are recommended in such patients.
- There may be an increased risk of tissue necrosis or osteonecrosis when methotrexate is given concurrently with radiotherapy.

Other Drug Properties:

- Carcinogenicity: Possible
  Lymphoma may occur in patients receiving low-dose methotrexate. This may regress after stopping methotrexate.

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Teratogenicity: Yes
  Methotrexate is **contraindicated** in pregnancy and breastfeeding. It has been reported to cause fetal death and/or congenital anomalies. Abortion is likely when administered to a pregnant woman. Adequate contraception should be used in both sexes, during treatment and for at least **6 months** after the last dose.
- Breastfeeding: Contraindicated
  Methotrexate is secreted in human breast milk in small concentrations and may accumulate in neonatal tissues.
- Fertility effects: Yes

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H - Interactions

Methotrexate given concurrently with radiotherapy may increase the risk of soft tissue necrosis or osteonecrosis.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Acitretin/etretinate	Risk of hepatotoxicity observed in patients on etretinate and methotrexate	Unknown	Contraindicated.
Alcohol	↑ hepatotoxicity	Additive	Avoid alcohol intake.

Asparaginase	↑ hepatotoxicity	Additive effect on liver	Monitor liver function.
Asparaginase	↓ effect of methotrexate if asparaginase is given immediately prior to or with methotrexate; ↑ effect of methotrexate when asparaginase is given after methotrexate	Suppression of asparagine concentrations; asparaginase decreases methotrexate cellular uptake or inhibits the cell replication necessary for methotrexate action	Give asparaginase 9-10 days before or 24 hours after methotrexate, or refer to specific protocol.
Carboxypeptidase-G	↓ toxicity of methotrexate	Cleaves the methotrexate molecule to inactive fragments	May be useful to treat IT methotrexate overdose or delayed methotrexate toxicity.
Certain oral antibiotics (tetracycline, chloramphenicol, or non-absorbable: neomycin, polymyxin B, nystatin, vancomycin)	May ↓ methotrexate serum concentration	↓ intestinal absorption of methotrexate, interferes with enterohepatic circulation	Observe for ↓ therapeutic response of methotrexate.
Cyclosporine	↑ methotrexate and cyclosporine toxicity	Blocks methotrexate oxidation to inactive metabolite; affects elimination of both drugs	If must use together, monitor patient closely for cyclosporine and methotrexate toxicity.
Cytarabine IV	Severe neurological reactions in children and adolescents	Unknown	Caution.
Digoxin	↓ digoxin effect	↓ absorption	Monitor digoxin therapeutic effects.
Hepatotoxins (e.g. leflunomide, retinoids, azathioprine, sulfasalazine)	↑ risk of hepatic toxicity (and myelosuppression – leflunomide)	Additive	Avoid concomitant use.
Highly protein bound drugs (i.e., tetracyclines, sulfonylureas, phenytoin, warfarin,	↑ methotrexate toxicity	Displacement and ↑ methotrexate bioavailability	Use with caution and monitor methotrexate levels (if applicable) or avoid concomitant use.

etc)			
Leucovorin and high doses of folic acid	↓ toxicity of methotrexate	"Rescues" cells from toxic effects of methotrexate	Administer leucovorin within 24-36 hours after start of methotrexate; refer to local protocols.
Nephrotoxic drugs (e.g. cisplatin, aminoglycosides, amphotericin B)	↑ methotrexate toxicity	↓ clearance of methotrexate	Caution; monitor for toxicity if co-administration cannot be avoided.
Nitrous oxide anesthesia	Severe myelosuppression, stomatitis, nephrotoxicity; Neurotoxicity (with IT methotrexate)	↑ methotrexate effect on folate metabolism	Contraindicated.
NSAIDs	↑ methotrexate toxicity due to prolonged serum levels, possibly fatal hematologic and GI toxicity	↓ renal excretion and/or tubular secretion of methotrexate	Avoid use prior to or in combination with high dose methotrexate. Caution when low doses of methotrexate are used (e.g. in rheumatoid arthritis).
Penicillins, ciprofloxacin	↑ methotrexate effect and toxicity	↓ renal excretion and/or tubular secretion of methotrexate	Caution; monitor carefully for toxicity if coadministration cannot be avoided.
PPIs (e.g. omeprazole, pantoprazole, etc)	↑ methotrexate toxicity, since may elevate and prolong serum levels of methotrexate and/or its metabolite	Inhibits renal elimination of methotrexate or its metabolite	Avoid concomitant use with high-dose methotrexate, especially in renal impairment. Caution with concurrent low-dose methotrexate. Consider use of ranitidine.
Procarbazine	↑ nephrotoxicity	Unknown	Allow at least 72 hours between the last dose of procarbazine and the start of high dose methotrexate.
Salicylates	↑ methotrexate toxicity	↓ renal excretion and/or tubular secretion of methotrexate, displace methotrexate from protein binding	Avoid concomitant use with high-dose methotrexate. Monitor for toxicity if coadministration cannot be avoided.

			Doses used for cardiovascular events prophylaxis are unlikely to be of concern.
Sulfonamides (e.g. sulfamethoxazole, cotrimoxazole)	↑ methotrexate toxicity	↓ renal excretion and/or tubular secretion of methotrexate, additive anti-folate effect, displace methotrexate from protein binding	Consider avoiding concurrent use of therapeutic doses of sulfonamide antibiotics. Monitor for toxicity if coadministration cannot be avoided.
Theophylline	↑ theophylline effect	↓ clearance	Monitor theophylline levels.
Thiazide diuretics, triameterene	↑ myelosuppression (also ↓ folate levels with triameterene)	Unknown	Consider alternative antihypertensive therapy.
Trimethoprim	↑ methotrexate toxicity	Additive antifolate effect and/or ↓ tubular secretion	Consider avoiding concurrent use of therapeutic doses of trimethoprim. Monitor for toxicity if co-administration cannot be avoided.
Thiopurines (azathioprine, mercaptopurine)	↑ thiopurines effect	↓ metabolism of thiopurines	May require thiopurine dose adjustment with high-dose methotrexate.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Methotrexate levels when dose > 1 g/m^2, or in patients with third space fluid accumulation, GI obstruction, previous cisplatin therapy, dehydration or renal impairment. Draw creatinine and methotrexate levels	As per local protocols

starting 24 hours after methotrexate initiation and at least once daily until methotrexate level is < 0.1 µM (toxic range depends on local policy and methotrexate assays used).	
CBC	Baseline and before each cycle
Liver function tests	Baseline and before each cycle
Renal function tests	Baseline and before each cycle
Chest x-ray	Baseline and as clinically indicated
Clinical assessment of infection, bleeding, GI, skin, pulmonary, or CNS toxicity	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Lung function tests if pulmonary toxicity suspected	As clinically indicated

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- methotrexate - oral tablets

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K - References

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November 2022 Modified Pharmacokinetics, Indications, Adverse Effects, Dosage in renal impairment, Contraindications, Precautions, Pregnancy/lactation, Interactions and Monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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