

**A DRUG NAME: METHOTREXATE****SYNONYM(S):** Amethopterin, MTX**COMMON TRADE NAME(S):** Methotrexate (Wyeth Canada) (Ratiopharm) (Novopharm) (Mayne Pharma)**B MECHANISM OF ACTION AND PHARMACOKINETICS**

Methotrexate has been in clinical use since 1948. It 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).

<b>Oral Absorption</b>	Well absorbed <math><30\text{ mg/m}^2</math> in most patients. 20% > 80 mg/m <sup>2</sup> , bioavailability decreased by food and milk.	
<b>Distribution</b>	Highest levels kidney, gallbladder, spleen, liver and skin, retained in liver for prolonged periods, crosses placenta, found in breast milk and malignant effusions. Some accumulation may occur with repeated dosing especially in liver.	
	Cross blood brain barrier?	Poorly
	PPB	50%
<b>Metabolism</b>	Liver and intracellular metabolism to polyglutamated products	
	Active metabolite(s)	Yes
	Inactive metabolite(s)	Yes
<b>Excretion</b>	Excreted principally by the kidney (80%), biliary excretion < 10%, significant inter- and inpatient variability. Clearance is delayed in the presence of a third compartment fluid collection (i.e. pleural effusion, ascites)	
	Urine	80-90% excreted unchanged
	t $\frac{1}{2}$	8-15 hours

**C INDICATIONS AND STATUS**

- \* Acute lymphocytic leukemia
- \* Breast cancer
- \* Bladder cancer
- \* Burkitt's lymphoma
- \* Choriocarcinoma
- \* Gastric cancer
- \* Head and neck cancer
- \* Mycosis fungoides
- \* Non-Hodgkin's lymphoma
- \* Metastasis of unknown primary

Other uses include:

Sarcoma, adult soft tissue  
leptomeningeal carcinomatosis  
Osteogenic sarcoma

- \* **Health Canada approved indication**

**D ADVERSE EFFECTS**

ORGAN SITE	SIDE EFFECT	ONSET	
Central nervous system	Chemical meningitis (IT use, rare)	I	
	Headache, Dizziness, Mood changes		E
	Convulsions, myelopathy		E
	Acute encephalopathy (with high doses)		E
	Leukoencephalopathy (rare)		L
Dermatologic	Radiation recall reaction	I	
	Alopecia		E
	Pruritis, rash	I	E
	Vasculitis, urticaria	I	E
	Depigmentation, hyperpigmentation		E
	Photosensitivity		E
	Toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme (rare)		E
<b>Extravasation hazard</b> (refer to <a href="#">Appendix 2</a> )	Minimal	I	

D	ADVERSE EFFECTS (continued)		
ORGAN SITE	SIDE EFFECT	ONSET	
Gastrointestinal	Nausea and vomiting (40% with high doses)	I	
	<u>Stomatitis</u>		E
	<u>GI hemorrhage, intestinal perforation</u>		E
	Abdominal pain		E
	Pancreatitis		E
	Diarrhea		E
	Anorexia		E
Cardiovascular	Thromboembolism		E
	Hypotension		E
	Pericarditis/ effusion		E
Neoplastic	Low grade lymphomas		L
Reproductive	Abortifacient, fetal defects		
	Infertility		E
	Gynecomastia, vaginal dryness, bleeding		E
	Reduced libido		E
Hematologic	<u>Myelosuppression</u>		
	Nadir 7-14 days, recovery 14-21 days		E
	Immunosuppression, infection		E
	Eosinophilia		E
	Thrombocytopenic bleeding		E
	Megaloblastosis		E

D ADVERSE EFFECTS (continued)			
ORGAN SITE	SIDE EFFECT	ONSET	
Hepatic	Elevated liver function tests (transient)	E	
	Acute hepatitis	E	
	Fibrosis, cirrhosis, hypoalbuminemia (with long-term, low-dose use)	L	
Hypersensitivity	Type I (anaphylactoid), (rare)	I	
	Type III (serum sickness), (rare)		E
	Fever and chills (rare)		
Ocular	Transient visual changes		
	Conjunctivitis		E
Pulmonary	Pleuritic chest pain	I	
	Interstitial pneumonitis, alveolitis and fibrosis		E
Renal	Hyperuricemia, tumor lysis	I	
	Cystitis / dysuria, proteinuria		E
	Toxic nephropathy (with high doses)		E
Other	Osteoporosis / stress fractures		D
	Infections		E
	Arthralgia/myalgia		E
	Fatigue		E
	Bone and soft tissue necrosis (with radiation)		E

Dose-limiting side effects are underlined.

I = immediate (onset in hours to days); E = early (days to weeks);

D = delayed (weeks to months); L = late (months to years)

**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.

**D ADVERSE EFFECTS (continued)**

Incidence and severity of **stomatitis** varies with dose and schedule. Stomatitis is rare with weekly doses of  $30\text{mg}/\text{m}^2$ , whereas doses of  $20\text{mg}/\text{m}^2$  on 5 consecutive days produce stomatitis in most patients. Risk factors for stomatitis include renal dysfunction, irradiation to head and neck area and prolonged infusion. Administration of leucovorin decreases the risk of toxicity to gastrointestinal tract.

**Renal toxicity** could be related to precipitation of methotrexate in the renal tubules and collecting ducts. Urinary methotrexate levels in excess of  $1\text{ mmol}/\text{L}$  exceed the solubility of methotrexate at pH 5.0 and promote drug precipitation. The risk of renal failure due to high-dose methotrexate ( $>1\text{ g}/\text{m}^2$ ) can be minimized by brisk diuresis, alkalinization of the urine (adjust urinary pH with IV sodium bicarbonate to maintain  $>7.0$ ).

**Acute hepatic dysfunction** (elevation of hepatic enzymes) may occur more frequently in patients receiving high-dose therapy and is reversible. Chronic hepatic fibrosis is more common in patients receiving long-term, low-dose therapy and may be fatal.

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.

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.

In **active CNS leukemia**, methotrexate clearance from the CNS may be delayed, possibly enhancing toxicity.

**Chemical meningitis** may occur with intrathecal methotrexate, beginning 2-4 hours after injection and lasting for 12-72 hours. This is characterized by stiff neck, headache, nausea and vomiting, fever and lethargy. The syndrome may be subacute or chronic, transient or permanent. Progression to spasticity, quadriplegia (transient or permanent), visual disturbances and slurred speech can occur.

Other CNS toxicities include an **acute encephalopathy** consisting of behavioural abnormalities, aphasia or hemiparesis, occasionally with seizures, in patients receiving high-dose methotrexate ( $>200\text{mg}/\text{kg}$  IV or  $8\text{ g}/\text{m}^2$ ).

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, 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. 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. Leucovorin administration does not appear to protect against pulmonary toxicity. Corticosteroids may hasten recovery.

## E

## DOSING

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 white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

Methotrexate is frequently administered in combination with other drugs. Higher (> 100mg) doses should be given with leucovorin rescue. Doses over 1gm/m<sup>2</sup> should be given with hydration and alkalization according to local protocols.

**Adults:**

<i>Oral:</i>	daily:	2.5 – 10mg/day
	Q 2-3 w:	15-30 mg/day for 5 days
	Weekly:	40-50mg/m <sup>2</sup>
	2 x weekly:	15-20mg/m <sup>2</sup>
<i>Intravenous:</i>	Q4w:	30-40 mg/m <sup>2</sup> day 1 and 8
	Q3-4w:	120mg/m <sup>2</sup> - 1.5 g/m <sup>2</sup> followed by leucovorin rescue within 2-24 hours
<i>Intrathecal:</i>	Q4-7d:	12 mg in 5-6 mL 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 GI toxicity:* Discontinue until recovery in presence of diarrhea or stomatitis

*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".

<i>Dosage with renal impairment:</i>	<u>CrCl (mL/min)</u>	<u>% usual dose</u>
	> 80	100%
	80	75%
	60	60%
	50	50%
	<50	discontinue

<i>Dosage with hepatic impairment</i>	<u>Bilirubin (µmol/L)</u>	<u>% usual dose</u>
	2-3 X ULN	50%
	> 3 x ULN	omit

*Dosage in elderly:* Methotrexate has not been well studied. Methotrexate should be used with extreme caution because of likely renal and hepatic dysfunction and reduced folate stores in the elderly.

**Children:** refer to protocols being used. Methotrexate solution contains benzyl alcohol and should not be used in neonates

**F ADMINISTRATION GUIDELINES (see [Appendix 3a](#))**

- Preserved formulation contains benzyl alcohol and should not be used for intrathecal, intraventricular or high dose treatment
- Do not admix with araC, 5FU, prednisolone, KCl or other drugs unless compatibility data are available

Slow push through sidearm of free flowing IV (5% Dextrose, Normal Saline or 2/3.1/3)

- May be given by IM or direct IV push, followed by a Normal Saline IV flush, if no IV line has been set up
- Doses from >100mg may be mixed in 50-100mL minibag (Normal Saline); Infuse over 30-60 minutes
- Doses from 250-500mg may be mixed in 500mL bag (Normal Saline); Infuse over 1-2 hours
- Doses from >500mg may be mixed in 1000mL bag (Normal Saline); Infuse over 2-4 hours
- May be given as Intrathecal injection; use unpreserved solution or mix in unpreserved diluent using strict aseptic technique

METHOTREXATE (HIGH-DOSE >1g/m<sup>2</sup>): Alkalinization and hydration: example

- Hydrate with Normal Saline at 100-125mL/hour, starting 6 to 12 hours before Methotrexate; measure urine output (>60mL/hour)
- Alkalinize urine, starting 6-12 hours before Methotrexate, with Sodium Bicarbonate 50mmol in alternating litres of IV hydration fluid (or in each litre); maintain urine pH>7.0 (may also give Sodium Bicarbonate 100mg/m<sup>2</sup> PO q6h)
- Continue hydration and alkalinization for 24 hours after completion of Methotrexate infusion
- Leucovorin rescue to start 24 hours after Methotrexate dosing finished; continue until serum levels drop below toxic range (<0.05µmol/L)

METHOTREXATE ORAL:

- Oral self-administration; drug available by retail prescription

**G SPECIAL PRECAUTIONS**

Methotrexate powder is classified as **dangerous goods** under the Transportation of Dangerous Goods Act and must be declared as such for the purposes of transportation (substance is considered toxic).

Methotrexate is contraindicated in patients with a known hypersensitivity to methotrexate. Methotrexate should be used with extreme caution in patients with a history of peptic ulceration or ulcerative colitis and in patients with poor performance status, chronic liver disease, cirrhosis and with renal impairment. The use of live vaccines should be avoided.

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 is recommended in such patients.

Methotrexate is **carcinogenic, fetotoxic and teratogenic** and is contraindicated in pregnancy. When administered to a **pregnant woman**, abortion is likely. Adequate contraception should be used in both men and women. It is **excreted in breast milk** in small concentrations and may accumulate in neonatal tissues, therefore, breast-feeding is not recommended.

Preservative free methotrexate must be used for intrathecal, intravesical and high dose administration

H	INTERACTIONS			
	AGENT	EFFECT	MECHANISM	MANAGEMENT
	Alcohol	enhanced hepatotoxicity	additive	avoid alcohol intake
	Asparaginase	enhanced hepatotoxicity and decreased effect of methotrexate	additive effect on liver. Reduced cellular uptake of methotrexate	monitor liver function
	Asparaginase	decreased effect of methotrexate if asparaginase is given 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 or shortly after methotrexate
	Carboxypeptidase-G (Investigational use only)	decreased toxicity of methotrexate	cleaves the methotrexate molecule to inactive fragments	may be useful to treat IT methotrexate overdose
	Protein bound drugs	increased toxicity	displacement and increased bioavailability	use with caution
	Cisplatin and other nephrotoxic drugs	increased toxicity	reduced clearance of methotrexate	caution
	Co-trimoxazole	increased risk of hematological toxicity from methotrexate	displacement of methotrexate from plasma protein binding sites or inhibition of renal tubular secretion or antifolate effect	avoid concomitant therapy when giving high-dose methotrexate; monitor when concomitant therapy is administered in lower dose methotrexate regimens

H	<b>INTERACTIONS (continued)</b>			
	<b>AGENT</b>	<b>EFFECT</b>	<b>MECHANISM</b>	<b>MANAGEMENT</b>
	Digoxin	decreased digoxin effect	reduced absorption	avoid concomitant oral use
	Etrexinate	increased serum methotrexate levels and/or enhanced hepatotoxicity	unknown	monitor therapeutic and toxic effects of methotrexate
	Hepatotoxins (leflunomide, retinoids, azothiaprine)	increased risk of hepatic toxicity	additive effect	avoid concomitant use
	Leucovorin and high doses of folic acid	decreased toxicity of methotrexate	"rescues" cells from toxic effects of methotrexate	administer leucovorin within 6-24 hours after methotrexate
	Non-steroidal anti-inflammatory drugs (NSAIDs) [e.g., ASA, ibuprofen, indomethacin]	severe, occasionally fatal toxicity	NSAIDs may inhibit renal secretion of methotrexate	avoid concomitant therapy; withhold NSAIDs at least 48 hours prior to methotrexate
	Non-absorbable oral antibiotics (neomycin, polymyxin B, nystatin, vancomycin)	methotrexate serum concentrations may be decreased	reduced absorption of oral methotrexate	observe for decreased therapeutic response of oral methotrexate; may be avoided by using IV methotrexate
	Phenytoin	increased toxicity	protein binding – displacement	monitor phenytoin serum level; adjust phenytoin dose prn
	Procarbazine	increased nephrotoxicity	unknown	avoid concomitant use
	Pyrimethamine	Increased toxicity	similar mode of action	caution with concomitant use

H	INTERACTIONS (continued)			
	AGENT	EFFECT	MECHANISM	MANAGEMENT
	Theophylline	increased effect of theophylline	reduced clearance	monitor
	Probenecid, penicillins	increased effect of methotrexate	inhibition of renal excretion and tubular secretion of methotrexate	avoid this combination with high-dose methotrexate; for lower doses
	Thiazide diuretics	prolonged leukopenia	unknown	consider alternative antihypertensive therapy
	Thiopurines (azothiaprines, mercaptopurines)	increased effect of thiopurines	inhibition of first-pass metabolism of thiopurines	probably not clinically significant
	Warfarin	increased pharmacological effect of warfarin	possibly altered hepatic metabolism of warfarin	monitor prothrombin time; adjust warfarin dose prn

I	RECOMMENDED CLINICAL MONITORING	
	Recommended Clinical Monitoring	Suggested Clinical Monitoring
	<ul style="list-style-type: none"> <li>• Clinical assessment of stomatitis</li> <li>• Baseline and regular renal function tests</li> <li>• Baseline and regular CBC</li> <li>• Baseline and periodic liver function tests</li> </ul>	<ul style="list-style-type: none"> <li>• Baseline CXR</li> <li>• Lung function tests if pulmonary toxicity suspected</li> <li>• Methotrexate levels when dose &gt; 1gm/m<sup>2</sup></li> </ul>

## J REFERENCES

Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA)

Compendium of Pharmaceuticals and Specialties. 2006. Methotrexate®. Canadian Pharmacists Association.