Best Practice Message

March 2026

Methotrexate Monitoring Reminder

Tips for safe prescribing of Methotrexate

Methotrexate is a highly effective and commonly used treatment for inflammatory conditions. However, safe prescribing depends on several key factors:

- **Clear dosing instructions:** Ensure patients understand that methotrexate tablets are taken **once weekly**, on the same day each week.
- **Regular monitoring:** Guidelines recommend blood tests every **three months** for stable patients, with more frequent monitoring for those at higher risk of toxicity.
- **Early recognition of adverse effects:** Patients should be advised to report symptoms promptly, including mouth ulcers, sore throat, persistent cough or shortness of breath, abdominal discomfort, or dark urine.
- **Awareness of drug interactions:** Prescribers should be mindful of medicines that may increase the risk of methotrexate toxicity.

Background

Methotrexate is a folic acid antagonist, inhibiting DNA and RNA synthesis required for normal cell division.[1] It is used as a cytotoxic agent. When used at low doses (25mg and under), methotrexate is effective and widely used for inflammatory conditions, such as psoriasis, vasculitis, Crohn's disease and rheumatoid arthritis (RA).

Methotrexate can rarely cause serious toxicity with a risk of hepatoxicity, bone marrow suppression, lung injury and death due to methotrexate toxicity. This is more likely to occur in the setting of high dose use in chemotherapy but should not be forgotten in low dose use. Since the start of 1 January 2000 until 1 December 2025 the NZ pharmacovigilance system had received 393 adverse event reports for methotrexate. Thirty-four were associated with a fatal outcome and these included reports coded with "pneumonitis and interstitial lung disease", "pancytopenia" and "sepsis" reaction terms. Several factors contribute to the risk of toxicity.

Risk factors for toxicity

The risk of toxicity is increased by:[1–3]

- Medication interactions. Examples of interactions can be found here. Patients should be advised to check with their health care professional before taking any new medicines and herbal medicines.
- Incorrect use - such as wrong strength, dose or frequency (for example daily rather than weekly use).
- Abnormal liver and kidney function.
- Advanced age.
- Multiple co-morbidities, including diabetes.
- Combination disease modifying anti-rheumatic drug (DMARD) treatment.
- Previous DMARD toxicity.
- Extremes of weight.

Monitoring

The New Zealand formulary recommends measuring full blood count, liver function tests (including albumin), and serum creatinine every 2 to 4 weeks initially, then monthly for 3 months, then every 3 months if normal and dose is stable.[1] Appendix 1 gives guidance on when to contact the specialist based on blood monitoring results.

When to complete more frequent blood monitoring

More frequent monitoring may be necessary if an abnormal test presents, with dose increases, and in individuals at higher risk of toxicity.[1]

Stay vigilant between monitoring

The usual cause of methotrexate-related mortality is pneumonitis, which can occur idiosyncratically. Bone marrow suppression is another cause of mortality, and may occur abruptly.[4]

Arguably, the most important monitoring is done by patients and whānau in watching out for adverse signs and symptoms. The general practice should have processes in place so that methotrexate adverse effect can be reported to the treating clinician. Advise patients to immediately report any signs of:

Respiratory symptoms:	Blood disorders:	Liver toxicity:
Shortness of breath Persistent cough	Mouth ulcers Unusual bruising or bleeding Persistent sore throat Fever	Nausea and vomiting Abdominal discomfort Dark urine Pale bowel motions Yellow skin or eyes Itching

Accidental overdose

If there is concern that methotrexate has been taken more often than the intended once-weekly schedule—especially if this has occurred for three or more consecutive days—prompt assessment should be arranged. This typically includes urgent monitoring blood tests, physical examination, and direct phone communication with the relevant treating specialist or specialty team.

Patients should also be advised to store their medications out of reach of children.

Tools and further reading:

- NZF: Interaction checker
- Medsafe Prescriber Update: **Interactions with low-dose methotrexate**.
  Interaction reminder: Methotrexate and trimethoprim or co-trimoxazole
- Health Hawke's Bay Best Practice: Focus on safety; Low dose methotrexate
- HealthPathways: Methotrexate share care guidance
- New Zealand Doctor article: Methotrexate prescribing without recent blood test monitoring
- CARM reporting: New Zealand Adverse Reactions Reporting Form

Patient resources:

- Healthify: **Methotrexate tablets for inflammatory conditions.**
- NZF: Methotrexate patient information leaflet

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SMARS disclaimer

Pharmacovigilance information about suspected adverse reactions reported to CARM was sources from the Suspected Medicines Adverse Reaction Search (SMARS) Database (up to 1/12/2025) and confirmed by Dr Jennifer Lee. Pharmacovigilance data (with the exception of company reports) are based on spontaneously submitted reports and are therefore not representative of all events occurring in the general population. ADR reports vary in information quality and quantity (e.g. description of symptoms, clinical observations or treatment provided). For a copy of the guidelines of information found on SMARS please see here.

Appendix 1: Adverse and toxic effects of methotrexate and when to review treatment

What to watch for:	What to do about it:
Gastrointestinal:	
Ulcerative stomatitis (mouth ulcers). • Often the earliest indications of toxicity. • Can occur in 2 to 10% of patients.[5]	This should trigger a review of treatment.
Nausea, vomiting and diarrhoea. • Occurs in around 10% of patients.[5]	May require interruption of therapy, dose reduction, folic acid dose review or symptomatic management.
Infections:	
RA patients have increased incidence of infection compared to the general population.[6] The risk is increased if the patient: • Is also on other immunosuppressive agents. • Has comorbidities, particularly pre-existing lung disease.	Consider withholding methotrexate in patients with active infection until clinically well and antibiotic course completed. If the antibiotic course is brief and withholding methotrexate is impractical, ensure close monitoring. Avoid trimethoprim and co-trimoxazole; risk of additive bone marrow suppression/pancytopenia with methotrexate. Monitor for methotrexate toxicity if a penicillin antibiotic started or its dose increased; may reduce methotrexate clearance, this is less clinically significant at low antirheumatic doses.
Cytopenias:	
Minor changes in blood count parameters. • Can occur in around 3-10 % of patients.[5]	This is usually temporary or reversible with dose adjustment or interruption of therapy.
Severe bone marrow suppression and a significant reduction in platelets or white blood cell count. • Can occur rarely but abruptly. • The risk is increased with concomitant use of other anti-folate medicines, such as trimethoprim.	Neutrophils <2.0 x 10^9/L; Platelets <150 x 10^9/L; WBC <3.5 x 10^9/L; requires immediate discontinuation of methotrexate and discussion with the hospital specialist.
Pulmonary Toxicity:	
Pneumonitis. • Rare (1%).[5] • The risk is higher in those who smoke tobacco and who have pre-existing lung disease. • **May occur at any time during treatment.**	**Advise patients to seek medical attention if dyspnoea, cough or fever occur.**[1] Withhold treatment and discuss with the hospital specialist.
Neurotoxicity:	
Headaches, dizziness, fatigue, and problems concentrating. • May develop gradually.	May require dose reduction, and in some patients will require drug discontinuation.
Hepatotoxicity:	
Increased liver enzymes. • Can occur in up to 15% of patients.[5] Hepatotoxicity. • Is more likely in patients with pre-existing liver disease, obesity, dyslipidaemia, and lack of folic acid supplementation.[1,2]	ALT <2x upper limit of normal: appropriate to continue treatment. ALT ≥2x upper limit of normal: withhold methotrexate and contact hospital specialist team. Alcohol should be minimised or if possible avoided, to reduce the risk of liver toxicity developing.
Skin complications:	
Photosensitivity reactions • Can occur in around 3-10 % of patients. Long term risk of non-melanoma skin cancers whilst on immunosuppression.	Patients should be warned to avoid unprotected exposure to sunlight or tanning beds. Recommend a skin check every 1-2 years.
Renal function:	
Methotrexate is not nephrotoxic, but it is mainly excreted by the kidney. Changes in renal function can lead to an increased risk of side effects and toxicity from methotrexate.	Methotrexate use should be considered carefully and doses reduced in anyone with eGFR <30ml/min/1.73m^2.
Congenital abnormalities:	
Increased risk of foetal malformation and miscarriage.	Both men and women of childbearing potential must have effective contraception during and for at least 3 months post-treatment cessation. In case of accidental pregnancy, please notify hospital specialist.

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