

METHOTREXATE - SAFE PRESCRIBING – ONCE A WEEK!

1

- ▶ ALWAYS DOUBLE-CHECK PRESCRIPTIONS - PRESCRIBING AND DISPENSING ERRORS CAUSE THE MOST HARM
- ▶ CLEARLY EXPLAIN THE DOSING SCHEDULE TO PATIENTS
- ▶ TELL PATIENTS TO REPORT ADVERSE REACTIONS AND CONTRAINDICATIONS
- ▶ BE AWARE OF INTERACTIONS THAT INCREASE THE RISK OF TOXICITY
- ▶ ENSURE THERE IS A MONITORING PLAN

Low-dose (less than 25mg) oral methotrexate therapy, taken as a single dose **once a week**, is a safe and effective treatment when prescribed for inflammatory conditions such as severe psoriasis and rheumatoid arthritis.¹ It is often the preferred option compared to other disease-modifying anti-rheumatic drugs (DMARDs), it is usually well tolerated^{3,4} and its side-effects are predictable.^{1,2}

ALWAYS DOUBLE-CHECK PRESCRIPTIONS

The most common cause of significant patient harm reported from methotrexate occurs when a medical practitioner unintentionally prescribes methotrexate to be taken **daily** rather than **once a week**, followed by a pharmacist dispensing the methotrexate accordingly.^{2,5,6}

The danger of this is well known to health professionals. In New Zealand, patients have died after taking their weekly methotrexate dose on a **daily** basis, after it was prescribed and dispensed as such.⁷

Harm may also occur when the wrong strength of methotrexate tablet is dispensed, or because of labeling errors.^{2,5,8,9} Always exercise caution when prescribing and dispensing oral methotrexate, including the management of repeat prescriptions.⁵

Please **double-check** prescriptions:

right strength **right dose** **right frequency (weekly)**

Prescribers are advised to specify a **day of the week** (written in full) on which the dose should be taken and to recommend the **strength** to be dispensed (eg consider specifying only 2.5mg tablets to be dispensed). The day of the week, in full, should also be printed on the label by the pharmacy.^{5,10}

CLEARLY EXPLAIN THE DOSING SCHEDULE TO PATIENTS

The unusual weekly dosing schedule can be confusing for patients and has promoted medication errors, some of which have been fatal.⁵ Health professionals can improve safety by providing patients with clear instructions about how and when to take their dose.

Verbal and written patient information may help with promoting effective self-management¹¹ see the patient guide available on www.saferx.co.nz, which also includes information about handling the tablets. A special effort may be needed when methotrexate is prescribed and English is not the patient's first language.

TELL PATIENTS TO REPORT ADVERSE REACTIONS AND CONTRAINDICATIONS

Adverse reactions

Many of the side-effects of low-dose oral methotrexate are due to the inhibition of folate metabolism and include nausea, stomatitis and bone marrow suppression. These symptoms can be reduced with oral folic acid tablets (5mg once a week taken on a different day to methotrexate) without affecting the efficacy of methotrexate^{5,12,1} and should be prescribed for all patients. A simple mnemonic tool is used by some patients 'Methotrexate on Monday and Folic acid on Friday' to help them remember which day to take their tablets.²

Health professionals should advise patients to be alert for **any** symptoms suggestive of methotrexate toxicity, and to report these to their GP or specialist without delay.² Toxicity may present as symptoms of bone marrow suppression (eg fever, sore throat, mouth ulcers), hepatotoxicity (eg abdominal pain, jaundice), or pulmonary toxicity (eg new or increasing dyspnoea, chest pain, hypoxaemia, dry cough). Pneumonitis can occur idiosyncratically (i.e. it is not dose related), even after one dose and can progress rapidly, it may not be fully reversible and is potentially fatal.^{2,14} Diarrhoea and ulcerative stomatitis can progress to potentially fatal haemorrhagic enteritis and intestinal perforation if methotrexate is continued.¹⁴ See Table 1 for more information.

→ continued

METHOTREXATE

Contraindications

Contraindications to treatment include active infection, alcoholism, peptic ulcer disease, poor nutritional status and recent exposure to chicken pox or herpes zoster infection.¹⁵ Advise patients to inform their GP or specialist if these conditions occur.^{14,15}

Women of child bearing potential should have pregnancy excluded before starting methotrexate. Women or men taking methotrexate whose partner is of child bearing potential should use effective contraception during treatment and for three months after cessation.¹⁴

BE AWARE OF INTERACTIONS THAT CAN INCREASE THE RISK OF TOXICITY

Methotrexate can be hepatotoxic, especially at higher doses or with prolonged therapy. Liver function should be checked prior to the initiation of treatment and monitored every fortnight for the first six weeks and then every 4 weeks.¹⁶ Concomitant use of methotrexate with other hepatotoxic agents (including alcohol) will increase the risk of toxicity, which can progress to cirrhosis in severe cases. It is not known precisely what level of drinking is safe with methotrexate; however there is general agreement that one to two standard drinks once or twice a week is unlikely to cause a problem. Drinking more than four standard drinks on one occasion, even if infrequently, is strongly discouraged.²

Methotrexate accumulates in the presence of renal impairment. Doses of methotrexate should be reduced in cases of poor renal function, whether caused by concomitant medications (such as non-steroidal anti-inflammatories (NSAIDs) and diuretics), dehydration, or kidney disease.¹ Advise patients to ask their specialist, GP or pharmacist before self-medicating with NSAIDs.

The risk of methotrexate toxicity can also be increased if it is taken together with some antibiotics. **Trimethoprim and cotrimoxazole significantly increase the risk of bone marrow aplasia and should be avoided.** The risk of toxicity can also be increased if taken together with penicillins and tetracycline. Live vaccines should be avoided; however inactivated vaccines such as the annual influenza vaccination may be given.¹

For a more comprehensive list of interactions with methotrexate, consult the full prescribing information or the 'Interaction' function on *New Zealand Formulary* online.^{15,19}

ENSURE THERE IS A MONITORING PLAN

Inadequate monitoring of patients on long-term methotrexate is another cause of serious events that have resulted in patient harm.²

A full blood count, renal and liver function tests, and in some cases, chest x-ray and respiratory function, need to be checked before treatment is started. Laboratory monitoring needs to be repeated at regular intervals until the patient is stabilised, and then on an ongoing basis so that the patient can be clinically evaluated, and to identify methotrexate toxicity.² Repeat prescriptions for methotrexate should not be provided without a full blood count and liver function test having been performed within the previous 4 to 8 weeks.^{2,4,10}

See Table 1 for more details, but please note that **local guidelines may vary**; follow the advice of the treating specialist about the frequency of testing.^{1,20}

In all cases, an agreed management plan should be in place for each patient specifying the doctor (GP or specialist) who will take primary responsibility for changes to dosing, and for arranging, reviewing and acting upon laboratory investigations.^{1,2,10}

Note: Methotrexate is also indicated for the treatment of neoplastic diseases, such as leukaemia. For these conditions it may be prescribed in daily doses. **Folic acid** (as opposed to **folinic acid**) is used to prevent toxicity in these patients.²

METHOTREXATE

3

ACKNOWLEDGEMENTS

We wish to thank Hugh de Lautour, Rheumatologist and Elizabeth Brookbanks, Pharmacist Team Leader, Medicine, at Waitemata District Health Board, for their valuable contribution to this bulletin.

REFERENCES

1. Highton J, Harrison A, Grainger R. Rheumatoid arthritis – monitoring of DMARDs. Best Practice Journal 2008; 17:22-26 www.bpac.org.nz/magazine/2008/october/docs/bpj17_rheumatoidarthritis_pages_22-26.pdf (Accessed 12-09-18)
2. Harrison A, Jones P. Safe Prescribing of high risk medicines. Methotrexate: potentially fatal in overdoses. Best Practice Journal 2014,64:48-52 <https://bpac.org.nz/BPJ/2014/October/safer-prescribing.aspx> (Accessed 12-09-18)
3. Grove M, Hassell A, Hay E, Shadforth M. Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. The Quarterly Journal of Medicine 2001;94:309-319
4. Methotrexate – Once Weekly Dosing Prescriber Update 2017; 38(4) : 57-59 www.medsafe.govt.nz/profs/PUArticles/December2017/Methotrexate.htm (Accessed 12-09-18)
5. Call to Action: Longstanding Strategies to Prevent Accidental Daily Methotrexate Dosing Must Be Implemented. Medication Safety Article, Institute for Safe Medication Practices (ISMP) August 9 2018 www.ismp.org/resources/call-action-longstanding-strategies-prevent-accidental-daily-methotrexate-dosing-must-be (Accessed 20-09-18)
6. Yeoh S, Siderov J. Methotrexate misadventure – a case for counselling. Rheumatology, Volume 40, Issue 2, 1 February 2001, Pages 230–232
7. Pharmacist not to blame for death, says coroner. 20-10-09 www.stuff.co.nz/national/health/2983300/Pharmacist-not-to-blame-for-death-says-coroner (Accessed 11-09-18)
8. Bookstaver PB, Norris L, Rudisill C et al. Multiple toxic effects of low-dose methotrexate in a patient treated for psoriasis. American Journal of Health-System Pharmacy 2008;65(22):2117-21 www.ajhp.org/content/65/22/2117 (Accessed 19-09-18)
9. Blinova E, Volling J, Koczmarc C, Greenall J. Oral methotrexate: Preventing inadvertent daily administration. Canadian Journal of Hospital Pharmacy 2008;61(4):275-77
10. Health Quality and Safety Commission. Methotrexate - once weekly dosing. Medication alert 14, April 2012. www.hqsc.govt.nz/assets/Medication-Safety/Alerts-PR/Oral-methotrexate-Alert-final.pdf (Accessed 17-09-18)
11. Grissinger M. Severe harm and Death Associated with Errors and Drug Interactions Involving Low-Dose Methotrexate PT 2018; 43 (4):191-248. www.ptcommunity.com/journal/article/full/2018/4/191/severe-harm-and-death-associated-errors-and-drug-interactions (Accessed 17-09-18)
12. Tsai A, Morton S, Mangione C, Keeler E. A Meta-analysis of Interventions to Improve Care for Chronic Illness. American Journal of Managed Care 2005;11(8):478-488
13. Bologna C, Viu P, Picot MC, Jorgensen C and Sany J. Long-term follow-up of 453 rheumatoid arthritis patients treated with methotrexate: an open, retrospective, observational study. British Journal of Rheumatology 1997;36:535-540
14. Best Practice Advisory Centre. Recommended Investigations for some commonly used DMARDs. Best Practice Journal 2008;17:29-32 www.bpac.org.nz/magazine/2008/october/docs/bpj17_dmards_pages_29-32_pf.pdf (Accessed 19-09-18)
15. Hospira New Zealand Limited. DBL Methotrexate injection and tablets data sheet 25 08/2017 www.medsafe.govt.nz/profs/datasheet/d/dblmethtrexateinjmayne.pdf (Accessed 18-09-18)
16. The New Zealand Formulary, methotrexate. www.nzf.org.nz/nzf_4548.html?searchterm=methotrexate (Accessed 18-09-18)
17. Best Practice Advisory Centre. Errors with methotrexate can be
18. The Australian Rheumatology Association. Patient information, methotrexate; April 2017. <https://rheumatology.org.au/patients/medication-information.asp> (Accessed 20-09-18)
19. The New Zealand Formulary, interactions www.nzf.org.nz/interactions/stockkeys/of/10029041000116107 (Accessed 19-09-18)
20. Rademaker, M. , Gupta, M. , Andrews, M. , Armour, K. , Baker, C. , Foley, P. , Gebauer, K. , George, J. , Rubel, D. and Sullivan, J. (2017), The Australasian Psoriasis Collaboration view on methotrexate for psoriasis in the Australasian setting. Australas J Dermatol, 58: 166-170 <https://onlinelibrary.wiley.com/doi/abs/10.1111/ajd.12521> (Accessed 02-10-18)

METHOTREXATE

4

Methotrexate Monitoring Recommendations ¹⁴ (Adapted from BPAC 2008;17:29)			
Monitoring	Frequency	Parameters	Action
Full blood count (FBC)	Baseline, then every 2 weeks until dose and monitoring has been stable for 6 weeks Thereafter every 4-12 weeks	WBC <3.5 x 10 ⁹ /L Neutrophils <2.0 x 10 ⁹ /L Platelets <150 x 10 ⁹ /L	Discuss with specialist team immediately
		MCV > 105 fL	Check vitamin B ₁₂ , folate, TSH and treat abnormalities
Liver function tests (LFTs)	Baseline, then every 2 weeks until dose and monitoring has been stable for 6 weeks Thereafter every 4 to 12 weeks	AST, ALT > twice the upper limit of reference range	Withhold, discuss with specialist and check: Alcohol intake NSAID intake - may cause liver dysfunction Other medication
		Unexplained decrease in albumin (in absence of active disease)	Withhold and discuss with specialist
Serum creatinine	Baseline, then every 2 weeks until dose and monitoring has been stable for 6 weeks Thereafter every 4-12 weeks	Significant deterioration in renal function	Reduce dose
Rash or oral ulceration	Inform patient to report immediately if occurs		Withhold, discuss with specialist. Try folinic acid mouthwash for mucositis.
Nausea and vomiting, diarrhoea	Inform patient to report immediately if occurs		Consider subcutaneous use to avoid nausea
Dyspnoea or dry cough (pneumonitis)	Baseline chest X-ray and respiratory function tests may be advised		Withhold and discuss URGENTLY with specialist team. Arrange chest X-ray and respiratory function tests
Severe sore throat, abnormal bruising	Inform patient to report immediately if occurs		Immediate FBC, withhold methotrexate until results available. Discuss abnormal results with specialist

ALT = Alanine transaminase

AST = Aspartate transaminase

MCV = Mean cell volume

NSAID = Non-steroidal anti-inflammatory drug

TSH = Thyroid stimulating hormone

WBC = White blood cells

For further information on other high-risk medicines visit our website at : www.saferx.co.nz

No: 0182-01-024, Issued February 2019; Review: February 2022

DISCLAIMER: This information is provided to assist primary care health professionals with the use of prescribed medicines. Users of this information must always consider current best practice and use their clinical judgement with each patient. This information is not a substitute for individual clinical decision making. Issued by the Quality Use of Medicines Team at Waitemata District Health Board, email: feedback@saferx.co.nz