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. It is often the preferred option compared to other disease-modifying anti-rheumatic drugs (DMARDs), it is usually well tolerated and its side-effects are predictable.

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. 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.

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

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.

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. 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-management 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 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.

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. 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. Diarrhoea and ulcerative stomatitis can progress to potentially fatal haemorrhagic enteritis and intestinal perforation if methotrexate is continued. See Table 1 for more information.
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. Advise patients to inform their GP or specialist if these conditions occur. 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.

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 four weeks. 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.

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-inflammatory drugs (NSAIDs) and diuretics), dehydration, or kidney disease. 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.

For a more comprehensive list of interactions with methotrexate, consult the full prescribing information or the ‘Interaction’ function on New Zealand Formulary online.

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. 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.

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. 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.

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.

Note: Methotrexate is also indicated for the treatment of neoplastic diseases, such as leukaemia. For these conditions it may be prescribed in daily doses. Folinic acid (as opposed to folic acid) is used to prevent toxicity in these patients.
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
Methotrexate Monitoring Recommendations (Adapted from BPAC 2008;17:29)

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Frequency</th>
<th>Parameters</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count (FBC)</td>
<td>Baseline, then every 2 weeks until dose and monitoring has been stable for 6 weeks Thereafter every 4-12 weeks</td>
<td>WBC &lt;3.5 x 10^9/L Neutrophils &lt;2.0 x 10^9/L Platelets &lt;150 x 10^9/L MCV &gt; 105 fl</td>
<td>Discuss with specialist team immediately Check vitamin B₁₂, folate, TSH and treat abnormalities</td>
</tr>
<tr>
<td>Liver function tests (LFTs)</td>
<td>Baseline, then every 2 weeks until dose and monitoring has been stable for 6 weeks Thereafter every 4 to 12 weeks</td>
<td>AST, ALT &gt; twice the upper limit of reference range</td>
<td>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</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Baseline, then every 2 weeks until dose and monitoring has been stable for 6 weeks Thereafter every 4-12 weeks</td>
<td>Significant deterioration in renal function</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Rash or oral ulceration</td>
<td>Inform patient to report immediately if occurs</td>
<td></td>
<td>Withhold, discuss with specialist. Try folinic acid mouthwash for mucositis.</td>
</tr>
<tr>
<td>Nausea and vomiting, diarrhoea</td>
<td>Inform patient to report immediately if occurs</td>
<td></td>
<td>Consider subcutaneous use to avoid nausea</td>
</tr>
<tr>
<td>Dyspnoea or dry cough (pneumonitis)</td>
<td>Baseline chest X-ray and respiratory function tests may be advised</td>
<td></td>
<td>Withhold and discuss URGENTLY with specialist team. Arrange chest X-ray and respiratory function tests</td>
</tr>
<tr>
<td>Severe sore throat, abnormal bruising</td>
<td>Inform patient to report immediately if occurs</td>
<td></td>
<td>Immediate FBC, withhold methotrexate until results available. Discuss abnormal results with specialist</td>
</tr>
</tbody>
</table>

ALT = Alanine transaminase  
AST = Aspartate transaminase  
MCV = Mean cell volume  
NSAID = Non-steroidal anti-inflammatory drug  
TSH = Thyroid stimulating hormone  
WBC = White blood cells