

# Medicine Guideline for the Safe Use of Methotrexate (oral)



## **METHOTREXATE (oral) IS A HIGH-RISK MEDICINE**

**USE WITH CAUTION AND ENSURE THE DIRECTIONS WITHIN THIS PROTOCOL ARE FOLLOWED CAREFULLY**

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| <b>Areas where Protocol/Guideline applicable</b> | SESLHD  |
| <b>Authorised Prescribers:</b>                   | SESLHD Prescribers within cancer, rheumatology, immunology, and dermatology services.   |
| <b>Important Safety Considerations</b>           | <p>Methotrexate (oral) is usually taken as a <b>single dose once a week</b> on the same day each week (however, occasionally, to improve tolerance in some people, the total weekly dose is taken in divided doses at 12 hourly intervals up to a maximum of 4 doses per week).</p> <p>The once-a-week dosage regimen is unusual compared to other medicines and has led to errors occurring with the use of methotrexate (oral).</p> <p>Catastrophic adverse events associated with methotrexate toxicity can occur following daily administration of oral methotrexate when weekly administration was indicated or intended.</p> <div style="border: 1px solid black; padding: 5px; margin: 5px 0;"> <p>Methotrexate oral tablets <b>must not</b> be prescribed, dispensed, or administered to any patient in hospital until approval has been obtained from the specialist who originally prescribed it for the patient. If the original prescriber cannot be contacted in a timely manner, a senior medical officer is to confirm the continuation of methotrexate (oral) during the admission prior to prescribing.</p> </div> <div style="border: 1px solid black; padding: 5px; margin: 5px 0;"> <p>The clinician taking a <b>medication history</b> on admission <b>MUST</b> confirm with the patient: the dose, indication and day methotrexate (oral) is administered, including the last day a dose was taken. This is to be documented in the patient's health care record (such as in a Medication Management Plan).</p> </div> <div style="border: 1px solid black; padding: 5px; margin: 5px 0;"> <p>Clinicians involved in the prescribing, dispensing, administration or monitoring of patients receiving methotrexate (oral) must review the work health and safety procedures that apply to the handling of cytotoxic medications and managing cytotoxic contaminated body waste related to methotrexate. Refer to the Safe Work NSW <a href="#">Cytotoxic Drugs and Related Waste – Risk Management</a> and eviQ webpage <a href="#">Safe handling and waste management of hazardous drugs</a> for more information.</p> </div> |
| <b>Indication for use</b>                        | <ul style="list-style-type: none"> <li>• Autoimmune and inflammatory disorders, AND</li> <li>• In accordance with eviQ approved protocols</li> </ul>  |

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| <p><b>Contra-indications</b></p> | <p>Methotrexate should not be given to:</p> <ul style="list-style-type: none"> <li>• pregnant women - <i>ensure effective contraception during treatment</i></li> <li>• breast-feeding women</li> <li>• patients with severe hepatic impairment</li> <li>• patients with severe renal impairment</li> <li>• patients with alcoholism or alcoholic liver disease</li> <li>• patients who have overt or laboratory evidence of immunodeficiency syndromes</li> <li>• patients with bone marrow depression or pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia, or anaemia</li> <li>• patients with severe, acute, or chronic infections</li> <li>• patients with a known hypersensitivity to methotrexate or to any of the excipients</li> <li>• psoriasis and rheumatoid arthritis patients with peptic ulcer disease or ulcerative colitis.</li> </ul>  |
| <p><b>Precautions</b></p>        | <div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> <p><b>Methotrexate (oral) must be used only by physicians experienced in antimetabolite chemotherapy or, in the case of non-oncological conditions, by a specialist physician.</b></p> </div> <ul style="list-style-type: none"> <li>• Third space fluid collection, eg pleural effusion, ascites—may delay excretion of methotrexate and increase toxicity; drain before treatment, if not possible consider dose reduction or cessation of therapy.</li> <li>• Bone marrow disorders causing leucopenia or thrombocytopenia (eg lymphoproliferative disease or myelodysplasia) or immunodeficiency syndromes—may worsen; seek specialist advice.</li> <li>• Clinically important pneumonitis or interstitial lung disease—may worsen; seek specialist advice.</li> <li>• Active peptic ulceration—methotrexate may delay ulcer healing; seek specialist advice.</li> <li>• May reactivate inactive hepatitis B and latent TB (begin TB treatment before starting methotrexate).</li> </ul> |

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| <p><b>Important Drug Interactions</b></p> | <p><b>When administered concurrently with other medications methotrexate can increase the risk of adverse effects.</b><br/>Please refer to The <a href="#">Australian Medicines Handbook</a>, and <a href="#">MIMS</a> for a complete list of drug-drug interactions.</p> <p>Combination with other folate antagonists (e.g., <b>trimethoprim</b>) increases the risk of myelosuppression; use alternatives if possible.</p> <p>Treatment with other hepatotoxic drugs (e.g., <b>leflunomide</b>), may increase risk of hepatotoxicity; use such combinations with caution and monitor aminotransferase concentration.</p> <p><b>Drugs which may reduce renal excretion of methotrexate include</b></p> <ul style="list-style-type: none"> <li>• <b>NSAIDs:</b> unlikely with immunomodulator doses of methotrexate; avoid combination if methotrexate is used in antineoplastic doses. Low-dose aspirin may be used.</li> <li>• <b>Probenecid:</b> avoid combination or reduce methotrexate dose and monitor for adverse effects.</li> </ul> <p><b>Penicillins and sulphonamides</b> have been associated with increased methotrexate concentrations and risk of toxicity, particularly with antineoplastic doses of methotrexate, but evidence is poor; monitor for adverse effects.</p> <p><b>Proton Pump Inhibitors (PPIs)</b> have been associated with increased methotrexate concentrations and risk of toxicity (mostly associated with high dose methotrexate), but studies are conflicting; avoid combination.</p> |
| <p><b>Dosage</b></p>                      | <p>As determined by authorised prescribers</p>   |
| <p><b>Duration of therapy</b></p>         | <p>As determined by authorised prescribers</p>   |

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| <p><b>Prescribing Instructions</b></p> | <p>Prescribers must refer to the <b>medication history</b> when prescribing methotrexate. Patients should continue to receive their methotrexate dose on the day of the week they normally take it.</p> <p>'Methotrexate' <b>MUST</b> be written in full. Abbreviations such MTX must not be used.</p> <p>The prescriber <b>MUST</b> include the indication for treatment in all orders or prescriptions for oral methotrexate.</p> <p>The intended dose is to be prescribing in milligrams. Doses are to be rounded to the nearest full tablet size. Where doses cannot be rounded to the nearest full table (for example, paediatric patients), the dose is to be discussed with the pharmacist or original prescriber (for continuing therapy).</p> <p>When a <u>weekly dose</u> is prescribed, the prescriber must clearly specify on the medication chart or prescription that:</p> <ul style="list-style-type: none"> <li>• Methotrexate is to be given once a week, written in full and not abbreviated</li> <li>• The day on which the drug is to be administered. For example, <b>Methotrexate 5 mg orally once a week on TUESDAY</b></li> </ul> <p>The indication for treatment <b>MUST</b> be clearly documented in all orders or prescriptions for methotrexate (oral). There are limited indications / circumstances where a more frequent dosage interval may be used. Inclusion of the indication is to alert pharmacists and nurses to any potential prescribing errors where once a week dosing was intended.</p> <p>Methotrexate <b>MUST</b> be prescribed on eMM (either eMEDs, eRIC, MOSAIQ or ARIA) for inpatients. Mechanisms have been built into eMM to prevent inadvertent daily administration of methotrexate.</p> <p><b><u>Concurrent folic acid</u></b>, see <i>Management of Complications</i>.</p> <p><b><u>On discharge</u></b>, the patient and/ or their carer must be informed when their next dose of methotrexate is due and the next dose is to be clearly documented in the discharge summary.</p> |
| <p><b>Dispensing Instructions</b></p>  | <ul style="list-style-type: none"> <li>• Administration should be deferred until a pharmacist is available to review the order and dispense the medication.</li> <li>• All patients receiving methotrexate (oral) are to have a pharmaceutical review by a pharmacist prior to supply and administration, confirming the dosage schedule is appropriate and clearly written. Drug interactions are to also be considered during this review.</li> <li>• Methotrexate must be dispensed by pharmacy for individual patients.</li> <li>• Pharmacy Departments are to supply only the amount required for the weekly dose, preferably on the day it is due.</li> <li>• The dispensing label is to state the prescribed <b>dose</b> and <b>day of the week</b> it is due and include a cytotoxic warning (for doses above 30 mg).</li> </ul>  |

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| <p><b>Administration Instructions</b></p> | <p style="text-align: center;"><b>Oral cytotoxic agents must NEVER be cut, crushed or dissolved</b></p> <p>If a patient is unable to swallow their methotrexate (oral), an alternative route of administration is to be discussed with the prescriber and pharmacist. Seek advice from Pharmacy where part doses are required (for example, paediatric patients).</p> <ul style="list-style-type: none"> <li>• To prevent the risk of accidental daily dosing, patient's own methotrexate must not be used for inpatients and all supplies must be obtained from the pharmacy department. Patient's own medication is to be returned to the patient or kept in locked storage to prevent duplication of dosing through self-administration.</li> <li>• All patients receiving methotrexate (oral) are to have a pharmaceutical review by a pharmacist prior to supply and administration. For patients admitted at times when the pharmacy department is closed, discuss with the prescriber if the dose can be delayed until the pharmacist is available to review the order. If this is not possible, the on-call pharmacist is to be contacted.</li> <li>• Nursing staff administering oral methotrexate must be fully familiar with this guideline.</li> <li>• Oral methotrexate must not be administered from an order that does not comply with the prescribing guidelines in this document.</li> <li>• Clarification from the prescriber or pharmacy must be obtained if the order is unclear, or the administering clinician has reason to query the dose, before administering a dose.</li> <li>• Methotrexate is available in 2.5mg and 10mg tablets.</li> <li>• Administering clinicians are to confirm with the patient and/or carers the day of the week on which the patient's dose is due, the normal dose and when it was last taken prior to administering a dose of methotrexate (oral).</li> <li>• Special handling precautions are required for methotrexate (oral) doses exceeding 30 mg per week. Personal Protective Equipment is to be worn during any activity which has potential to cause exposure to the medicine and related waste products. Refer to the Safe Work NSW <a href="#">Cytotoxic Drugs and Related Waste – Risk Management</a> and evIQ webpage <a href="#">Safe handling and waste management of hazardous drugs</a> for more information.</li> <li>• An independent second person check is to be employed when administering methotrexate (oral). The second person check processes are outlined in the <a href="#">NSW Health Policy Directive Medication Handling PD2022_032</a>.</li> </ul> |
| <p><b>Monitoring requirements</b></p>     | <p><b>Outpatients:</b> a full blood count, liver function tests and assessment of renal function should be done on commencing treatment and at a minimum of every 3 months for the duration of methotrexate (oral) treatment.</p> <p><b>Inpatients</b> are likely to be medically unstable. Full blood count, liver and renal function should be checked before each dose.</p> <p>Patients receiving oral methotrexate should be monitored to identify possible signs of toxicity. Be aware of patients with symptoms such as breathlessness, dry persistent cough, nausea, vomiting, diarrhoea headache, fatigue or mouth sores as these may be signs of methotrexate toxicity or intolerance.</p>  |

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| <p><b>Adverse Effects</b></p>             | <p>Clinical staff are to recognise patients with potential symptoms that may be signs of <b>methotrexate toxicity</b> or intolerance. Examples include nausea, vomiting, diarrhea, headache, fatigue and mouth sores.</p> <p><u>Common (&gt;1%):</u> nausea and vomiting, oral mucositis, myelosuppression, increased aminotransferases (usually transient), rash, itch, urticaria, photosensitivity, nephrotoxicity including acute renal failure, alopecia (generally mild and reversible), neurotoxicity (eg aseptic meningitis, encephalopathy, leucoencephalopathy)</p> <p><u>Infrequent (0.1–1%):</u> malaise, chills, fever, headache, dizziness, tinnitus, blurred vision, ocular irritation, oligospermia (transient)</p> <p><u>Rare (&lt;0.1%):</u> anaphylactic/anaphylactoid reactions, severe skin reactions (eg Stevens-Johnson syndrome, toxic epidermal necrolysis), radiation recall (including reactivation of sunburn), osteoporosis, skin and bone necrosis, pneumonitis, pulmonary fibrosis, serious hepatotoxicity (eg hepatic fibrosis)</p> |
| <p><b>Management of Complications</b></p> | <p>Oral methotrexate should be taken with food and is usually prescribed at night to reduce the nausea adverse effect during the day (minimal emetic potential). If the patient has a history of nausea and vomiting, metoclopramide may be prescribed as a premedication prior to methotrexate<sup>4</sup></p> <p>Methotrexate is prescribed with <b>folic acid</b> which is usually administered the day after methotrexate (this can vary) to reduce the gastrointestinal and haematological adverse effects associated with methotrexate. Folic acid doses may need to be increased in older patients or patients with poor nutritional status</p> <p><b>Folinic acid</b> may also be used as an alternative to folic acid, although folinic acid is predominately used for intractable nausea/vomiting or as rescue therapy after acute overdose or in malignant chemotherapy protocol.</p>   |

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| <p><b>Patient Education</b></p>    | <ul style="list-style-type: none"> <li>• All patients receiving methotrexate, and/ or their carer, should be provided with information and education by the prescriber and/ or pharmacist and provided with written information, for example:             <ul style="list-style-type: none"> <li>○ Methotrexate <a href="#">Consumer Medicine Information leaflet</a></li> <li>○ Methotrexate <a href="#">Adult Medication Information</a>, Australian Rheumatology Association</li> <li>○ Low-Dose Methotrexate <a href="#">Action Plan</a>, NPS</li> <li>○ Oral anti-cancer medicines <a href="#">Patient fact sheet</a>, eviQ</li> </ul> </li> <li>• Information and education should include:             <ul style="list-style-type: none"> <li>○ Emphasis on the once a week dosage by naming the day of the week (when a weekly dose is prescribed). It is to be reinforced that additional doses of the medicine must not be taken 'as needed' for symptom control</li> <li>○ Actions to be taken if a dose is missed</li> <li>○ Information on the importance of regular monitoring tests, symptoms of toxicity and the need for early intervention if such symptoms appear</li> <li>○ Emphasis on the similar appearance of methotrexate and folic acid tablets (if the patient is also on this supplement) and the difference in dosage of the two medicines</li> <li>○ Emphasis on confirming with the administering clinician the day of the week on which their dose is due, their normal dose and when it was last taken prior to taking a dose of methotrexate (oral).</li> <li>○ Details about appropriate personal protective equipment when handling high dose methotrexate (oral)</li> <li>○ Specifications regarding approved containers for disposal of cytotoxic contaminated waste.</li> <li>○ Safe administration of methotrexate (oral)</li> <li>○ How to deal with accidental ingestion</li> <li>○ How to dispose of unwanted or expired supply.</li> </ul> </li> <li>• Patients and/or carers who are newly initiated on methotrexate are to also be provided individualised written information on their dosage regimen (for example, a medication list) that specifies the patient's dose and day of the week for taking the medicine.</li> <li>• Professional Health Care Interpreters are to be utilised for patients and/ or carers who are not fluent in English or who are Deaf.</li> </ul> |
| <p><b>Storage requirements</b></p> | <p>Methotrexate must be dispensed by pharmacy for individual patients and <b>MUST NOT</b> be available in wards imprest stock or in the 'After Hours' drug cupboard.</p> <p>If a patient brought their own methotrexate into hospital, these must be locked in the normal storage area for patient's own drugs and must not be used to administer a dose under any circumstances.</p>  |
| <p><b>Further information</b></p>  | <p><b>For patients unable to tolerate oral dosing:</b> subcutaneous or intramuscular injection are sometimes appropriate alternate routes of administration. This requires a prescription by a methotrexate (oral) authorised prescriber and administration must occur with reference to <a href="#">eviQ Clinical procedure – administration of anti-cancer drugs – intramuscular and subcutaneous</a>.</p>   |

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| <b>Additional Resources</b>                              | <ol style="list-style-type: none"> <li>1. Cancer Institute NSW. eviQ. <a href="#">Oral anti-cancer medicines</a>. June 2024</li> <li>2. Australian Rheumatology Association. Adult Medication Information. <a href="#">Methotrexate</a>. June 2022</li> <li>3. Australian Rheumatology Association. <a href="#">Patient Information on Methotrexate</a>. April 2019</li> <li>4. National Prescribing Service. NPS. <a href="#">Managing Rheumatoid Arthritis</a>. January 2021</li> <li>5. Cancer Institute NSW. eviQ. <a href="#">Clinical procedure – administration of anti-cancer drugs – oral</a>. May 2023</li> <li>6. Council of Australian Therapeutic Advisory Groups (2020) <a href="#">Supporting safe practices for low-dose methotrexate – Position Statement on the use of low-dose methotrexate</a></li> </ol> |
| <b>Basis of Protocol/Guideline</b>                       | <ol style="list-style-type: none"> <li>1. NSW Health Policy Directive. <a href="#">High-Risk Medicines Management</a>. PD2024_006. November 2020.</li> <li>2. NSW Health Policy Directive. <a href="#">Medication Handling</a>. PD2022_032. August 2022</li> <li>3. SafeWork NSW. <a href="#">Cytotoxic Drugs and Related Waste – Risk Management</a>. July 2017</li> <li>4. MIMs Online. <a href="#">Methoblastin</a> (Methotrexate). October 2023</li> <li>5. AMH. <a href="#">Methotrexate (immunomodulator)</a>. January 2024</li> <li>6. AMH. <a href="#">Methotrexate</a>. Drug Interactions. January 2024</li> <li>7. AMH. <a href="#">Methotrexate (antineoplastic)</a>. January 2024</li> </ol>  |
| <b>Groups consulted in development of this guideline</b> | POWH Cytotoxic Working Party, SGH Oncology & Medicines Information.   |

## AUTHORISATION

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| Department  | Clinical Governance Unit                  |
| Position Responsible<br>(for ongoing maintenance of Protocol) | Quality Use of Medicines, Lead Pharmacist |

## GOVERNANCE

|                                    |                  |
|------------------------------------|------------------|
| Enactment date                     | August 2023      |
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| Chairperson, DTC                   | Dr John Shephard |
| Version Number                     | V2.1             |