

Supporting safe practices for low-dose methotrexate

Position Statement on the use
of low-dose methotrexate

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CATAG

Council of Australian
Therapeutic Advisory Groups



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+ TARGETED THERAPIES ALLIANCE

Helping consumers and health professionals make safe and wise therapeutic decisions about biological disease-modifying antirheumatic drugs (bDMARDs) and other specialised medicines. Funded by the Australian Government Department of Health through the Value in Prescribing bDMARDs Program Grant.

The Alliance is led by NPS MedicineWise and includes Arthritis Australia, Australia and New Zealand Musculoskeletal (ANZMUSC) Clinical Trials Network, Australian Rheumatology Association, Cochrane Musculoskeletal, Council of Australian Therapeutic Advisory Groups, Pharmaceutical Society of Australia, Quality Use of Medicines and Pharmacy Research Centre (University of South Australia) and Society of Hospital Pharmacists of Australia.

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Summary of key recommendations

1. Methotrexate is not considered chemotherapy at low doses.

2. The risk of harm from occupational exposure is low when handling low-dose methotrexate tablets.

3. For subcutaneous low-dose methotrexate, pre-filled syringes are preferred to those prepared from a vial.

4. People undergoing treatment with low-dose methotrexate do not need to avoid close person-to-person contact or use special precautions when disposing of their bodily fluids.

5. Provide clear information and advice to people on low-dose methotrexate at every opportunity.

Purpose

This position statement provides guidance to health professionals and medicines governance committees* on dispensing and administering low-dose methotrexate (oral and subcutaneous dosage forms). It aims to provide clear information on safety for those dispensing and administering low-dose methotrexate and assists them with providing reassurance to people undergoing treatment with low-dose methotrexate.

Background

Low-dose methotrexate is commonly used to manage people with various inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease (crohn disease and ulcerative colitis), systemic lupus erythematosus and severe psoriasis. In rheumatoid arthritis, methotrexate is first-line therapy¹ and is classified as a conventional synthetic disease-modifying antirheumatic drug (csDMARD).²

Methotrexate (in high doses) is used for other medical conditions, such as various cancers, which can contribute to confusion regarding the safety of low-dose methotrexate. There are several misconceptions circulating about methotrexate³, which may result in people having concerns with therapy and leading to poor adherence and suboptimal outcomes.

In some Australian hospitals, there is no discrimination with regard to handling recommendations of methotrexate, based on the dose being used. Handling of antineoplastic (or cytotoxic) medicines is considered an occupational risk to workers. Exposure may occur during preparation, administration, transportation, waste disposal and when handling bodily fluids/waste or in the event of a spill.⁴ Precautions intended for handling antineoplastic medicines may be required by local hospital policies when dispensing and administering methotrexate, no matter the dose.

In community pharmacy, methotrexate oral tablets and pre-filled injections are received in a separate package labelled: 'Caution cytotoxic'. The Quality Care Pharmacy Program requires any antineoplastic medicine to be flagged on the dispensary shelf by a 'Cytotoxic' label. These requirements can potentially add to the confusion that low-dose methotrexate is

harmful and result in pharmacists taking unnecessary precautions when handling low-dose methotrexate tablets or pre-filled subcutaneous injections. Pharmacists usually apply cautionary advisory label 21: 'Special handling and disposal required – ask your pharmacist' to the dispensed prescription.⁵ In the acute care setting pharmacists usually annotate methotrexate prescriptions on medication charts with a warning 'cytotoxic'. This may perpetuate the notion of low-dose methotrexate being a hazardous medicine to dispense and administer.

The use of handling precautions intended for antineoplastic medicines can promote alarm and concern for people being treated with low-dose methotrexate (and their carers) and impede their acceptance. Health professionals, either due to lack of familiarity or as a result of notifications relating to dosing errors, may also contribute to this fear.⁶ It is imperative to provide clear directions and written information, emphasising the importance of once-weekly dosing to people being treated with low-dose methotrexate.

As for all medicines, medication safety principles and strategies should be applied to ensure the safe prescribing, dispensing and administration of low-dose methotrexate.

Scope

This document applies to the circumstances when a health professional is dispensing or administering low-dose methotrexate (given weekly), either orally (intact whole tablets) or subcutaneously (pre-filled syringes), for an individual person. This position statement should be read in conjunction with other relevant policies, procedures or guidelines.

Definition of low-dose methotrexate

Low-dose methotrexate is usually defined as between 5mg and 25mg of methotrexate per week⁷, although doses up to 30mg may be used.^{3,8} This can be administered either orally or via a subcutaneous injection.

When used for immunomodulation to treat inflammatory disorders, methotrexate is administered **ONCE** a week.⁸

* Examples of medicines governance committees include drug and therapeutics committees, medicines advisory committees or equivalent, medication safety committees

Recommendations

1. Methotrexate is not considered chemotherapy at low doses

Methotrexate performs two distinct therapeutic functions at different doses:

- A. Low-dose methotrexate, given once weekly is an immunomodulator, used as a cornerstone treatment for rheumatoid arthritis and other autoimmune diseases. Although the pharmacology is unclear, low-dose methotrexate does not appear to exert its effects through its antineoplastic effect.^{9,10} Low-dose methotrexate is **NOT** considered chemotherapy and as such does not require handling as for antineoplastic medicines.¹⁰
- B. At all other doses, when used as an antineoplastic medicine, methotrexate works as a folic acid antagonist used to treat malignancies.¹¹ When preparing methotrexate for use as chemotherapy, precautions for handling antineoplastic medicines are required in both preparing and administering the medicine and caring for those undergoing treatment with high doses.

2. The risk of harm from occupational exposure is low when handling low-dose methotrexate tablets

The risk of harm from occupational exposure, during the dispensing or administering of whole tablets is low. Precautions intended for handling antineoplastic medicines are not necessary for the dispensing or administering of low-dose methotrexate (intact whole tablets).^{6,10,12} As is the case for all medicines, when dispensing intact whole methotrexate tablets (e.g. to include in a dose-administration aid) or preparing the medicine, a 'non-touch' technique should be used. Use of personal protective equipment should be guided by local policy and procedure.

Methotrexate is unable to be absorbed across the skin, as it is not lipophilic¹³ whether in solid form (tablet) or liquid (solution for injection).³

In an Australian study, six volunteers were exposed to a 25mg dose of methotrexate solution on their skin for 30 minutes, with regular serum levels taken and monitoring for toxicity.¹³ There was no significant methotrexate detected in serum (less than 0.02 micromol/L, which is 500 times below the concentration for which folic acid rescue therapy is recommended) or urine at any time point and at 24 hours. There was no evidence to suggest methotrexate toxicity. Mild erythema was reported in 3 of the 6 volunteers that resolved within 24 hours.¹³ The study concluded that 'Precautions to prevent contact with methotrexate designed for oncology protocols are unnecessary for our rheumatology patients or their carers using these much lower immunosuppressant doses for autoimmune diseases.'¹³

Methotrexate tablets should not be crushed.¹⁴ Seek advice from a pharmacist if the person is unable to swallow tablets whole or tablets need to be broken in half.

Pregnancy and occupational exposure

Balancing the evidence and risk of harm of occupational exposure to low-dose methotrexate, it is recommended that women who are pregnant or trying to conceive should be excluded from handling all dosage forms of this medicine.¹⁵⁻¹⁷ The risk from taking low-dose methotrexate in men trying to conceive is considered negligible based on recent literature.¹⁸⁻²¹ Therefore, men trying to conceive are able to continue to handle low-dose methotrexate tablets.

3. For subcutaneous low-dose methotrexate, doses from pre-filled syringes are preferred to those prepared from a vial

Oral methotrexate has a bioavailability of about 70% and its absorption can vary.³ Where the oral dose form is not tolerated or an optimal clinical response is not achieved, subcutaneous administration of low-dose methotrexate is more efficacious and generally better tolerated, with significantly fewer associated gastrointestinal adverse effects (e.g. nausea and diarrhoea).²²

Methotrexate is not an irritant or a vesicant and is not considered an extravasation risk.^{3,23} The introduction of a pre-filled syringe has reduced the risk of exposure for health professionals and carers and is therefore preferred for subcutaneous administration. The use of pre-filled syringes compounded in an approved Good Manufacturing Practice (GMP) facility provides a similar reduction in risk of harm.

As is appropriate for all injections, health professionals administering low-dose methotrexate injections should wear disposable gloves.^{15,16} It is suggested that aprons, goggles or masks are not necessary when administering pre-filled methotrexate syringes.²⁴

4. People undergoing treatment with low-dose methotrexate do not need to avoid close person-to-person contact or use special precautions when disposing of their bodily fluids

The precautions recommended for people receiving antineoplastic doses of methotrexate are not necessary in those receiving low-dose methotrexate.

The *Therapeutic Guidelines: Rheumatology* state: 'at the doses typically used in rheumatology, there is no risk of toxicity to close contacts of patients taking methotrexate and special precautions in handling bodily fluids are not required'.²

Pregnancy

Methotrexate is classified as pregnancy category D (drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage).²⁵ These medicines should not be administered to pregnant women or those with reproductive capacity unless reliable contraception measures are employed.³ Pregnant women do not need to avoid social contact with people who are taking low-dose methotrexate for an inflammatory or autoimmune condition.^{3,10}

5. Provide clear information and advice to people on low-dose methotrexate at every opportunity

When health professionals are interacting with the person receiving low-dose methotrexate at any stage, and in particular at the point of dispensing or administering the medicine, it is an opportunity to educate and counsel the person. Providing clear information and advice will assist people to feel safe and supported whilst undergoing treatment with low-dose methotrexate.

Key discussion points*:

- Emphasise the medicine is to be given **ONCE** each week and specify the day of the week the dose is to be taken.
- When methotrexate is used in low-doses it is not chemotherapy and is not used for cancer treatment at these doses.
- Methotrexate can be used safely and effectively, when taken as directed (reiterate once-weekly dosing regimen).
- It is safe for the person receiving low-dose methotrexate to handle 'whole' or 'intact' tablets however they should not be broken or crushed.
- Health professionals may take extra precautions because they handle the medicine many times in a day.
- People undertaking treatment with low-dose methotrexate can safely make physical contact with others including pregnant women.
- Methotrexate prefilled syringes administered subcutaneously can be safely self-administered.

Labelling

The *Australian Pharmaceutical Formulary and Handbook* recommends label 21: 'Special handling and disposal required – ask your pharmacist' for methotrexate.⁵ Pharmacists use their knowledge and professional judgement in deciding to use or omit ancillary labels except where legislation requires that certain labels must be used.⁵ For people, receiving low-dose methotrexate, special handling is not required by the person and applying label 21 may cause confusion. If applying label 21, appropriate counselling with the person should be conducted.

Additional instructions for labelling of low-dose methotrexate include:

- Specify the dose on the label
- Specify the day of the week (written in full, not abbreviated) to be used
- Use the phrase 'each week' NOT 'weekly'
Example: 'Take **one** tablet on **Wednesday** each week'
- Avoid 'As directed'
- Affix a 'To be taken once a week only' sticker to the dispensed methotrexate container
- If packing a dose administration aid ensure it is packed correctly **ONCE** each week.

* Note: This is not an exhaustive list of counselling points, see further information on page 7.

Further information

For people taking low-dose methotrexate

- NPS MedicineWise Patient Action Plan for low-dose methotrexate.
- Arthritis Australia (AA) information for consumers on Methotrexate
- My RA rheumatoid arthritis support program (<https://myra.org.au/>)
 - Self-injecting low dose methotrexate for the treatment of arthritis
- ISMP Consumer MedSafety information on methotrexate

For health professionals

- Notes for prescribers of low-dose once weekly methotrexate (MTX)
- Metro North Hospital and Health Service Shared Care Fact Sheet – Low Dose Methotrexate
- International Medication Safety Network (IMSN): IMSN Global Targeted Medication Safety Best Practice 3 – Prevent inadvertent daily dosing of oral methotrexate for non-oncologic conditions.
- Institute for Safe Medication Practices (ISMP) newsletter article: [August 2018](#)

Appendices

APPENDIX 1: Glossary

TERM	DEFINITION
antineoplastic	Inhibits or prevents the growth and spread of tumors or malignant cells.
chemotherapy	Treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. ²⁶
cytotoxic medicine/agents	A substance that kills cells, including cancer cells. These agents may stop cancer cells from dividing and growing and may cause tumors to shrink in size. ²⁶
dispensing	The review of a prescription and the preparation, packaging, labelling, record keeping and transfer of the medicine, including counselling, to a patient. ^{27,28}
health professional	For the purpose of this position statement health professional includes nurses, midwives, medical practitioners, pharmacists and other individuals deliver health care. ²⁹
immunomodulator	A chemical agent that modifies the body's immune system, by activating or suppressing its function. ²⁶

APPENDIX 2: How this position statement was developed

Position statements are intended to provide short summarised best practice recommendations to hospital Drug and Therapeutics Committees using a consensus development model. The position statements are written to be adapted to local environments.

This policy was developed in consultation and with the endorsement of CATAG member organisations listed below:

- ACT Health
- NSW Therapeutic Advisory Group (NSW TAG)
- Northern Territory Drug and Therapeutics Committee
- Queensland Health Medicines Advisory Committee (QHMAC)
- South Australian Medicines Advisory Committee (SAMAC)
- Statewide Therapeutic Drug Committee, (STDC) Tasmania
- Victorian Therapeutics Advisory Group (Vic TAG)
- Western Australian Therapeutics Advisory Group (WATAG).

External consultation with key national organisations was also undertaken.

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- **Ms Jane Donnelly** – National Coordinator, Council of Australian Therapeutic Advisory Groups
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- **Ms Lisa Ciabotti** – Professional Officer, Victorian Therapeutics Advisory Group
- **Ms Quyen Du** – Pharmacist – Training & Delivery, Pharmaceutical Society of Australia
- **Associate Professor Sean O’Neill** – Institute of Bone and Joint Research, Kolling Institute, University of Sydney and Consultant Rheumatologist Royal North Shore Hospital. Honorary Chair of the Australian Rheumatology Association Therapeutics Committee
- **Ms Clarissa Rentsch** – Senior IBD Pharmacist, The Royal Melbourne Hospital
- **Mr Jerry Yik** – National Policy Manager, Society of Hospital Pharmacists of Australia.

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