Methotrexate

Traffic light classification- Amber 1
Information sheet for Primary Care Prescribers
Part of the Shared Care Protocol: Management of Dermatological Conditions With Disease-Modifying Anti Rheumatic Medications in Adults

Indications[1, 2]
Patients with severe, uncontrolled psoriasis (licensed) and eczema (unlicensed), which is not responsive to other therapy

Any patient groups to be excluded from shared care
Patients receiving:

- doses more frequently than once a week
- 10mg tablets
- receiving subcutaneous therapy

are excluded from shared care, i.e. classified as RED on the Nottinghamshire Joint Formulary.

Medicines Initiation
Dermatologists.

Therapeutic Summary[5]
Methotrexate is used to induce remission or partial remission in patients with inflammatory conditions, including arthritis, psoriasis, connective tissue disease and vasculitis. Clinical benefit may take up to 3 months. NSAIDs and simple analgesics may need to be continued. Patient-reported adverse effects usually occur early in therapy, but please see explicit criteria for review below.

Products available
Methotrexate tablets 2.5mg ONLY
(Methotrexate tablets 10mg – are NOT recommended as per NPSA guidance[5]).

Dosages and route of administration
Methotrexate is given orally ***once per week***. The patient is advised to take the treatment on the same day each week, and the day of the week is defined in the NPSA booklet to avoid confusion. The initial dose and subsequent dosing will be determined by secondary care and recorded within the NPSA monitoring booklet and by written communication.

The usual starting dose is 2.5-10mg **once weekly**. The weekly dose is increased to the maintenance dose as specified by the dermatology specialist team.

The recommended maximum dose of methotrexate for psoriasis is 25mg once per week[3, 4]. The maintenance dose should be adjusted according to disease response and kept as low as possible.[1]

The prescriber should decide with the patient which day of the week the patient will take their methotrexate and specify the day of intake on the prescription.[8]

Methotrexate is the subject of a National Patient Safety Agency (NPSA) alert available from: www.npsa.nhs.uk. This alert recommends that all prescribers must avoid the use of 'as directed' in the dosage instructions box. Prescribers should be aware that patients often understand their dose by the number of tablets they take; therefore, **it should be clear which strength tablets the patient is taking**.

Example prescription: Methotrexate **2.5mg tablets;** take **six tablets (15mg)** once a week**.**

Folic acid 5 mg should be prescribed concurrently to reduce the likelihood and severity of side effects associated with methotrexate and improves continuation of therapy and compliance[5]. The dosing will be specified by a letter from the Dermatology Specialist Team and in the NPSA booklet.

Duration of treatment
Methotrexate for psoriasis is a long-term treatment. Clinical benefit may take up to 3 months.

Monitoring Requirements and Responsibilities[1, 3, 5]
Pre-treatment assessments to be performed by a dermatologist and will include:

- FBC, LFT, U&E, Procollagen 3 (PIIINP)*, Chest X-ray Hepatitis B & C and assessment of Varicella Zoster immune status.

* Procollagen 3 (PIIINP) is recommended by BAD for the early detection of methotrexate-induced liver disease. Blood samples should be sent in a yellow-topped bottle (SST II vacutainer). The cost of the test to GP practices is £18.93.

Note that PIIINP is not monitored in rheumatology patients because:
The role of this test in the background of inflammatory arthritis is unclear as it can be falsely positive, and it is not routinely recommended in rheumatology patients.

Secondary care will continue to monitor patients until they are stable for at least 3 months.

Ongoing monitoring required in primary care once a patient is stable:
If the dose is changed or monitoring becomes unstable, the patient reverts back to secondary care monitoring. Primary care monitoring for dermatology patients is, therefore, less frequent than for rheumatology patients.

Frequency of monitoring	**Tests to be done**			
	FBC	**LFT (including AST or ALT)**	**U+ E**	**Procollagen 3**
Every 3 months	✓	✓	✓**	✓

**U&Es should be checked more frequently if there is any reason to suspect deteriorating renal function.

- Patients should be asked about a rash, oral ulceration, sore throat or unexplained dyspnoea/cough, abnormal bruising or bleeding at each visit.
- The clinician actioning results from monitoring, and thereby prescribing, is responsible for entering results in the monitoring document.
- **Routine annual influenza and one-off pneumococcal vaccinations are highly recommended.**

Explicit criteria for review and discontinuation of the medicine[3, 5] – Other benchmark values may be set by secondary care in specific clinical circumstances. This will be communicated by secondary care.

Adverse Event	**Action**
Nausea and vomiting or diarrhoea	Withhold until discussed with dermatology specialist team.
Hair loss	Usually mild, rarely significant
WBC<3.0 x10^9/l	Withhold until discussed with dermatology specialist team
Neutrophils < 1.6 x10^9 /l	Withhold until discussed with dermatology specialist team
Platelets <140 x 10^9 /l	Withhold until discussed with dermatology specialist team
ALT, AST or ALP > x2 upper limit of reference range AND the ALT: AST ratio is greater than 0.8	Withhold until discussed with dermatology specialist team
Rash or oral ulceration	Withhold until discussed with dermatology specialist team
New or increasing dyspnea or dry cough	Withhold until discussed with dermatology specialist team

Macrocytosis (MCV > upper limit of reference range) *Unexplained eosinophilia >0.5 x 10^9/l	Withhold[3] and Check serum folate and B12 & TFT. Treat any underlying abnormality. If results are normal, interrupt treatment until discussed with the dermatology specialist Withhold until discussed with dermatology specialist team. *eosinophilia is commonly seen in patients with eczema and, therefore, not 'unexplained'.
Abnormal bruising/severe sore throat/fever	Immediate FBC. Withhold until results are available and discuss with the dermatology specialist team.
Unexplained fall in albumin (in the absence of active disease)	Withhold until discussed with dermatology specialist team
PIIINP > 8µg/l in at least 3 samples over a 12-month period	Withhold until discussed with dermatology specialist team
PIIINP > 13µg/l in two consecutive samples	Withhold until discussed with dermatology specialist team
Significant (20%) reduction in renal function	Withhold until discussed with dermatology specialist team. Must not be used if CrCl <30.[9]

In addition to absolute values for haematological or biochemical indices, a rapid fall or rise or consistent downward or upward trend in any value should prompt caution and extra vigilance[3].

For a full list of Side Effects, refer to the BNF or Summary of Product Characteristics.

IF YOU ARE IN ANY DOUBT ABOUT ANY POTENTIAL ADVERSE REACTION, PLEASE CONTACT THE DERMATOLOGY SPECIALIST TEAM.

Relevant Contraindications[1, 2, 3]

- **TRIMETHOPRIM - see interactions**
- Anti-folate medications (e.g. co-trimoxazole) - see interactions
- Hypersensitivity to methotrexate or to any of the excipients
- Pregnancy (see below) and breastfeeding
- Significant hepatic impairment and excessive alcohol consumption
- Liver disease, including fibrosis, cirrhosis, recent or active hepatitis, unless specified specifically by the secondary care team
- Severe / significant renal impairment (i.e. CrCl <10ml/min)
- Severe acute or chronic infections, immunodeficiency syndromes and malignancies
- Pre-existing blood dyscrasias (i.e. bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia) Underlying lung disease
- Stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcer disease
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' - chapter 6, page 42): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. N.B. Routine influenza and pneumococcal vaccinations are highly recommended.

Relevant Precautions[1, 2, 3]

- Localised or systemic infection including hepatitis B or C and history of tuberculosis.
- Severe / significant renal failure (dose reductions may be required when GFR < 60ml/min).
- Blood disorders
- Photosensitivity—psoriasis lesions aggravated by UV radiation (skin ulceration reported).
- Alcohol – advise patient to remain well within national guidelines.
- Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur, and deaths have been reported. Patients should be advised to contact their GP immediately should they develop persistent cough or dyspnoea.

- Patients who have no history of exposure to varicella zoster virus (VZV), i.e., chickenpox or herpes zoster (shingles), should avoid contact with individuals with chickenpox or herpes zoster. Varicella– zoster immunoglobulin (VZIG) is recommended for individuals who are at increased risk of severe varicella (including patients taking immunosuppressant medicines, e.g., azathioprine, ciclosporin, methotrexate, leflunomide) and who have no antibodies to varicella–zoster virus and who have significant exposure to chickenpox or herpes zoster. Contact the on-call microbiologist via the hospital switchboard for advice if required.
  See 'The Green Book' for detailed guidance. If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.

Pregnancy[1, 2, 3, 5]

Methotrexate is teratogenic and embryotoxic, henceforth, patients ***must not become pregnant*** whilst taking this medication. Women need to stop the medication for 6 months before attempting to become pregnant.[7, 9] The same advice applies to men wishing to start a family. It is recommended that sexually active female patients use two methods of contraception throughout this period, and should have a pregnancy test prior to starting therapy.

In the event of a woman falling pregnant whilst taking methotrexate, the medication should be discontinued immediately, and a high dose of folic acid (15mg daily) provided for at least 6 weeks.[7] Please access urgent advice from the local fetomaternal medicine / obstetric unit.

Clinically relevant medicine interactions and their management[1, 2, 3, 5]

- **TRIMETHOPRIM – do not give concurrently with methotrexate.**
- Co-trimoxazole (Septrin®) and Nitrous oxide: should be avoided because of their antifolate properties (severe bone marrow depression has been reported).
- Aspirin and Non-steroidal anti-inflammatory medications (NSAIDs): Aspirin or other NSAIDs are thought to increase the potential toxicity of methotrexate, and therefore, the type and dose of NSAID should not be altered during methotrexate therapy without prior consultation with the dermatology specialist team. However, they should not be stopped just because the patient is starting methotrexate, as the medication takes 1-2 months to exert an effect
- Phenytoin and levetiracetam: antifolate effect of methotrexate increased (increase toxicity) – caution in use, increase frequency of monitoring.
- Proton Pump Inhibitors (e.g. omeprazole, lansoprazole, pantoprazole): prolongs the elimination of methotrexate via the kidneys. Stop 4 to 5 days before initiation and consider alternatives such as H2-receptor antagonists.
- Antibacterials *other than* trimethoprim and co-trimoxazole: Excretion of methotrexate may be reduced (increased risk of toxicity) – caution in use, increase the frequency of monitoring.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' - chapter 6), Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. N.B. Routine influenza and pneumococcal vaccinations are highly recommended. Inactivated polio is available, although a suboptimal response may be seen.
- *Clozapine* – increased risk of agranulocytosis
- *Probenecid* - reduces the excretion of methotrexate, increasing its toxicity
- Acitretin and ciclosporin: Avoid concomitant use – increased Methotrexate concentration and hepatotoxicity.

For a full list of contraindications, precautions, and drug interactions, refer to the BNF or Summary of Product Characteristics.

Information given to patient

- Patients will be given a National Patient Safety Agency pre-treatment leaflet and patient-held monitoring and dosage record booklet by dermatology when they start methotrexate treatment.
- The patient must be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, fever, bruising, bleeding, unusual weakness and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, diarrhoea and dark urine), and respiratory effects (e.g. shortness of breath or dry cough) to the GP.

- Patients should be advised to avoid contact between themselves and individuals with chickenpox or shingles if they have no prior history of exposure. Any exposure of patients with no varicella-zoster virus antibodies to chickenpox and shingles sufferers should be reported to the GP for assessment and possible treatment.
- The patient will also be given a BAD Patient information sheet and a printed sheet giving details of the pathway that the patient will follow and contact details.
- The patient should be advised to abstain from alcohol while taking methotrexate
- Female patients will be advised of the need to avoid pregnancy during therapy and for 6 months after stopping methotrexate[7, 9], and male patients of the need to avoid fathering children within the same timeframe.

Patient's roles and responsibilities

- The patient should take the methotrexate medicine on the same day every week unless otherwise instructed by an appropriate healthcare professional.
- Inform all healthcare professionals of their current medication prior to receiving any new prescribed or over-the-counter medication.
- Store their medication securely away from children.
- Read the information supplied by their GP, specialist and pharmacist and contact the relevant practitioner if they do not understand any of the information given.
- To attend regular blood tests. Failure to attend blood tests will result in medication being stopped on specialist advice.
- The patient will report any suspected adverse reactions (as above) to the GP for assessment.
- The patient will report to their GP or specialist any new onset breathlessness, dry persistent cough, vomiting or diarrhoea, fever or sore throat, mouth ulcers, skin rashes, bleeding or unusual weakness, as these can be signs of toxicity or intolerance of methotrexate.
- Patients who are taking methotrexate will ensure they have a patient information leaflet and monitoring document and bring it to all appointments with healthcare professionals, including GPs, consultants, pharmacists, dentists etc.
- Patients are advised to avoid self-medication with over-the-counter aspirin or Ibuprofen.
- Always attend your scheduled clinic visits and blood test appointments.
- Attend routine influenza and pneumococcal vaccinations
- Request supply of maintenance therapy in a timely manner

Community Pharmacist Roles and Responsibilities

For patients taking methotrexate:

1. The pharmacist will ask to see the patient's monitoring booklet and check if any dose changes have been made since the last prescription issue.
2. The pharmacist must ensure the strength of the tablet supplied to the patient is consistent to prevent any confusion about the number of tablets the patient must take. Confirm strength to be supplied with the prescription. If in any doubt, contact the prescriber for confirmation.
3. Counsel the patient about their methotrexate, telling them the dose in terms of quantity of tablets and (in the vast majority of cases) weekly frequency, and providing the patient with a monitoring booklet if they do not already have one.
4. Ensure the patient can differentiate between their folic acid and methotrexate and know how to take them both.
5. Be aware of patients who attend with symptoms such as breathlessness, dry, persistent cough, vomiting or diarrhoea, as these can be signs of oral methotrexate toxicity or intolerance. Refer them back to the prescriber for further investigation. It is good practice to maintain a record of any over-the-counter items supplied to the patient.

References

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Version Control- **Methotrexate: Management of Dermatological Conditions with DMARDs in Adults**			
Version	Author(s)	Date	Changes
2.1	Shary Walker	19/11/2020 09/09/2022	1. Added the new MHRA update regarding: prescriber should specify the day of methotrexate intake on the prescription. 2. Explicit criteria for review and relevant contraindications updated. 3. New updates for pregnancy: "In the event of a woman falling pregnant whilst taking methotrexate, the medication should be discontinued immediately and high dose folic acid (15mg daily) provided for at least 6 weeks". 4. Additionally, the interval of stopping methotrexate for women trying to be pregnant was extended from 3 months to 6 months. 5. Relevant interactions updated. Interaction with proton pump inhibitors added. Consider H2 antagonists as the alternative. 6. Added more patients' and pharmacists' roles and responsibilities. 7. PIL link updated.