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 (www.nottinghamshireformulary.nhs.uk).

Medicines Initiation
Dermatologists.

Therapeutic Summary\(^3\)
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 maintenance dose as specified by 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.\(^1\)

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 likelihood and severity of side-effects associated with methotrexate and improves continuation of therapy and compliance. The dosing will be specified by 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

Pre-treatment assessments to be performed by dermatologist and will include:

* 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 patient is stable:
If dose is changed or monitoring becomes unstable, patient reverts back to secondary care monitoring. Primary care monitoring for dermatology patients is therefore less frequent than for rheumatology patients.

<table>
<thead>
<tr>
<th>Frequency of monitoring</th>
<th>Tests to be done</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FBC</td>
</tr>
<tr>
<td>Every 3 months</td>
<td>✓</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting or diarrhoea</td>
<td>Withhold until discussed with dermatology specialist team.</td>
</tr>
<tr>
<td>Hair loss</td>
<td>Usually mild, rarely significant</td>
</tr>
<tr>
<td>WBC&lt;3.0 x10^9/l</td>
<td>Withhold until discussed with dermatology specialist team</td>
</tr>
<tr>
<td>Neutrophils &lt; 1.0 x10^5/l</td>
<td>Withhold until discussed with dermatology specialist team</td>
</tr>
</tbody>
</table>
Platelets <100 x 10⁹/l

ALT, AST or ALP > x2 upper limit of normal

Rash or oral ulceration

New or increasing dyspnea or dry cough

Macrocytosis (MCV > upper limit of reference range)

Abnormal bruising / severe sore throat

Unexplained fall in albumin

PIIIINP > 8μg/l in at least 3 samples over a 12 month period

PIIIINP > 13μg/l in two consecutive samples

Significant (20%) reduction in renal function

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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.

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

- TRIMETHOPRIM - see interactions
- Anti-folate drugs (e.g. co-trimoxazole) - see interactions
- Pregnancy (see below)
- Breast feeding
- Significant hepatic impairment
- Liver disease including fibrosis, cirrhosis, recent or active hepatitis unless specified specifically by the secondary care team.
- Severe / significant renal impairment (i.e. GFR <20ml/min)
- Immunodeficiency syndromes
- Excessive alcohol consumption
- Underlying lung disease
- Active infection and malignancy

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Part of the Shared Care Protocol: Management of Dermatological Conditions with Disease-Modifying Anti Rheumatic Drugs in Adults

Approved by NottsAPC May 2015, REVIEW DATE: Nov 2020

Page 3 of 6
Relevant Precautions

- Localised or systemic infection including hepatitis B or C and history of tuberculosis.
- Severe / significant renal failure (dose reductions may be required when GFR < 50ml/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 [www.dh.gov.uk/en/Publichealth/Immunisation/Greenbook](http://www.dh.gov.uk/en/Publichealth/Immunisation/Greenbook) for detailed guidance. If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.

Pregnancy

Methotrexate is teratogenic and patients must not become pregnant whilst taking this drug. Women need to stop the drug for 3 months before attempting to become pregnant. 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 she should stop the drug immediately but continue folic acid, 5mg daily. Please access urgent advice from the local fetomaternal medicine / obstetric unit.

Clinically relevant medicine interactions and their management

- **TRIMETHOPRIM** – do not give concurrently with methotrexate.
- Co-trimoxazole (Septrin®) and Nitrous oxide: should be avoided because of their anti-folate properties (severe bone marrow depression has been reported).
- Aspirin and Non-steroidal anti-inflammatory drugs (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 drug takes 1-2 months to exert an effect.
- **Phenytoin**: antifolate effect of Methotrexate increased – caution in use, increase frequency of monitoring.
- Antibacterials other than trimethoprim and co-trimoxazole: Excretion of methotrexate may reduced (increased risk of toxicity) – caution in use, increase frequency of monitoring.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at [https://www.gov.uk/government/collections/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 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 a patient-held monitoring and dosage record booklet by dermatology when they start methotrexate.
- The patient must be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort 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 within 3 months and preferably 6 months of taking methotrexate and male patients of the need to avoid fathering children within the same timeframe.

**Patient’s roles and responsibilities**
- To attend for regular blood tests. Failure to attend for 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 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.

**Community Pharmacist Roles and Responsibilities**
For patients taking methotrexate:
1. 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.
2. 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, providing the patient with a monitoring booklet if they do not already have one.
3. Ensure the patient can differentiate between their folic acid and methotrexate and know how to take them both.
4. 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


