Rheumatology Methotrexate Shared Care Guideline

Based upon the NPSA Safety Alert this Shared Care Guideline outlines arrangements for patients taking methotrexate, including:

- Clarity of prescribing and monitoring responsibilities
- How often blood tests will be conducted and in which location
- Review of the results, and action required if abnormal
- Communication and documentation of information, including dosage changes, frequency of monitoring, and test results

This guideline should be used in conjunction with the NPSA document 'Towards the safer use of oral methotrexate' and the Summary of Product Characteristics (SPC) for methotrexate.

Licensed indications	Methotrexate is used in the treatment of adults with severe, active, classical or definite rheumatoid arthritis who are unresponsive or intolerant to conventional therapy. Methotrexate has also been used in the treatment of severe, uncontrolled psoriasis, which is not responsive to other therapy.
Typical dosage	Initiation and dose adjustment will be the responsibility of the consultant specialist. Typical dose: 7.5mg-25mg ONCE weekly. The initial dose may be 5-10 mg ONCE weekly, increasing by 2.5mg-5mg every 2-6 weeks until disease stabilised. The maximum licensed dose in rheumatoid arthritis is 25 mg/week. Rarely, the maximum dose can be 30 mg/week. Lower doses should be considered for frail elderly patients who often have poor renal function. It is preferable to use 2.5mg strength tablets only, to avoid the risk of confusion and potential overdose. Patients should be reminded of the need to check the dose and strength of the tablets with each prescription. Co-prescribe folic acid 5mg once weekly, preferably the day after the methotrexate. Folic acid can be given any day as long as it is not on the same day as methotrexate. Folic acid reduces toxic effects and improves continuation of therapy and compliance.
Cautions	• Patients with clinically significant renal impairment from any cause. • Localised or systemic infection including hepatitis B or C and history of tuberculosis. • Unexplained anaemia and/or cytopenia associated with marrow failure.

Contra-indications	• Severe/significant renal or significant hepatic impairment. Liver disease including fibrosis, cirrhosis, recent or active hepatitis. • Active infectious disease. • Overt or laboratory evidence of immunodeficiency syndrome(s), and serious anaemia, leucopenia or thrombocytopenia. • Methotrexate should not be used concomitantly with drugs with antifolate properties (e.g. trimethoprim, co-trimoxazole). • Bone marrow failure with unexplained anaemia and cytopenia • Pregnancy and breastfeeding. Following administration to a man or woman conception should be avoided by using an effective contraceptive method for at least 3 months after. • Patients with a known allergic hypersensitivity to methotrexate or any of the excipients should not receive methotrexate.
Drug interactions	Notable drug interactions (refer to BNF and SPC for further drug interactions). • Phenytoin: Antifolate effect of methotrexate is increased. • Probenecid, penicillin, NSAIDs: Methotrexate excretion is reduced (clinically significant interaction between NSAID and methotrexate is rare, although patients should be advised to avoid self-medication with over the counter aspirin or ibuprofen). • Tolbutamide: Serum concentration of methotrexate may be increased. • Co-trimoxazole (Septrin®) and trimethoprim should be avoided: Antifolate effect of methotrexate is increased and greatly increases the risk of marrow aplasia. • Retinoids: Plasma concentration of methotrexate increased by acitretin, also increased risk of hepatotoxicity-avoid concomitant use. • Patients must not receive immunisations with live vaccines. Pneumococcal and annual influenza vaccines are recommended. In patients exposed to chickenpox or shingles, passive immunisation should be carried out using VZIG.
Baseline investigations	To be undertaken by hospital specialist: -FBC, U&Es, creatinine, LFTs and CXR (unless CXR done within the last 6 months). Pulmonary function tests should be considered in selected patients.
Ongoing monitoring by GP once stabilised-to be detailed by hospital specialist	BSR: FBC, U&Es, LFTs **every 2 weeks** until dose and monitoring **stable for 6 weeks**; thereafter **monthly** until the dose and disease is stable for **1 year**. Thereafter the monitoring may be reduced in frequency to **every 2 to 3 months**, based on clinical judgement with due consideration for risk factors including age, comorbidity, renal impairment, when monthly monitoring is to continue.

<table>
<tr><td></td><td>BAD: Initially once a week FBC, U&Es, creatinine, LFTs; gradually increase interval between tests until therapy stabilised; thereafter monitor every 2–3 months.

Update patient held monitoring booklet accordingly.</td></tr>
<tr><td>Adverse drug reactions and actions to be taken</td><td>
<table>
<tr><th>Abnormal result</th><th>Action to be taken</th></tr>
<tr><td>WBC < 3.5 x 10^9/l</td><td rowspan="5">Withhold until discussed with specialist team.</td></tr>
<tr><td>Neutrophils < 2.0 x 10^9/l</td></tr>
<tr><td>Platelets < 150 x 10^9/l</td></tr>
<tr><td>AST, ALT > twice upper limit of reference range</td></tr>
<tr><td>Albumin-unexplained fall (in absence of active disease)</td></tr>
<tr><td>Rash or oral ulceration, nausea and vomiting, diarrhoea</td><td></td></tr>
<tr><td>New or increasing dyspnoea or dry cough</td><td>Withhold and discuss urgently with specialist team.</td></tr>
<tr><td>MCV > 105 fl</td><td>Withhold and check serum B12, folate and TFT and discuss with specialist team if necessary.</td></tr>
<tr><td>Mild to moderate renal impairment</td><td>Withhold until discussed with specialist team.</td></tr>
<tr><td>Severe sore throat, abnormal bruising</td><td>Immediate FBC and withhold until the result of FBC is available.</td></tr>
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Patients should 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).</td></tr>
<tr><td>Secondary care responsibilities</td><td>

To provide a patient information leaflet indicating the risks and benefits associated with methotrexate therapy. To confirm patient understanding and consent to treatment. To advise the patient on potential side effects (and the action to be taken should they occur).
To initiate methotrexate and prescribe until patient is stabilised, make any dosage adjustments and undertake baseline monitoring. To communicate any dosage changes and frequency of monitoring to the GP.
To inform the patient of the need for blood monitoring and provide them with a monitoring and dosage record book.
To refer patient to their GP for shared care once stabilised on

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	treatment. Contact patient's GP to request prescribing under shared care and provide the shared care guideline. • To review the patient in clinic twice per year.
Primary care responsibilities	• To agree to prescribe methotrexate in accordance with the shared care guideline, and if do not agree to participate in shared care, discuss with specialist on receipt of shared care request. • To monitor and prescribe methotrexate in accordance with the specialist and the shared care guidelines. • To ensure that the monitoring and dosage record book is completed and kept up to date, and that results are within the normal range.
Patient responsibilities	• To attend all hospital and GP clinic appointments and bring monitoring booklet. • To report adverse effects to the specialist or GP. • To check the dose and strength of the tablets with each prescription.
Prescribing Information	• All prescribers should follow the NPSA's Safe Practice Checklist. • All prescribers must avoid the use of 'as directed' in prescribing- a specific dose must be applied to each prescription and the strength of methotrexate tablets to be supplied. • It is preferable to use 2.5mg strength tablets only, to avoid the risk of confusion and potential overdose. Patients should be reminded of the need to check the dose and strength of the tablets with each prescription. • Repeat prescriptions should be retained separately for prescriber review prior to authorising. • Any suspected serious adverse reactions should be reported to MHRA via the yellow card scheme.

References:

- BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists, 2008.
- Quick reference guideline for monitoring of disease modifying anti-rheumatic drug (DMARD) therapy, prepared by the BSR/ BHPR DMARD guideline group, May 2007 updated November 2009.
- Methotrexate Summary of Product Characteristics (SPC), http://www.medicines.org.uk/EMC/medicine/12033/SPC/Methotrexate+2.5+mg+Tablets/, accessed 11/02/2013
- BNF 64 September 2012