Health and Social Care Board

Interface Pharmacist Network Specialist Medicines

Methotrexate subcutaneous injection (adult)

Dermatology / Rheumatology / Gastroenterology / Ophthalmology shared care guideline.

Specialist details	Patient identifier
Name: _____	
Location: _____	
Tel: _____	**Date:** _____

Introduction

This shared care guideline refers to the use of the licensed subcutaneous methotrexate products in the treatment of **NON-CANCER CONDITIONS ONLY.**

Subcutaneous methotrexate is used as an alternative to oral methotrexate to reduce GI toxicity or to improve efficacy.
Licensed indications: rheumatoid arthritis, psoriasis, psoriatic arthritis, juvenile idiopathic arthritis.
Unlicensed indications: Crohn's disease, severe eczema, cutaneous and systemic lupus erythematosus, scleroderma, dermatomyositis, inflammatory eye disease.

Adult dosage and administration

The dose is variable with the usual range being between 5mg and 25mg **once a week**. Treatment is generally started at a dose of 10 - 15mg and adjusted gradually as determined by the specialist. A weekly dose of 25mg should in general not be exceeded. Doses outside these ranges may be considered with prior agreement of initiating specialist and GP.

Once weekly dosing – specify day of administration (not Monday).

Patients previously established on oral methotrexate may transfer to subcutaneous methotrexate at higher initial doses. Doses exceeding 20mg once weekly are associated with a significant increase in toxicity, especially bone marrow suppression. Dose reduction should be considered in frail elderly patients or if there is significant renal or hepatic impairment.

Patients must be willing to self-administer or have a carer who is willing to administer the injection.

Available as:

- 50mg/mL methotrexate solution **pre-filled pens (Metoject®)** in a range of doses: 7.5mg (0.15mL), 10mg (0.2mL), 12.5mg (0.25mL), 15mg (0.3mL), 17.5mg (0.35mL), 20mg (0.4mL), 22.5mg (0.45mL), 25mg (0.5mL), 27.5mg (0.55mL), and 30mg (0.6mL)
- 25mg/mL methotrexate solution **pre-filled pens (NORDiMET®)** in a range of doses: 7.5mg (0.3mL), 10mg (0.4mL), 12.5mg (0.5mL), 15mg (0.6mL), 17.5mg (0.7mL), 20mg (0.8mL), 22.5mg (0.9mL), 25mg (1.0mL).
- 25mg/mL methotrexate solution **pre-filled syringes (Zlatal®)** in a range of doses: 7.5mg (0.3mL), 10mg (0.4mL), 12.5mg (0.5mL), 15mg (0.6mL), 17.5mg (0.7mL), 20mg (0.8mL), 22.5mg (0.9mL), 25mg (1.0mL).

Note training in self-administration must be provided based on device/brand selected.

Folic acid: usual dose 5mg once each week, taken one to two days after the methotrexate. This may reduce the risk of gastrointestinal and haematological toxicity. In some instances, dose of folic acid may vary – specialist will advise.

Hospital specialist responsibilities

- Agree shared care with patient's GP and document in patient's notes.
- Advise GP on dose of methotrexate and folic acid to be prescribed.
- Advise **which methotrexate device/brand patient** has been trained on.
- Provide patient/carer with relevant written information on use, side-effects and need for monitoring of medication.
- Advise on need for adequate contraception.
- Provide specialist training programme including training on safe self-administration, cytotoxic spillage (provide a cytotoxic spill kit and cytotoxic sharps box if necessary), and waste disposal, based on training recommended in RCN guidance[1].
- Assess patient competence as per RCN training checklist in RCN guidance[1].
- Provide pre-treatment information as per NPSA methotrexate monitoring record booklet (can be ordered from pharmacystationeryorders@hscni.net).
- Undertake baseline tests as indicated in monitoring table.
- Review results of safety monitoring and request additional tests as required.
- Monitor disease response to treatment and need to continue therapy.
- Continue to review the patient at agreed specified intervals sending a written summary to the GP whenever the patient is reviewed.
- Provide any other advice or information for the GP if required.

[1] RCN guidance: 'Administering subcutaneous methotrexate for inflammatory arthritis' RCN 2013.

<table>
<tr><th colspan="2">Monitoring table</th><th>Hospital specialist</th><th colspan="4">GP</th><th>Hospital specialist</th></tr>
<tr><th rowspan="2">Test</th><th rowspan="2">Indication</th><th rowspan="2">Pre-treatment baseline</th><th colspan="4">During treatment</th><th rowspan="2">Annual review</th></tr>
<tr><th>Until on stable dose for 6 weeks</th><th>Next 3 months</th><th>Thereafter *</th><th>Only where indicated by specialist**</th></tr>
<tr><td>FBC
LFTs
U&Es, eGFR</td><td>Baseline assessment, dose adjustment</td><td>✓</td><td>Every 2 weeks</td><td>Every month</td><td>Every 3 months*</td><td rowspan="2">Every 6 months**</td><td rowspan="2">As part of annual review or as clinically indicated</td></tr>
<tr><td>ESR/CRP (Rheumatology and Gastroenterology only)</td><td>Disease activity scoring</td><td>✓</td><td colspan="3">Every 3 months</td></tr>
<tr><td>Height & weight
PIIINP (Dermatology only)</td><td>Baseline assessment</td><td>✓</td><td colspan="4" rowspan="2">Not routinely required</td><td rowspan="2">If clinically indicated</td></tr>
<tr><td>Blood pressure
Chest x-ray
PFTs, TB screening if indicated</td><td>Baseline assessment, respiratory and TB screening</td><td>If clinically indicated</td></tr>
<tr><td colspan="2">Ask about oral ulceration/sore throat, unexplained rash or unusual bruising/bleeding</td><td>✓</td><td colspan="4">At every consultation</td><td>✓</td></tr>
<tr><td colspan="8">If a further DMARD is added as combination therapy, or the dose is increased, the initial starting schedule should be reinstated.
There may be clinical circumstances where the frequency of monitoring may vary and this should be specified by the initiating specialist.
* If used in combination with leflunomide, monthly monitoring should continue.
** Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis as recommended by specialist at review or by specialist communication</td></tr>
</table>

GP responsibilities

- Prescribe methotrexate (**dose and device/brand as specified** by hospital specialist) once each week (specify day not Monday) “As required” or “as directed” are **unsuitable** dosage instructions for subcutaneous methotrexate.
- Prescribe folic acid as specified by the hospital specialist.
- Prescribe Sharpsguard or Sharpsafe container 1 litre (each will hold up to four pens).
- Arrange and record ongoing monitoring as advised by specialist (see monitoring table), ensuring practice systems are in place to recall patients for monitoring blood tests.
- Follow-up any non-compliance with the monitoring schedule. The risks of cessation of therapy versus risks of toxicity should be considered. Contact the specialist if treatment is stopped or further advice required.
- Report any adverse drug reactions to initiating specialist and the usual bodies (eg. MHRA/CHM).
- Ensure no drug interactions with other medicines.
- Check patient using adequate contraception.
- Administer inactivated influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check patient has had ONE DOSE of pneumococcal vaccine (revaccination is not recommended except every five years in patients whose antibody levels are likely to have declined more rapidly eg. asplenia), see BNF or Green Book.
- Passive immunization using varicella immunoglobulin (VZIG) should be considered in non-immune patients if exposed to chickenpox or shingles. Contact Regional Virus Laboratory, Royal Group of Hospitals, duty virologist 07889 086 946 for advice if exposure is suspected. For other queries eg. those concerning exposure, infection or any recommendations relating to healthy susceptible household contacts, consult the Green Book and/or take additional advice from Regional Virus Laboratory, Royal Group of Hospitals.
- Ask about oral ulceration, sore throat, unexplained rash or unusual bruising/bleeding at every consultation.

Withhold methotrexate and contact specialist if:

- WCC < 3.5 x 10^9/L
- Neutrophils < 1.6 x 10^9/L
- Unexplained eosinophilia > 0.5 x 10^9/L
- Platelets < 140 x 10^9/L
- MCV > 105fL, (check B12 & folate & TFT)
- AST/ALT > 3 times the upper limit of normal (for results between 2 - 3 x ULN, continue methotrexate, repeat bloods and seek specialist advice) Minor elevations of AST/ALT are common
- If renal impairment develops
- Unexplained fall in serum albumin
- Oral ulceration / sore throat
- Unexplained rash / abnormal bruising
- New or increasing dyspnoea or dry cough.

Normal reference range may vary slightly between labs.
Results should be recorded in the patient’s NPSA methotrexate monitoring record booklet.
Please note an unusual fall or rise or a consistent downward or upward trend in any value should prompt review of the patient and extra vigilance. Some patients may have abnormal baseline values, specialist will advise.

Adverse effects, precautions and contraindications

Infection. Immunosuppressants can increase susceptibility to infection. It is advisable not to commence or continue treatment with methotrexate when patients have a confirmed or established local or systemic infection. It is advisable to recommence once the infection has been treated. Precise period of discontinuation depends on the nature and severity of infection and the activity of the underlying disease.
Blood disorders: leucopenia, thrombocytopenia and anaemia. GPs should be alert to any unexplained bruising or bleeding.
Hepatotoxicity: methotrexate may be hepatotoxic, particularly at high cumulative dosages.
Cancer risk. Patients receiving long-term immunosuppressive drugs are at increased risk of developing a malignancy. The most frequently occurring types are lymphoma and skin malignancy. The avoidance of excessive exposure to the sun, and the use of high factor sunscreen and protective clothing are advised. Adherence to population screening programmes is particularly important in this population.
Nausea, dizziness and **headache** may be encountered, and may resolve with dose reduction and in the case of nausea, addition of anti-emetic medication.
Alopecia, stomatitis, diarrhoea: contact the initiating specialist if severe or persistent.
Respiratory function. Infrequently, methotrexate can cause interstitial pneumonitis, pulmonary oedema and fibrosis. Patients complaining of unexplained dyspnoea or unexplained non-productive cough should be referred immediately to the initiating specialist.
Alcohol: patients should be advised that alcohol consumption should be avoided or kept well within recommended safe national guidelines, due to the increased potential for liver toxicity.
Contraindications include:

- Immunodeficiency syndrome
- Severe renal or hepatic impairment
- Active, chronic or recurrent infections especially respiratory or urinary tract
- History of alcohol abuse/cirrhosis
- Untreated folate deficiency
- Ulcers of the oral cavity and known active gastrointestinal ulcer disease
- Severe anaemia, leucopenia or thrombocytopenia.

Pregnancy / contraception. Methotrexate at any dose should be avoided in pregnancy. A reliable form of contraception should be used by men and women whilst on methotrexate and for at least 3 months after discontinuing it. In women treated with methotrexate within 3 months prior to conception, folic acid supplementation (5mg/day) should be continued prior to and throughout pregnancy. In the case of accidental pregnancy on methotrexate, the drug should be stopped immediately, folic acid supplementation (5 mg/day) continued and refer to initiating specialist.
Breast feeding. Women being treated with methotrexate should not breastfeed.
Live vaccines. Consult the Green Book and take additional advice from initiating specialist if required.

Common drug interactions

Trimethoprim or **co-trimoxazole** increase the risk of pancytopenia. Do not co-prescribe except on specialist advice.
Co-prescription of **drugs with potential hepatotoxic effects** is not advisable eg. Retinoids.
Ciclosporin: increased risk for nephrotoxicity - can be prescribed concomitantly on specialist advice.
NSAIDs & **aspirin** (<300mg) may reduce excretion of methotrexate. Clinically significant interactions between NSAIDs and methotrexate are rare but clinicians should be vigilant. Additional monitoring may be required.
Clozapine: increased risk of agranulocytosis.
Leflunomide: increased risk of toxicity.
Herbal remedies: avoid if possible due to unknown interaction potential.

Communication

For any queries relating to this patient's treatment with methotrexate, please contact the specialist named at the top of this document.

This information is not inclusive of all prescribing information and potential adverse effects.
Please refer to full prescribing data in the SPC or the BNF

Date prepared: January 2021 Date of review: June 2022