NHS Shropshire Clinical Commissioning Group

The Robert Jones and Agnes Hunt NHS Orthopaedic Hospital NHS Foundation Trust

Oral and Parenteral Methotrexate
Rheumatology Local Safety Monitoring Schedule

This local safety monitoring schedule supports clinicians under the Local Enhanced Service for High Risk Drug Monitoring (formerly Near Patient Testing). Aligning clinical and prescribing responsibility enhances patient safety because the individual signing the prescription will also be responsible for ensuring that any necessary monitoring has been undertaken and will have access to the results of this.

The prescriber and specialist assume joint clinical responsibility for the drug and the consequences of its use.

Specialist details	GP details	Patient details
Name:	Name:	Name:
Address:	Address:	Contact number:
Email:	Email:	
Contact number:	Contact number:	

Introduction

Methotrexate is an anti-metabolite and folate antagonist.
Licensed indications: rheumatoid arthritis; psoriasis
Unlicensed indications: psoriatic arthritis; juvenile idiopathic arthritis; connective tissue disease (SLE, myositis and vasculitis); sarcoidosis

Adult dosage and administration

Rheumatology: dose range is 5mg to 25mg ONCE each week.

Always prescribe oral methotrexate in multiples of 2.5mg tablet strength.
The 10mg tablets must NOT be used.
Patients on s/c methotrexate may have supplies made through the hospital via a homecare company.

Once weekly dosing – it is good practice to specify the day of administration on the prescription, and state "Take ONCE a week on xxxxday" to avoid confusion.

Dose adjusted, as recommended, by specialist according to response.
Doses outside these ranges may be considered with prior agreement of initiating specialist and GP. Lower doses should be used in the frail elderly or if there is significant renal or hepatic impairment.
Methotrexate may take up to 12 weeks to take effect, so steroids/NSAIDs may be needed initially.

Folic acid: Folic acid is always co-prescribed alongside methotrexate, to reduce the risk of gastrointestinal and haematological toxicity. A typical dose is folic acid 5mg once each week, taken two to three days after methotrexate dose. Sometimes the dose/frequency of folic acid is increased and occasionally folinic acid is used instead.

Specialist responsibilities

- Provide GP with clear written advice on required dosage and frequency of both methotrexate and folic acid, written monitoring guidelines and drug information. Check for interactions with other medicines.
- Provide the patient/carer with relevant (written) information on use, side-effects and need for monitoring of infection. **Advise on need for adequate contraception.**

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- Varicella Zoster -consider immunisation of non- immune patients before starting immunosuppression (after discussion with appropriate specialist)

Specialist responsibilities continued

- Arrange pre-treatment baseline investigations either in secondary or primary care.

- Baseline tests:
  - **FBC**
  - **LFT**
  - **U&E**
  - **Chest X-ray/pulmonary function tests**
  - **ESR or CRP**
  - **Varicella zoster IgG in suspected non-immune patients** and notify general practitioner as appropriate

- Review results of safety monitoring and request additional tests as required
- Provide patient with handheld monitoring booklet and record baseline results
- Monitor disease response to treatment and need to continue therapy.
- Identify and report adverse events to the GP and the MHRA (via yellow card).
- 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.

Primary Care responsibilities

- Ensure the correct formulation of methotrexate is prescribed. Parenteral methotrexate is usually prescribed by the hospital specialist only (and should be added to the "hospital only" section of the medicines list). **Oral and parenteral methotrexate must <u>not</u> be prescribed concomitantly.**
- Prescribe oral methotrexate (2.5mg tablets only) once each week (specifying the day as outlined above – not Monday); "as required" or "as directed" instructions are unsuitable.
- Ensure an oral methotrexate dose is prescribed as XX tablets of 2.5mg .
- Ensure no drug interactions with other medicines.
- Check patient is using adequate contraception.
- Continue to prescribe Methotrexate if patient is having regular appropriate blood monitoring and monitoring results are within acceptable range.
- Repeat prescriptions should be removed from the surgery repeats pile and retained separately for prescribers to review prior to signing. Maximum 28 days supply.
- Administer influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check patient has had ONE DOSE of pneumococcal vaccine (revaccination is not recommend except every five years in patients whose antibody levels are likely to have declined more rapidly (e.g. asplenia) – see BNF or Green Book.
- **Varicella zoster**
  - *Non-immune patients* should avoid contact with people with chicken pox or shingles; consider passive immunisation using varicella immunoglobulin (VZIG) if exposure is suspected (contact Public Health England/Blood Transfusion Service for advice). Consider active immunisation of non-immune subjects before starting immunosuppression (if recommended by specialist)

  - Varicella infection can be severe in immunosuppressed patients, and early systemic anti-viral and supportive therapy may be required. Suspend methotrexate if possible until recovered.
- Arrange and record ongoing monitoring as agreed with specialist:
  - **FBC, U&E and LFT**
    - Every 2 weeks until 6 weeks after last dose increase and provided it is stable, monthly thereafter.

    - **ESR & CRP**
        - May be required every 3 months
- Report any adverse drug reactions to initiating specialist and the usual bodies (e.g. MHRA)
- Any dosage change should be followed by an FBC one week later.
- Patients on combination DMARD therapy may need more frequent monitoring. Please check the Local Safety Monitoring Schedule for each drug.
- Ask about oral ulceration/sore throat, unexplained rash or unusual bruising at every consultation.
- If patient develops symptoms/signs of systemic infection, this should be treated promptly and methotrexate withheld until the infection has cleared.
- Ensure a clinician updates the patient's record following specialist review.

Withhold methotrexate and contact specialist if:

- WBC $< 3.5 \times 10^9$ /L
- Neutrophils $< 2 \times 10^9$ /L
- Platelets $< 150 \times 10^9$ /L
- AST/ALT > 2 times the upper limit of normal (minor elevations are common)
- Unexplained fall in albumin
- New or increasing dyspnoea or cough (CONTACT ON CALL MED REG IF PNEUMONITIS STRONGLY SUSPECTED)
- MCV >105 fl Withhold and check serum B12, Folate and TFT and discuss with specialist team if necessary.
- Oral ulceration/sore throat
- Unexplained rash or bruising
- Nausea and vomiting, diarrhoea
- Mild to moderate renal impairment (eGFR 30-60ml/min) may require dose adjustment (if eGFR < 30 ml/min, methotrexate is contra-indicated)
- Established local or systemic infection

Please note: A rapid increasing or decreasing trend in any values should prompt caution and extra vigilance. Some patients may have abnormal baseline values, specialist will advise
Results should be recorded in the patient's monitoring booklet

Adverse effects, precautions and contra-indications

Myelosuppression & decreased resistance to infection: especially respiratory/ urinary tract or shingles/chickenpox. Temporarily withhold methotrexate if patient is systemically unwell with significant infection and / or requiring anti-infective intervention.
Hepatotoxicity: methotrexate may be hepatotoxic, particularly at high cumulative dosages.
Nausea: commonly encountered, may resolve with dose reduction and/or addition of anti-emetic medication.
Alopecia, stomatitis, diarrhoea: contact the initiating specialist if severe or persistent.
Respiratory function: infrequently, methotrexate can cause interstitial pneumonitis and fibrosis. Patients complaining of unexplained dyspnoea or unexplained non-productive cough should be referred immediately to the initiating specialist. **If pneumonitis strongly suspected contact on-call medical registrar.**
Alcohol: patients are advised that alcohol consumption should be avoided or kept to a minimum due to the increased potential for liver toxicity.

Vaccines: Avoid immunisation with live vaccines during treatment, and consider live vaccines prior to commencing methotrexate (see Green Book re zoster vaccine)

Contraindications include:

- Hypersensitivity to methotrexate
- Severe renal impairment (CKD stage 4/5) or hepatic impairment
- Chronic or recurrent infections especially respiratory or urinary tract
- Severe anaemia, leucopenia or thrombocytopenia

- Untreated folate deficiency
- History of alcohol abuse/cirrhosis

Pregnancy: female patients must be advised not to conceive whilst receiving methotrexate. A reliable form of contraception should be used by men and women whilst on methotrexate and for at least 3 months after discontinuing it. Discontinue methotrexate and refer immediately if a patient or partner discovers they are pregnant whilst taking methotrexate.

Breast Feeding: Women being treated with methotrexate should not breastfeed.

Common drug interactions

Do **NOT** prescribe concomitant **Trimethoprim** or **Co-trimoxazole** due to risk of pancytopenia

Co-prescription of drugs with potential marrow suppressive, hepatotoxic or nephrotoxic effects is not advisable.

NSAIDs, & spirin (<300mg): unlikely to cause any clinically significant adverse effects and treatment can be continued

Herbal remedies: avoid if possible due to unknown interaction potential

Clozapine may cause increased risk of agranulocytosis

Communication

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

This information is not inclusive of all prescribing information, potential adverse effects and drug interactions

Please refer to full prescribing data in the SPC or the BNF

References

GMC: Prescribing guidance: Shared care www.gmc-uk.org/guidance/ethical_guidance/14321.asp(accessed 20/10/2014)

NMC : Standards of proficiency for nurse and midwife prescribers http://www.nmc-uk.org/Documents/NMC-Publications/NMC-Standards-proficiency-nurse-and-midwife-prescribers.pdf (accessed 3/11/2014)

SPC Matrex : http://www.medicines.org.uk/emc/medicine/6003

Chakravarty, K., McDonald, H., Pullar, T. et al. (2008) BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology* **47**(6), 924-925.

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