Methotrexate

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

Indications

Rheumatoid arthritis – licensed[1,2]
Connective tissue disease (SLE, myositis and vasculitis) – outside of licence (supported by national guidance)[3].

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).

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[1,2,3,5]

Methotrexate is given orally once per week (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 10-15mg once weekly. The weekly dose is increased to maintenance dose as specified by rheumatology specialist team.
The maximum licensed dose[2] of methotrexate for rheumatoid arthritis is 20mg/week but higher doses to 30mg may be used as per national guidelines[3].

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 at a minimal dose of at least 5 mg weekly should be prescribed concurrently to reduce likelihood and severity of side-effects associated with methotrexate and improves continuation of therapy and compliance[3]. The dosing will be specified by letter from the Rheumatology Specialist Team and in the NPSA booklet.

Duration of treatment[3]

All DMARDs are long term treatments. Clinical benefit may take up to 3 months

Monitoring Requirements and Responsibilities[3]

Pre-treatment assessment to be performed by specialist and will include:

- FBC, LFT, U&E and chest X-ray

Ongoing monitoring:

Time period in treatment	Frequency of monitoring	Tests to be done		
		FBC	LFTs	U&Es
0-6 weeks	Fortnightly	✓	✓	✓
6 weeks – 3 months	Monthly	✓	✓	✓
>3 months and stable dose for 6 weeks	3 monthly	✓	✓	✓
Any dose increase	2 weeks post dose increase then revert to above protocol	✓	✓	✓

- Patient to report any rash, oral ulceration, sore throat, abnormal bruising or bleeding.
- GP to assess and manage cardiovascular risk factors – patient at higher risk of cardiovascular events due to rheumatological disease activity.
- No additional monitoring requirements are required in primary care for patients receiving additional biological therapy including anti-TNF therapy.
- Patients receiving methotrexate with leflunomide need to continue with monthly blood tests throughout their treatment
- Routine influenza and pneumococcal vaccinations are highly recommended.

Explicit criteria for review and discontinuation of the medicine[3] – 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 rheumatology specialist team.
WBC <3.5x10^9/l	Withhold until discussed with rheumatology specialist team.
Neutrophils <2x10^9/l	Withhold until discussed with rheumatology specialist team.
Platelets <150x10^9/l	Withhold until discussed with rheumatology specialist team.
AST / ALT > x2 upper limit of reference range	Withhold until discussed with rheumatology specialist team.
Rash or oral ulceration	Withhold until discussed with rheumatology specialist team.
New or increasing dyspnoea or dry cough	Withhold until discussed with rheumatology specialist team.
Macrocytosis (MCV>upper limit of reference range)	Withhold[3] and Check serum folate and B12 & TFT. Treat any underlying abnormality. If results normal discuss with rheumatology specialist team.
Abnormal bruising / severe sore throat	Immediate FBC. Withhold until results available and discuss with rheumatology specialist team.
Albumin- unexplained fall (in absence of active disease)	Withhold until discussed with rheumatology specialist team.
Mild to moderate renal impairment	Withhold until discussed with rheumatology specialist team. (refer to BNF).

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 RHEUMATOLOGY SPECIALIST TEAM.

Relevant Contraindications[1,2,3,4,6]

- **TRIMETHOPRIM – see interactions**
- **Anti-folate medicines (eg. 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 failure (i.e. GFR <10ml/min)
- Immunodeficiency syndromes
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at www.dh.gov.uk): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. N.B. Routine influenza and pneumococcal vaccinations are highly recommended.
- Herpes zoster vaccination may be given when the patient is receiving 15 mg methotrexate per week or less in line with the current Green Book recommendations

Relevant Precautions[1,2,3,4]

- 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
- 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. See 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[1,2,3,4]

Methotrexate is teratogenic and patients ***must not become pregnant*** whilst taking this medicine. Women need to stop methotrexate for 3 months before attempting to become pregnant. The same advice applies to men wishing to start a family. In the event of a woman falling pregnant whilst taking methotrexate she should stop the medicine 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[1,2,3,4,7]

- **TRIMETHOPRIM – do not give concurrently with methotrexate.**
- 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 rheumatology specialist team. However, they should not be stopped just because the patient is starting methotrexate as the medicine takes 1-2 months to exert an effect and the patient is likely to need the NSAID in the longterm.
- Co-trimoxazole (Septrin®), and Nitrous oxide: Avoid concomitant use – due to anti-folate properties (severe bone marrow depression has been reported).
- 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 www.dh.gov.uk): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. Inactivated polio is available although suboptimal response may be seen.
- Acitretin: 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 must be given an NPSA pre-treatment information leaflet and a patient held monitoring and dosing booklet by rheumatology 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, 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 an approved drug information leaflet from Arthritis Research UK. Further copies available at www.arthritisresearchuk.org.

Patient's roles and responsibilities

The patient will:

- ensure they have a methotrexate patient information leaflet and monitoring document, and bring it to all appointments with healthcare professionals, including GPs, consultants, pharmacists, dentists etc.
- avoid self-medication with over-the-counter aspirin or Ibuprofen.
- Take their medication as agreed, unless otherwise instructed by an appropriate healthcare professional.
- Attend for all regular blood tests and all follow-up appointments with GP and specialist. If they are unable to attend any appointments they should inform the relevant practitioner as soon as possible and arrange an alternative appointment.
- Inform all healthcare professionals of their current medication prior to receiving any new prescribed or over-the-counter medication.
- Report all suspected adverse reactions (as above) to medicines to their GP.
- 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.
- 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.

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 and the patient's monitoring booklet. 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, 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.
See overarching SCP for general community pharmacy responsibilities.

References

1. Maxtrex Tablets 2.5mg – Pfizer Ltd. Summary of Product Characteristics [23/12/2019] on Electronic Medicines Compendium: (accessed on 22/06/2020) via www.medicines.org.uk/emc
2. Methotrexate 2.5mg Tablets – Hospira UK Ltd. Summary of Product Characteristics [17/12/2019] on Electronic Medicines Compendium: (accessed on 22/06/2020) via www.medicines.org.uk/emc
3. Ledingham J, Gillick N, Irving K. et al. (2017) BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology doi:10.1093/rheumatology/kew149
4. BNF [online] via www.medicinescomplete.com [accessed 22/06/2020]
5. NPSA Patient Safety Alert: Improving compliance with oral methotrexate guidelines 1st June 2006.
6. Ashley C, and Currie A [Eds]. The Renal Drug Handbook [3rd edition] Oxford: Radcliffe Publishing Ltd [2009].
7. Baxter K (ed), Stockley's Drug Interactions. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com (accessed on 22/06/2020)