Torbay and South Devon NHS
NHS Foundation Trust

Oral Methotrexate (MTX) Shared Care Guideline for GPs

Please note: This guideline only covers oral therapy with methotrexate. Subcutaneous methotrexate injections are prescribed by the specialist team at TSDFT

Indication:

Active rheumatoid arthritis and other types of inflammatory arthritis, steroid sparing agent in Giant Cell Arteritis and Polymyalgia Rheumatica and Vasculitis.

Specialist Responsibility:

- Assess patient for co-morbidities
- Request baseline tests including FBC, U+Es and eGFR, LFTs, chest X-ray and lung function tests
- Counsel patient on benefits, side effects, frequency of dosing and monitoring requirements and provide written information
- **Treatment with these drugs will be initiated by the specialist, who is responsible for prescribing until shared care is agreed. Any GP who does not feel confident to undertake the clinical and legal responsibility for a shared care drug is not obliged to undertake the prescribing and should discuss this with the specialist.**
- Refer to MHRA Drug safety update, Sept 2020: Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing (see “cautions” section below)
- Specify target doses, monitoring and review dates at clinically relevant time intervals for both the GP and specialist team and any other patient specific information.
- **Initiate therapy and provide at least the first 6 weeks of methotrexate and until GP has confirmed willingness to share care.**
- Provide advice as required by the GP and review patient as necessary

GP responsibility

- On-going prescription of Methotrexate and folic acid
- Refer to MHRA Drug safety update, Sept 2020: Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing (see “cautions” section below)
- Monitoring as per instructions below
- Report adverse events to specialist team and to the MHRA via the yellow card scheme
- Report and seek advice from the specialist team on any aspect of patient care which is of concern and may affect treatment
- Inform specialist team if treatment is stopped for any reason

Dosage:

Methotrexate is only ever prescribed as a ONCE WEEKLY dose to be taken on the SAME DAY EACH WEEK

- All prescribing should be in **2.5 mg tablets** to avoid confusion.
- The **starting dose is usually 10 mg per week**. The tablets are taken in one 24 hour period, usually as a single dose, after food.
- The dose range for oral MTX is 2.5 – 20 mg per week and occasionally 25mg.
- Dose should be increased as set out in the dosing letter. This is usually an increase of 2.5- 5mg every 2 weeks.
- In common with other 2nd line agents, MTX will take 10-12 weeks to have any effect.
- **Routine co-prescription of folic acid** is recommended from the outset to guard against GI side effects - 5mg o.d. taken 6 days per week (i.e. avoiding the day on which the MTX is taken).

Monitoring:

- **Blood tests:**
  - **FBC, U+Es and eGFR, LFTs and albumin**
- **Frequency:**
  - **every 2 weeks for 6 weeks**
  - **Then monthly for 3 months**
  - **Then 12 weekly thereafter unless there are exceptions as detailed below**
- **For dose increases monitor blood tests every 2 weeks until stable dose for 6 weeks**
- **Exceptions to monitoring rules**
  - Monthly monitoring required if:
    - MTX taken in combination with Leflunomide, azathioprine or mycophenolate
    - High risk patients or significant co-morbidities i.e. co-existing liver or renal disease, highly fluctuant blood results.
  - The specialist will inform the GP if this is required
- Consider stopping MTX and seek advice (e-mail: tsdft.rheumatologydmards@nhs.net or **01803-654939**) if any of the following occur:
  - WCC or platelet count falls on 3 successive occasions
  - Total WCC <3.5 or
  - Neutrophils < 1.6
  - Isolated lymphopenia is not usually an indication for cessation of MTX therapy
  - Platelet count < 140
  - MCV >105

    - Unexplained eosinophilia >0.5
    - ALT or AST >100 U/l
    - Unexplained drop in albumin <30g/l
    - Creatinine >30% above baseline +/- eGFR <60
- The MCV may rise on MTX – if >105, consider checking B12 / folate if patient is anaemic.
- If evidence of renal impairment (MTX metabolites are renally excreted) dose reduction may be required.
- The patient should be advised to report signs of infection (e.g. persistent sore throat, fever) or easy bruising.

Side effects:

- This list is not exhaustive, for additional information please consult the BNF and product SPCs

Common	• **Nausea, vomiting, GI upset* (~20%), stomatitis / mouth ulcers** - can occur at any stage. Advise patient to take methotrexate with food and in the evening. May resolve with methotrexate dose reduction. Withhold treatment if does not resolve or is severe and discuss with specialist.
Less common	• **Alopecia, rash & diarrhoea*** • **Haematopoietic suppression -** may occur abruptly; factors likely to increase toxicity include advanced age, renal impairment and concomitant anti-folate medication. The patient should be advised to report easy bruising or infection. • **LFT abnormalities** • **Headache, mood disturbance**
Uncommon	• **Pulmonary symptoms (~1%) -** symptoms of interstitial pneumonitis, often within first 6-8 weeks after treatment, indicated by persistent dry cough, shortness of breath or fever. Patient should report these symptoms, stop methotrexate, have urgent CXR and urgent specialist advice should be sought. • **Hepatitis**

*GI side-effects can be abolished in 80% of patients by co-prescription of folic acid.

Drug interactions:

- This list is not exhaustive, for additional information please consult the BNF and product SPCs

Acitretin	**Avoid**	May increase serum concentration of methotrexate & increase risk of toxicity
Aspirin, NSAIDs		Reduced methotrexate excretion. Clinically significant interaction with NSAIDs is rare, continue standard doses advised by specialist, but patients should be advised to avoid self-medication with over the counter aspirin or ibuprofen. Low dose aspirin can be continued
Azathioprine		Increased risk of toxicity
Ciclosporin		Monitor closely, risk of toxicity
Ciprofloxacin		Reduced methotrexate clearance may increase toxicity
Clozapine	**Avoid**	Increased risk agranulocytosis
Co-Trimoxazole	**Avoid**	Increased anti-folate effect of methotrexate which increases risk of marrow aplasia.
Digoxin	**Caution**	Methotrexate possibly reduces absorption of digoxin.
Fluorouracil topical	**Avoid**	Risk of toxic skin reaction
Leflunomide		Increased risk liver/haemotoxicity
Phenytoin	**Caution**	Increases anti-folate effect of methotrexate
Probenecid	**Avoid**	Reduces methotrexate excretion and increases toxicity
Proton pump inhibitors		Possibly reduce methotrexate excretion
Sulphonamides		Risk of increased toxicity
Tetracycline/ doxycycline		Increased risk of methotrexate toxicity
Tolbutamide		Increased serum concentration of methotrexate
Trimethoprim	**Avoid**	Increased antifolate effect of methotrexate with risk of marrow aplasia
Warfarin		Monitor INR closely

Cautions and Contraindications

MHRA Drug Safety Update (September 2020): Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing

Advice for prescribers:

- before prescribing methotrexate, make sure that the patient is able to understand and comply with once-weekly dosing
- consider the patient's overall polypharmacy burden when deciding which formulation to prescribe, especially for a patient with a high pill burden
- decide with the patient which day of the week they will take their methotrexate and note this day down in full on the prescription
- inform the patient and their caregivers of the potentially fatal risk of accidental overdose if methotrexate is taken more frequently than once a week; specifically, that it should not be taken daily
- advise patients of the need to promptly seek medical advice if they think they have taken too much
- Refer to the MHRA Drug Safety Update for more information

Alcohol:

- Alcohol should be limited to less than 14 units of alcohol per week
- Methotrexate is contraindicated in alcohol abuse

Vaccines:

A single dose of pneumococcal vaccine (Pneumovax® II) and **annual influenza vaccinations** are strongly recommended for patients with **inflammatory arthritis**. Pneumococcal vaccination boosters are required at five yearly intervals in individuals with no spleen, splenic dysfunction or chronic renal disease as outlined in Green Book

- Methotrexate should be withheld for 2 weeks after immunisations to improve efficacy
- Live vaccinations are contraindicated until 3 months after cessation of methotrexate
- Although the shingles (Zostavax) vaccine is a live attenuated vaccine, treatment with low dose methotrexate (<0.4mg/kg/week) is not considered sufficiently immunosuppressive and is not a contraindication to administering the vaccine.
- Passive immunisation may be given with varicella zoster immunoglobulin (VZIg) in non-immune patients exposed to chicken pox or shingles. Contact specialist for advice.

Pregnancy, breastfeeding and fertility:

- MTX is **contraindicated** in pregnancy and in breastfeeding women
- Reliable and effective **contraception** must be practised by **female** patients during treatment and for 3 months after treatment prior to conception
- Limited evidence suggests that Methotrexate may be compatible with paternal exposure. Seek specialist advice

Elective surgery

- Continue methotrexate but consider infection risk and drug interactions

Infection

- Methotrexate can be continued while patient receiving oral antibiotics
- Methotrexate should be stopped in the acutely unwell older person or while receiving IV antibiotics.
- Seek advice if there are recurrent infections

Advice and Support

- Rheumatology.sdht@nhs.net
- Nurses helpline: 01803 654939
- Rheumatology secretaries: 01803 655897/54832/55759

References

1. BNF 74. September 2017-March 2018

2. SPC Methotrexate 2.5mg tablets. Accessed via www.medicines.org.uk June 2018

3. Ledingham J et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Rheumatology*, Volume 56, Issue 6, 1 June 2017, Pages 865–868

4. Flint J et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology*, Volume 55, Issue 9, 1 September 2016, Pages 1693–1697

5. MHRA Drug Safety Update (September 2020): Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing

Appendix 1 Shared Care Agreement Letter

Consultant Request

To Dr ……..

Practice Address:

Patient Name
Hospital number
Date of birth
Address

Diagnosed condition:…….

I recommend treatment with the following drug:… Methotrexate …….

I am requesting your agreement to sharing the care of this patient according to the South Devon Shared Care Guideline for this drug. If you agree, I will send you, in writing, any additional information required for you to undertake prescribing responsibility, as laid down in the Shared Care Guideline.

Signed:…….. Date……

Consultant name:……..

Department:……..……

Contact telephone number: …….

GP Response

I agree / do not agree* to share the care of this patient in accordance with the Shared Care Guideline.

Signed:…….. Date……

GP name:……...
*Delete as appropriate