NHS
Bedfordshire
Clinical Commissioning Group

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DMARDs in Adult Rheumatology –Information for GPs

METHOTREXATE (oral and subcutaneous)

(BEDFORD HOSPITAL)

Clinicians should also refer to the overarching DMARD shared care guideline document for details of the individual responsibilities for each group e.g. e.g. GP / Specialist Rheumatology team under this shared care agreement.

IMPORTANT AMENDMENT TO THE MANAGEMENT OF PATIENTS CURRENTLY PRESCRIBED DMARDs DURING THE COVID-19 PANDEMIC OUTBREAK

Click here to read the full guidance for this patient cohort which also includes advice on the frequency of blood test monitoring of DMARDs in stable patients.

Original Information for GPs

NB:

- **Patients who are prescribed methotrexate in combination with another DMARD e.g. leflunomide require more frequent monitoring (see Blood test monitoring section below).**
- **When prescribing oral methotrexate, ONLY 2.5mg tablets should be prescribed (to avoid confusion and reduce risk to patients.**

Bedford Hospital Treatment pathway –Dosage and Blood test monitoring Information

Initiation Phase (Up to week 4)	Dose escalation Phase	Stable maintenance dose Phase
• Initiate methotrexate oral therapy at 7.5mg-10mgs orally **once weekly**. • **Blood tests should be monitored every 2 weeks.**	• If blood results are satisfactory at week 4 and based on clinical response, the weekly dosage may be increased by increments of 2.5mg- 5mg at intervals of every 2 - 4 weeks (in patients who can tolerate it) , to a maximum of 25mg **once weekly.** • **Blood tests should be continued to be monitored every 2 weeks until the patient has been on a stable maintenance dose for 6 consecutive weeks.** • A switch from oral to subcutaneous route may be recommended by the Specialist Rheumatology team if patient cannot tolerate oral methotrexate. • If changing from oral to subcutaneous administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.	• Frequency of blood test monitoring can then be reduced **to monthly for a further period of 3 months**, and then reduced to **every 12 weeks*** (if the blood tests results are within acceptable range ***More frequent monitoring is appropriate in patients at higher risk of toxicity.**

(NB: The dosage regimen used in the Bedford Treatment Pathway differs from the licensed recommendations)

Type of Blood Tests required:

- U&Es , LFTs and FBC, ESR, CRP (DMARD panel on ICE)

VARIATION TO METHOTREXATE DOSING

- The dose of Methotrexate may be lower than those outlined above in certain patient populations e.g. frail elderly, patients with renal impairment.)
- If changing from oral to subcutaneous administration a **reduction** of the dose may be required due to the variable bioavailability of methotrexate after oral administration.

FOLIC ACID

Folic acid should be prescribed to reduce the possibility of methotrexate toxicity (unlicensed indication).

Typical Regimen: Folic acid 5mg orally once a week (to be taken the day after the methotrexate). This is the typical regimen however a different dosing regimen (e.g. upto 3 times per week) may be recommended in selected patients. (This is dependent on individual patient factors). (NB: Regardless of regimen used, it is important to inform the patient not to take folic acid on the same day as methotrexate).

Prescribing and Blood test monitoring Information

Indication	• Methotrexate is recommended by NICE and National Societies for the treatment of numerous rheumatological conditions including Rheumatoid arthritis, Psoriatic arthritis, Connective tissue disorders, Vasculitis. • Clinicians should refer to the Summary of product characteristics (SPC) for specific licensing information. • Use outside of the licensed indications is regarded as "off label" use.
Drug Information	Methotrexate is given **ONCE WEEKLY** by the oral route. • If oral route is not tolerated, the Specialist Rheumatology team may suggest an oral anti-emetic or if still not tolerated, advise switching to the subcutaneous route, likewise a switch to subcutaneous route may be tried if the disease is still active after 16 weeks of oral therapy. NB: If changing from oral to subcutaneous administration, a **reduction** of the dose may be required due to the variable bioavailability of methotrexate after oral administration. • Dosage details are outlined in the Bedford Hospital Treatment pathway above.
Contra-indications / Cautions/ Dose modifications in Special Populations	• Clinicians should refer to the Summary of Product Characteristics (SPC's) and current electronic BNF for full details www.medicines.org.uk/emc www.bnf.org/products/bnf-online
Side effects	• Clinicians should refer to the Summary of Product Characteristics (SPC) and current electronic BNF for full details of side effects. • The BNF contains further information regarding Pulmonary toxicity, Liver toxicity and gastro-intestinal toxicity. www.medicines.org.uk/emc www.bnf.org/products/bnf-online • **Blood dyscrasias** (e.g. leucopenia and neutropenia) can occur hence the importance of regular blood tests • As methotrexate is an immunosuppressant, clinicians should note to inform patients to contact their doctor immediately if they have any side effects, in particular – breathlessness, dry cough, whites of eyes becoming yellow, severe itching of skin, rash, dark urine, infections (including fever, chills or severe sore throats), new unexplained bleeding or bruising, mouth ulcers, vomiting and diarrhoea (particularly at the start of treatment, or if it is severe, at any stage in treatment). Examples of some side effects include: ○ Nausea ○ Vomiting ○ Diarrhoea ○ Mouth ulcers ○ Hair loss Skin rashes

	Clinicians should also refer to Table 1 for details of when to contact the Specialist Rheumatology team with regards blood test results and development of certain side effects etc.
Drug Interactions	• Methotrexate can interact with a variety of drugs, some of which can be **significant.** Examples include: ○ co-trimoxazole, ○ trimethoprim , ○ phenytoin, ○ theophylline ○ clozapine. ○ acitretin ○ ciclosporin ○ probenicid • NSAIDs NSAID's may reduce methotrexate excretion but can continue as long as monitoring is regular. Patients should be advised not to use over the counter NSAID's / aspirin without informing the GP / Specialist Rheumatology team. Caution with LFT and renal function. • **This list is not exhaustive** and clinicians should check the Summary of Product Characteristics (SPC) and the current electronic BNF for a **full list of potential drug interactions** before starting any new medication or when stopping any existing medication www.medicines.org.uk/emc www.bnf.org/products/bnf-online
Pre-treatment Blood Test Monitoring *(To be done by Specialist Rheumatology team*	• FBC, U+E, LFT, CXR. Pulmonary function tests in selected patients.
Blood Test Monitoring Requirements *(Typically to be monitored by the GP from week 4 onwards.)* **(Ref: Based on British Society of Rheumatology Guidelines , 2017 and current clinical practise)**	• FBC, U+E, LFT **fortnightly until dose and monitoring stable for 6 weeks**, then **monthly for 3 months** then **every 12 weeks* thereafter.** ***More frequent monitoring is appropriate for patients at a higher risk of toxicity**. • (**NB: After any dose increase,** blood test monitoring should be carried out every fortnight until on a new stable dose for 6 weeks and then the frequency can revert back to the previous schedule). • CRP / ESR should be monitored every 3-6 months as this can help assess disease activity. **Patients who are prescribed methotrexate in combination with another DMARD e.g. leflunomide will require more frequent monitoring :** ○ FBC, U&Es, LFT **every 2 weeks until on a stable dose for 6 weeks, then monthly* blood tests long term.** ***More frequent monitoring is appropriate for patients at a higher risk of toxicity.**

	(Patients who have been stable for 12 months on combination therapy can be reviewed by the Specialist team and considered for reduced frequency of monitoring on an individual basis.) • Ensure a prompt two way communication of blood test results between GP and Specialist Rheumatology team is available. (Paper copies should be sent between parties if electronic access via ICE is not available.) • **Patient-held Blood Test Monitoring Booklets** o The NPSA patient-held monitoring booklet or local equivalent monitoring booklet will be issued to the patient by the Specialist Rheumatology team. o It has been agreed locally that there is no need to record blood test results in the patient-held blood test monitoring booklet when both the GP and the Specialist can access the blood test results electronically via ICE system.
Co-prescribe folic acid	• Folic acid 5mg orally once a week (to be taken the day after the Methotrexate). This is the typical regimen however a different dosing regimen (e.g. upto 3 times per week) may be recommended in selected patients. (This is dependent on individual patient factors). (NB: Regardless of regimen used, it is important to inform the patient **not** to take folic acid on the same day as methotrexate).
Time to response	• 3 – 12 weeks
Infections	• Methotrexate is an immunosuppressant and increases the patient's susceptibility to infections, including opportunistic infections. • Initiate prompt anti-infective treatment when indicated on the basis that the patient may be immunosuppressed to some degree. • During a serious infection*, methotrexate should be temporarily discontinued until the patient has recovered from the infection. (* Serious infection: warrants admission to hospital or requires parenteral anti-microbial therapy.) • <u>If exposed to measles and / or chickenpox</u>: Check immunity to measles and varicella-zoster; if non-immune and exposed to measles or chickenpox contact the Specialist Rheumatology team ASAP for consideration of the appropriate immunoglobulin therapy. • <u>If patient develops shingles or chickenpox</u>, stop the drug and treat with aciclovir.
Vaccinations	• The immune response to vaccination may be impaired. • Pneumovax and annual flu vaccination are recommended. • L**ive vaccines should be avoided** and GPs should contact the Specialist Rheumatology team for advice regarding the use of any live vaccine in patients who are prescribed methotrexate. • Herpes zoster vaccine (Zostavax®) is a live attenuated vaccine that may be administered to patients on low-doses of Methotrexate (<0.4mg/Kg/week).

	Before considering Zostavax® however, GPs should contact the Specialist Rheumatology team for advice and to check that the patient is not receiving any additional immunosuppressants or biologic drugs, noting that these are often prescribed in secondary care.
Alcohol	• As both alcohol and methotrexate can affect the liver, patients should be advised to only drink alcohol in small amounts and stay within government guidelines, which state that adults shouldn't drink more than 14 units per week and should have alcohol free days without 'saving units up' to drink in one go.
Elective surgery	• **Contact the Specialist Rheumatology team for advice:** – • Generally, methotrexate should not routinely be stopped in the peri- operative period, although individualised decisions should be made for high-risk procedures (e.g. 'contaminated', or duration over 60 minutes), in which case it can be stopped 2 weeks prior to surgery and then restarted once wound healing is satisfactory. • Caution for early detection of infections.
Contraceptive advice (males and females)	• The Specialist Rheumatology team should discuss family planning with both female and male patients before initiating treatment with methotrexate. • Patients should be advised that methotrexate is contraindicated in pregnancy and that they should contact their GP and Specialist Rheumatology team if they wish to start a family. • Female patients should use contraception **during and for 3 months after** stopping therapy. • Male patients –to discuss with Specialist Rheumatology team
Pregnancy and Breast feeding	• Methotrexate is contra-indicated in pregnancy and breast feeding. • Patients should be advised to stop taking methotrexate and contact their GP and Specialist Rheumatology team as soon as possible if they become pregnant.
Photosensitivity	• Encourage use of sunscreens / protective covering to reduce sunlight exposure.
Cytotoxic Handling and Waste Disposal	• Patients should be advised by the Specialist Rheumatology team on the handling and safe disposal of methotrexate as it is a cytotoxic agent. <u>Handling Advice</u> • Methotrexate should not come into contact with the skin or mucosa. In event of contamination, the affected area must be rinsed immediately with ample amount of water. • Tablets should not be crushed. • Pregnant individuals should not handle and /or administer s/c methotrexate. <u>Waste Disposal</u> • Patients should be issued with a cytotoxic waste disposal bin by Bedford Rheumatology Department and returned to the department when ¾ full. • Bedford Rheumatology department will issue replacement bins.

Drug Formulations	Oral	Subcutaneous (Metoject PEN®)
	Available as 2.5mg and 10mg tablets. To avoid confusion and to reduce the risk to patients, it has been agreed locally that **ONLY 2.5mg tablets should be prescribed.** Tablets contain lactose.	Available as a solution for injection of Methotrexate in prefilled pens as follows:- 7.5 mg in 0.15ml; 10mg in 0.20ml; 12.5mg in 0.25ml; 15mg in 0.30ml; 17.5mg in 0.35ml; 20mg in 0.40ml; 22.5mg in 0.45ml; 25mg in ml; 27.5mg in 0.55ml; 30mg in 0.60ml
Practical Points for GPs to note:	• Advise patients to attend for a blood test a week before their next prescription is due to ensure that the results can be reviewed before the next prescription is requested for issue. • Check the results of recent blood test **before** issuing a prescription. (Refer to table 1 for actions to take in the event of blood test abnormalities and side effects - page 7). • Increase the frequency of blood test monitoring after a dose increase as detailed above. • **Patients who are prescribed methotrexate in combination with another DMARD e.g. leflunomide require more frequent monitoring.** • Prescribers should note that whilst absolute blood test values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance. • Advise patients to contact their doctor immediately if they experience any side effects, in particular – breathlessness, dry cough, whites of eyes becoming yellow, severe itching of skin, rash, dark urine, infections (including fever, chills or severe sore throats), new unexplained bleeding or bruising, mouth ulcers, vomiting and diarrhoea (particularly at the start of treatment, or if it is severe, at any stage in treatment). • **For oral therapy:** o Prescribe **2.5mg tablets only** to avoid confusion. o Advice patients to swallow the tablets whole, do not crush or chew. • **For sub-cutaneous therapy:** o Ensure the patient is trained in how to dispose of cytotoxic waste (if prescribed s/c methotrexate pre-filled syringes) and advise them to contact the Rheumatology Specialist Nurse for advice regarding the disposal of cytotoxic waste / issue of new sharps bin. • Ensure folic acid is co-prescribed at the frequency specified by the Specialist Rheumatology team and reiterate that folic acid should not be taken on the same day as methotrexate. • Advise any patients who wish to consider starting a family to contact their GP and Specialist Rheumatology team as soon as possible for advice. • Advise that any patient who becomes pregnant should stop taking methotrexate and contact their GP and Specialist Rheumatology team as soon as possible. • Provide a maximum of 4 weeks supply of methotrexate at a time.	

Patient Information Leaflets	• Patients should be advised to read the Arthritis Research UK patient information leaflet and the package insert. • The current Arthritis Research UK leaflet can be downloaded from: http://www.arthritisresearchuk.org/arthritis-information/drugs/methotrexate.aspx

Table 1:

Actions to be taken

Prescribers should note that whilst absolute values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance and urgent discussion with Specialist Rheumatology team.

WBC <3.5 x 10^9/L	**Withhold and contact Specialist Rheumatology team urgently if any of the results opposite develop.**
Neutrophils <1.6 x 10^9/L	
Unexplained eosinophilia >0.5 x 10^9/L	
Platelet count <140 x 10^9/L	
MCV > 105 f/L	
Creatinine >30% above baseline and/or calculated GFR <60	
ALT and/or AST >100 units/L	
Unexplained fall in serum albumin	
Any rapid fall or consistent downward trend in any indices	
Rash or oral ulceration, nausea, vomiting, diarrhoea	**Withhold until discussed with Specialist Rheumatology team**
New or increasing dyspnoea or dry cough	**Withhold until discussed with Specialist Rheumatology team**
Severe sore throat, abnormal bruising	**Immediate FBC and withhold until result available and contact the Specialist Rheumatology team.**

BACK-UP ADVICE AND SUPPORT

- **GP queries should be directed to the Rheumatology consultants.**
- **Patient queries should be directed to the Rheumatology Specialist Nurses**

All urgent requests should be answered within one working day.

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References:

- BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with British Association of Dermatologists. Rheumatology.2008 K Chakravarty et al. www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmard_therapy.pdf
- SPC (Summary of product characteristics)

  www.electronicmedicinescompendium.com
- BSR/BHPR Non-biologic DMARD guidelines ((2017) https://academic.oup.com/rheumatology/article/56/6/865/3053478
- BNF (electronic)

  www.bnf.org/products/bnf-online