

**794FM.2.1 METHOTREXATE FOR USE IN RHEUMATOLOGY, DERMATOLOGY,  
GASTROENTEROLOGY AND RESPIRATORY MEDICINE  
Shared care protocol**

This protocol provides prescribing and monitoring guidance for methotrexate therapy. It should be read in conjunction with the [shared care responsibilities](#), the Summary of Product Characteristics (SPC) available on [www.medicines.org.uk/emc](http://www.medicines.org.uk/emc) and the [BNF](#).

### BACKGROUND FOR USE

- Methotrexate is a folic acid antagonist and is classified as an antimetabolite cytotoxic agent. It is prescribed for a wide range of conditions.
- It is also used as a disease modifying antirheumatic drug (DMARD) and as a steroid-sparing agent.
- Indications, dose adjustments and monitoring requirements for DMARDs (licensed and unlicensed indications) defined in the Bucks shared care protocols are in line with national guidance published by the British Society for Rheumatology (BSR), the British Association of Dermatologists (BAD), the British Society of Gastroenterology (BSG) and British Thoracic Society (BTS) (see [references](#)). The NPSA alert on improving compliance with oral methotrexate<sup>8</sup> recommends the use of shared care guidelines based upon the BSR/BAD guideline.
- Methotrexate uses in this protocol are limited to:

### RHEUMATOLOGY

- Active rheumatoid arthritis (licensed):
  - It is commonly used as a first line treatment for this indication.
  - It can be used with other DMARDs such as leflunomide, sulfasalazine and hydroxychloroquine to achieve disease remission. It is also used in combination with biological therapies.
  - Parenteral methotrexate is licensed for rheumatoid arthritis and can be administered subcutaneously or intramuscularly.
- Other rheumatic conditions including psoriatic arthritis, undifferentiated inflammatory arthritis, juvenile idiopathic arthritis (JIA), spondylarthropathies, systemic lupus erythematosus (SLE), myositis, mixed connective tissue disease, scleroderma, vasculitis and polymyalgia rheumatica. Use in these conditions is unlicensed and recommended by the British Society of Rheumatology<sup>1</sup>.

### DERMATOLOGY

- Severe skin psoriasis (licensed).
- Atopic eczema (unlicensed).
- Other unlicensed inflammatory and autoimmune conditions: e.g. sarcoidosis, bullous pemphigoid, morphoea, etc.

### GASTROENTEROLOGY

- Inflammatory bowel disease (unlicensed).
- Used as 3<sup>rd</sup> or 4<sup>th</sup> line of treatment in Crohn's disease and ulcerative colitis.
- Its use is recommended by the British Society of Gastroenterology<sup>2</sup>.

### RESPIRATORY MEDICINE

Interstitial lung diseases, sarcoidosis and pulmonary vasculitis (unlicensed uses). Its use in these conditions is recommended by the British Thoracic Society<sup>3</sup>.

### SUPPORTING INFORMATION

Methotrexate is an established drug with a known side effect profile.

### CONTRAINDICATIONS TO METHOTREXATE

- Pregnancy. Methotrexate is contraindicated in pregnancy and recommended to be stopped 3 months in advance of conception. In women treated with low dose oral methotrexate (<20 mg/week) within 3 months prior to conception, folate supplementation of 5 mg/day orally should

be continued prior to and throughout the pregnancy. In case of accidental pregnancy on low dose methotrexate the drug should be stopped immediately, folate supplementation 5 mg/day continued and a careful evaluation of foetal risk carried by the local experts.

- Breastfeeding – not recommended.
- Men prior to conception – methotrexate does not impair male fertility and may be compatible with paternal exposure. There is no evidence for adverse foetal outcomes in male patients on low dose methotrexate.<sup>13</sup> The BAD guidelines recommend that males should avoid fathering a child for at least three months after the last dose of methotrexate<sup>14</sup>.
- Stage IV and V chronic kidney disease (CKD) (eGFR <30 ml/min). 50% dose reduction is recommended in patients with CKD stage III (eGFR 30 - 59 ml/min).
- Untreated folate deficiency, leucopenia, thrombocytopenia.
- Suspected local or systemic infection.
- Being on dialysis.
- Severe hepatic dysfunction/cirrhosis.
- Active tuberculosis or other active infection.
- Active peptic ulceration.
- Concurrent trimethoprim/co-trimoxazole therapy.

#### RELATIVE CONTRAINDICATION TO METHOTREXATE

- Chronic liver disease (if synthetic function is impaired), alcoholism - should be used with extreme caution.
- Patients with chronic hepatitis B and C should be discussed with gastroenterologists before initiation of treatment and antiviral treatment should be considered.
- Active gastritis.

#### PRECAUTIONS

- Alcohol intake should be limited (maximum 4 - 6 units a week).
- **Peri-operative management.** Methotrexate should NOT routinely be stopped in the peri-operative period. Attention to renal function is important and dose may need to be adjusted accordingly. In surgical settings where there is a high risk of infections methotrexate may need to be stopped 2 weeks prior to the procedure. These patients should be discussed with a specialist.
- **Intercurrent infections.** During a serious infection (i.e. requiring IV antibiotics or hospitalisation) methotrexate should be temporarily discontinued until the patient has recovered from the infection. Treatment can be continued in patients with minor infections requiring a short course of oral antibiotics.
- Chickenpox/shingles – stop methotrexate if proven infection. For those with exposure to chickenpox or shingles and no history of infection/vaccination, check that immunity to Varicella zoster virus (VZV) infection has been checked. If the patient is susceptible, a course of oral aciclovir or valaciclovir is recommended unless there are significant concerns of renal toxicity or malabsorption. Discuss with a Microbiologist.

#### DOSAGE<sup>2,3</sup>

Indication	Dose	Ref
Severe psoriasis	Initial dose: 2.5 mg to 5 mg weekly, increasing to 15 to 25 mg weekly depending on response.	1, 4, 9
Rheumatology indications (above)	Initial dose: 15 mg weekly <sup>6</sup> , adjusted to 7.5 to 25 mg weekly depending on response. In some cases up to 30 mg weekly may be prescribed. Oral and s/c doses are usually the same.	1, 4, 6, 7, 9
Inflammatory bowel disease	Usual dose: 15 to 25 mg weekly.	2, 4, 5
Respiratory indications (above)	Initial dose: 10 mg weekly <sup>6</sup> , adjusted to 7.5 to 25 mg weekly depending on response.	3

### Prescribing points

- Prescriptions must state the form, strength, dose and directions in full.
- The use of 'as directed' in prescribing should be avoided. A specific dose must be applied to each prescription<sup>8</sup>.

### Oral methotrexate

- This is available as 2.5 mg and 10 mg tablets. The NPSA recommends that only one strength of tablet should be supplied to the patient and that this should remain consistent in order to avoid confusion. It is therefore recommended to standardise on multiples of the 2.5 mg tablet which also allows for dosing flexibility. The tablet strength should be recorded in the monitoring booklet<sup>8</sup>.
- Rosemont and Therakind make methotrexate suspension 2 mg/ml.

### Parenteral methotrexate

- This is licensed for use in rheumatoid arthritis and active juvenile idiopathic arthritis where response to NSAIDs is inadequate and in severe recalcitrant psoriasis.
- Consider using it by s/c administration and only on the advice of a specialist for:
  - Patients with severe gastrointestinal (GI) side effects despite regular folic acid 5 mg, 6 days a week.
  - Non-responders to oral therapy after an 8 - 12 week trial in order to improve drug bioavailability.
- It is available in 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg and 30 mg pre-filled syringes as Metoject<sup>®</sup> (manufactured by Medac). Only these standard doses should be prescribed by GPs. Other strengths are difficult to obtain in the community.
- There are other brands of parenteral methotrexate which can be considered in special circumstances but only on the advice of the rheumatologist and when the patient has been trained on the use of the new device by the manufacturer.
- In order for a patient to use the product under the care of the GP, he/she should be able to administer the injection. Training on self-administration of Metoject<sup>®</sup> will be given by the hospital specialist nurse. After 2 to 3 months of s/c injection the specialist will re-assess if the treatment is of benefit and should be continued.
- **Disposal of sharps.** Cytotoxic sharps boxes will be provided by the hospital specialist nurse on initiation of treatment when attending for the self-administration training. Once full, the sealed sharps boxes should be exchanged for a new box at the GP practice or, in exceptional pre-arranged circumstances, as part of a planned follow up clinical appointment to the rheumatology outpatient department. Patients are advised to return their boxes for disposal and replacement when full or approximately every 3 - 6 months.

### Folic acid

- Folic acid reduces the risk of hepatotoxicity, gastrointestinal side effects and methotrexate discontinuation.
- For rheumatology and respiratory indications, folic acid should be prescribed routinely at a dose of 10 mg weekly, to be taken 2 days after methotrexate. Folic acid can be given more frequently but not on the day of methotrexate, up to 5 mg 6 times a week.
- For psoriasis, folic acid should be prescribed at a dose of 5 to 10 mg weekly, to be given 2 days after methotrexate.
- In inflammatory bowel disease, folic acid 5 mg is usually given daily for 2 to 3 days after the methotrexate, e.g. on days 3, 4 and 5 after the weekly methotrexate dose on day 1 (i.e. 3 x 5 mg weekly)<sup>4, 5</sup>.
- To aid monitoring folic acid usage, prescribe a quantity for the same duration of supply as methotrexate (e.g. four weeks).

### TIME TO RESPONSE

Methotrexate can take between 6 weeks to 3 months to have a full effect.

## PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

- Height, weight and blood pressure where relevant to the speciality.
- Full blood count (FBC), liver function tests (LFTs), urea and electrolytes (U&E) and eGFR.
- Chest X-ray if not done in the last 6 months for rheumatology patients. For other specialties to be considered by treating clinical based on a history of smoking or lung disease.
- Lung function tests and high resolution computed tomography (HRCT) should be considered in individual patients where there is clinical suspicion of lung disease. Baseline lung function tests may be indicated in patients with pre-existing lung disease i.e. chronic obstructive pulmonary disease (COPD). Any patient currently smoking should be offered an access to smoking cessation services.
- C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) for rheumatology patients.
- Offer testing for hepatitis B, C and human immunodeficiency virus (HIV) serology in particular if patient is at risk of occult viral infection.
- Check VZV serology (if no history of varicella). The specialist should give advice about treatment required if there is exposure to or new diagnosis of chickenpox or shingles.
- Recommend vaccinations for influenza and pneumococcus.
- Procollagen 3 (P3NP) for patients treated for skin psoriasis.

## COMMENCING METHOTREXATE

- The decision to initiate methotrexate should be made in conjunction with the patient/carer and supervised by a specialist. Patients should be provided with written information and education about their treatment. When appropriate they should be advised about the impact of methotrexate upon fertility, pregnancy and breastfeeding.
- Supply with methotrexate monitoring booklet.

## VACCINATION

- Pneumococcal vaccination should be administered as a single dose polysaccharide PPV-23 (Pneumovax<sup>®</sup>), if possible, prior to initiation of methotrexate therapy or as soon as possible after.
- Annual influenza vaccine should be recommended to all patients.
- A shingles vaccine (Zostavax<sup>®</sup>) is recommended for people over the age of 69 taking less than 0.4 mg/kg of methotrexate weekly.
- Other live vaccines should not be given to patients on methotrexate treatment and within 4 weeks of commencing the treatment.

## ONGOING MONITORING SCHEDULES

Monitoring recommendations for the different indications are not the same because risk factors for methotrexate toxicity vary according to the patient population.

<b>Rheumatology, Indications</b>	<p><b>FBC, alanine aminotransferase (ALT), albumins, creatinine/calculated eGFR</b> every 2 weeks until dose remains unchanged for 6 weeks; thereafter every month for 3 months; thereafter every 3 months. More frequent monitoring is appropriate for patients at higher risk of toxicity, i.e. on combination therapies. The specialist will advise the GP if this is necessary. After dose increase, blood tests should be monitored 2 weekly for 6 weeks followed by return to the previous schedule.</p> <p>Patients taking methotrexate in combination with leflunomide should have monthly blood tests monitoring for 12 months before it can be reduced in frequency. The specialist will advise the GP on the monitoring necessary when the patient is transferred back to primary care.</p> <p><b>CRP or ESR</b> every 3 - 6 months depending on disease activity. The rheumatologist will advise on frequency.</p>
<b>Gastroenterology</b>	<p><b>Same as for Rheumatology.</b></p>
<b>Dermatology</b>	<p><b>FBC, LFT AND U&amp;E every 1 - 2 weeks for 1<sup>st</sup> month and until steady dose regimen is achieved.</b></p> <p><b>Once stable assess every 2 - 3 months (as advised by Dermatology consultant)</b></p> <p><b>In addition to above: P3NP</b> 3 monthly (specialist responsibility). This can either be done at the GP surgery or in secondary care (most commonly done in secondary care by the specialist).</p>

## ROLES AND RESPONSIBILITIES

Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Unless otherwise stated in the protocol, the responsibilities are as follows:

### **Specialist**

- Initiate treatment and prescribe until the dose is stable and/or the GP formally agrees to shared care.
- Ensure the patient understands the nature and complications of drug therapy and their role in reporting adverse effects promptly.
- Provide copy of patient information leaflet and drug monitoring card where appropriate.
- Send a letter to the GP requesting shared care. Outline shared care protocol criteria and how often monitoring should be done.
- Inform GP promptly regarding changes in disease management, drug dose, change in the monitoring schedule and missed clinic appointments.
- Be available to give advice to GP and patient throughout treatment.

### **GP**

- Prescribe medication once the dose is stable and shared care is agreed.
- Ensure all monitoring is completed in accordance to the specific shared care protocol.
- Check and record results then advise the specialist of any deteriorations or abnormal results.
- Notify the specialist to any changes in patient's condition, any adverse drug reactions or failure to attend tests.

### **Patient**

- Agree to treatment and monitoring after making an informed decision.
  - Agree to being under the shared care of the GP and specialist.
  - Attend for blood tests and monitoring when required.
  - Ensure monitoring card is kept up to date and is brought to all appointments.
  - Report any side effects to the GP or a member of the specialist team.
- Note: if the patient does not attend blood monitoring, then treatment will be stopped. If the patient is more than 4 weeks late with their monitoring, then treatment should be stopped.

SIDE EFFECTS	ACTION
<b>Sore throat or other unusual infection where patient unwell and there is a possible bacterial infection</b>	<b>Urgent FBC and withhold until FBC result available.</b>
White blood cell count (WBC) $<3.5 \times 10^9/l$ OR Neutrophils $<1.6 \times 10^9/l$ OR Platelets $<140 \times 10^9/l$ Unexplained eosinophilia $>0.5 \times 10^9/l$	Withhold and discuss with specialist urgently.
Mean cell volume (MCV) $>105 - 110$ fl MCV $>110$ fl	Check folate, B <sub>12</sub> and thyroid function tests (TFT), and treat if appropriate. If WBC normal repeat in 4 weeks. Stop methotrexate and seek advice.
Liver function tests ALT rise  Mild $<1.5 \times$ upper limit of normal (ULN)  Moderate $1.5 - 3 \times$ ULN Severe $>3 \times$ ULN (or ALT $>100$ ) or unexplained reduction in albumin $<30$ g/l	Check if there was a recent increase in methotrexate dose or change from oral to s/c administration, check if any other medications were added recently such as antibiotics, statins, has patient has a recent viral or bacterial infection, check for increased alcohol intake, increased use of NSAIDs, use of over-the-counter (OTC) products. Repeat in 2 weeks. If still raised, discuss with specialist.  Reduce the dose by 2.5 mg and repeat in 1 - 2 weeks. Withhold and discuss with specialist urgently.

SIDE EFFECTS	ACTION
Creatinine rise >30% over 12 months or eGFR <60 ml/min/1.73 m <sup>2</sup>	Dose adjustment may be needed. Patients who develop dehydration, pre-renal or acute renal failure while on methotrexate should have methotrexate withheld and FBC monitored closely. Review any changes in medication particularly angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB). Contact specialist for advice.
Nausea	Usually improves over time. If troublesome consider: <ul style="list-style-type: none"> <li>- Increasing the dose of folic acid to 5 mg PO daily up to 6 days a week - omitting on the day methotrexate is taken.</li> <li>- Splitting methotrexate dose over one evening and next morning.</li> <li>- A short-term anti-emetic.</li> </ul> If unable to tolerate refer back to specialist for review.
Hair loss	Usually mild, rarely significant.
Rash	Withhold treatment and discuss with consultant.
Mouth ulcers, mucositis	Mouth ulcers may respond to increasing folic acid as above. If severe despite extra folic acid stop methotrexate and refer to a specialist for advice.
Menstrual dysfunction/amenorrhoea	May occur during treatment and for a short while after cessation.
Otherwise unexplained dyspnoea or cough	Methotrexate pneumonitis may occur. Withhold treatment, arrange chest X-ray and discuss urgently with consultant.
Abnormal bruising	Withhold until FBC result available.
Elevation of P3NP	Normal P3NP levels in adults are 1.7 – 4.5 microgram/l. Elevation of P3NP between 4.2 microgram/l and 8 microgram/l on more than three occasions in a 12 month period or a single elevation of >8 microgram/l should prompt referral for a hepatology opinion.

**Please note that in addition to absolute values for haematological indices, a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance. In order to monitor trends, it is recommended that all blood test results are entered in the patient held monitoring booklet.**

#### DRUG INTERACTIONS (See SPC for full list.)

<ul style="list-style-type: none"> <li>• Co-trimoxazole</li> <li>• Trimethoprim</li> <li>• Phenytoin</li> <li>• Malaprim<sup>®</sup></li> <li>• Fansidar<sup>®</sup></li> </ul>	Avoid co-prescribing: Increased anti-folate effect which may induce toxic effects of methotrexate on FBC.
Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin	<b>Under specialist advice this combination is not contraindicated.</b> NSAIDs and aspirin may reduce tubular excretion of methotrexate and enhance its toxicity. OTC products containing NSAIDs or aspirin are NOT recommended.
Ciclosporin	Patients co-prescribed ciclosporin with methotrexate should initially be re-stabilised by the specialist as it can increase methotrexate toxicity.
Leflunomide	Although the BNF states that leflunomide is not usually used with methotrexate, it is appropriate to use the combination in rheumatoid arthritis under specialists' advice <sup>7</sup> . Various studies have shown benefit of this combination therapy where combination with other DMARDs is not effective and patients are not eligible for biologics <sup>12</sup> . There can be increased risks of side effects (e.g. liver and haematological), but with careful monitoring experience suggests they may be used together. Long term monthly blood test monitoring of this combination therapy is recommended by BSR guidelines.

#### NOTES

- One weekly dose of methotrexate can be withheld without inducing a flare.
- Folinic acid (given as calcium folinate) should be used for methotrexate induced myelosuppression, severe mucositis or methotrexate overdose, in the initial dose 20 mg IV and followed by 15 mg qds orally until abnormalities improve. This should be given in the hospital setting.

## BACK-UP INFORMATION/ADVICE

Contact Details	Wycombe and Amersham	Stoke Mandeville
Dermatology	09:00 – 17:00 contact on-call registrar or consultant via switchboard 01494 526161	09:00 – 17:00 contact on-call registrar or consultant via switchboard 01296 315000
Rheumatology	01296 315960 (specialist nurse helpline) In an emergency contact consultant rheumatologist 01494 734079	01296 315960 (specialist nurse helpline – may take 48 hours for response; not for urgent queries) In an emergency contact consultant rheumatologist of the week 01296 316664 Rheumatology Registrar: Bleep 905/907 via switchboard
Respiratory Medicine		Chest Office: 01296 315686/315687
Gastroenterology	Registrar bleep 543 via switchboard Consultant secretary: Dr Cullen 01494 425267 Dr Gorard 01494 425267 Dr Johns 01494 425595 Dr Maggs 01494 425595	Registrar bleep via switchboard  01296 312599 (ask for irritable bowel disease (IBD) specialist nurse helpline – may take 48 hours for response; not for urgent queries)  In emergency contact consultant gastroenterologist of the week (GOW) via switchboard.  Consultant secretary: Dr Sekhar 01296 312599 Dr Hossain 01296 312599 Dr Blackwell 01296 312599 Dr Khan 01296 312599
Medicines Resource Centre	01494 425355	

## SHARED CARE AGREEMENT FORM

Available on DocGen. When not available, use the Word version linked [here](#).

## REFERENCES

1. Flint 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 (Oxford)* 2016; 55 (9): 1693-1697. doi: 10.1093/rheumatology/kev404
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See also:

[Guideline 222](#) [Adult and Paediatrics Injectables Guide](#) (BHT users only)

[Guideline 280FM](#) [Management of Patients on Immunosuppressants admitted with Suspected Infections](#)

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