Oxford University Hospitals NHS
NHS Trust

NHS
*Oxfordshire*
*Clinical Commissioning Group*

# METHOTREXATE FOR USE IN DERMATOLOGY, NEUROLOGY, 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 Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.**

## Shared Care Protocol – Responsibilities

Shared care assumes communication between the specialist, GP, District Nurse or Community Children's Nurse if required* 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 patients understand 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
- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments
- Be available to give advice to GP and patient throughout treatment

***GP***

- Prescribe medication once the dose is stable or shared care is agreed. Including referring to District Nursing service/phlebotomy service is patient is housebound and unable to attend GP surgery for monitoring*
- 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 patients condition, any adverse drug reactions or failure to attend tests

For parenteral methotrexate, if patient/relatives/carers unable to administer and patient is housebound, provide direction to administer to District Nursing team/Community Childrens Nursing team to cover period of administration before next monitoring is due, with end date included (at which point safety monitoring and review required)

****District Nurse/Community Childrens Nurse***
***NB. Input only required if patient is unable to self-administer parenteral methotrexate, relatives/carers are unable to administer and patient is housebound and unable to attend GP surgery/OUH for monitoring or administration***

- Complete blood test as requested by GP (This should be done by the Community Phlebotomy service if you have one in your locality)
- Be aware of **side effects** section (see guidance document), checking with patient and escalating any concerns to GP before administering

- Complete administration of methotrexate injection as requested by GP via Direction to Administer
- Update the Primary Care Record by recording the fact of administration as a consultation (or as agreed with the patient's practice)
- Plan subsequent administration dates into scheduling tool for period of administration covered by Direction to Administer – NB. Note DTA end date (where patient safety checks and review will be carried out) and do not exceed this

***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

**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 drug and is often referred to as a steroid-sparing agent or an immunomodulator.

Indications, dose adjustments and monitoring requirements for disease modifying drugs (licensed and unlicensed indications) defined in the Oxfordshire shared care protocol are in line with national guidance published by the British Society for Rheumatology (BSR), British Society for Paediatric and Adolescent Rheumatology (BSPAR), the British Association of Dermatologists (BAD), NICE, European Crohn's and Colitis Organisation (ECCO), the British Society of Gastroenterology (BSG) and British Thoracic Society (BTS) (see references). The NPSA alert on improving compliance with oral methotrexate[8] recommends the use of shared care guidelines based upon the BSR/BAD guideline.

Methotrexate is an established medicine with a known side effect profile. All new patients must be initiated by a specialist. Methotrexate uses in this protocol are limited to:

**Dermatology**

- Severe skin psoriasis (licensed).
- Unlicensed indications recommended by the British Association Of Dermatologist Guidelines on the safe use of methotrexate Atopic eczema, cutaneous lupus, sarcoidosis, lymphoproliferative disorders, pemphigoid, vasculitis, chronic urticaria, dermatomyositis , granuloma annulare , necrobiosis lipoidica , alopecia areata, Hailey-Hailey disease, oral lichen planus, pyoderma gangrenosum.

**Neurology**

- Used as a second-line therapy (unlicensed) for a range of neurological disorders including; myasthenia gravis, inflammatory myopathies and neuropathies, vasculitis and other immune-mediated central and peripheral nervous system diseases

**Gastroenterology**

- Inflammatory bowel disease (unlicensed).
- Its use is recommended by the National Institue of Clinical Excellence (NICE)[11,12] , BSG[10] and ECCO[13]. It is reserved for patients who fail to respond to or are intolerant of thiopurines

(azathioprine or mercaptopurine). NICE recommends methotrexate for Crohn's disease but not ulcerative colitis unless there is no alternative.

**Respiratory**

- Interstitial lung diseases, sarcoidosis and pulmonary vasculitis (unlicensed uses)[2].

**Paediatrics**

- Juvenile Idiopathic Arthritis, Juvenile Systemic Lupus Erythematosus, Juvenile Dermatomyositis, Uveitis, Vasculitis and Other Connective tissues such as Scleroderma (localised & systemic) and Sarcoidosis.
- Methotrexate should only be initiated by and under the direction of a consultant paediatric rheumatologist, or a rheumatologist with an interest in paediatric rheumatology

**Ophthalmology**

- See separate Shared Care Protocol

**Rheumatology** – see separate protocol

**CONTRAINDICATIONS AND PRECAUTIONS**

| **Contraindications** | |
|---|---|
| Pregnancy | It is essential that both female and male patients of child bearing age should use effective and reliable contraception whilst on methotrexate and for at least 3-4 months after stopping it. Patients planning on becoming pregnant or who think they are pregnant should be seen by the specialist. |
| Breastfeeding | Do not use. |
| Significant renal disease | Do not use in GFR less than 10 ml/min |
| Untreated folate deficiency, leucopenia, thrombocytopenia. | Do not use. |
| Chronic liver disease and alcoholism | Relative contraindications |
| Severe COPD | Do not use. |
| Immunodeficiency | Do not use. |
| Suspected local or systemic infection | Treat infection vigorously. Continue methotrexate unless symptoms significant. |
| **Precautions** | |
| Elective surgery | Methotrexate can be continued (caution for early detection of infection and complications). |
| Renal impairment | Reduce the dose (avoid if GFR <30 ml/min). |
| Chickenpox/shingles | Stop methotrexate if proven infection. For those with exposure to chickenpox or shingles and no history of infection/vaccination, passive immunisation with VZIG should be carried out. |

**DOSAGE[2, 3]**

| Indication | Dose |
|---|---|
| Dermatology | Initial dose between 5- 15 mg weekly, increasing to a maximum of 25 mg weekly depending on response.<br>Folic acid should be prescribed at a dose of 5 mg weekly, to be given 4 days after methotrexate. |
| Inflammatory bowel disease | Usual dose: 15 to 25 mg weekly orally or subcutaneously.<br>Folic acid 5 mg is given once weekly 4 days after methotrexate. The specialist may decide to increase the dose of folic acid if side effects occur. |
| Respiratory | Initial dose: 10 – 15 mg weekly[6], adjusted to 7.5 to 20 mg weekly depending on response. Maximum dosage is 20mg weekly.<br>Folic acid should be prescribed routinely at a dose of 5mg weekly, to be taken 4 days after methotrexate. |
| Neurology | The initial starting dose is 7.5 mg weekly, increased as necessary by 2.5 mg increments to a maximum of 15mg weekly. In exceptional circumstances, the Neurologist may advise higher doses up to 25 mg, If the oral route is not effective or tolerated, subcutaneous administration may be considered.<br>Folic acid 5mg weekly is taken on a day other than the day of methotrexate. If side effects from methotrexate occur, the neurologist may decide to increase the dose of folic acid |
| Paediatrics | Dose range 10-15 mg/m$^2$ per week (although BSPAR guidance does state a maximum of 25mg/m$^2$), up to a maximum of 25 mg per week. It is usually given on the same day each week, but on occasions there may be an agreement to give a dose a day or two either side to help compliance.<br><br>Folic Acid supplementation is not an absolute requirement. It may be used to reduce side effects at a dose of 1- 5mg per week, to be given 4 days after the methotrexate is recommended (not on the same day as methotrexate). |

- Methotrexate can take between 6 weeks to 3 months to have a full effect.
- Folic acid reduces the risk of hepatotoxicity and gastrointestinal side effects.
- To aid monitoring folic acid usage, prescribe a quantity for the same duration of supply as methotrexate (e.g. four weeks).
- To aid memory, some departments advise patients to take **M**ethotrexate on **M**ondays and **F**olic acid on **F**ridays.

## PRESCRIBING INFORMATION

- Prescriptions must state the form, strength, dose and directions in full.
- The use of 'as directed' in prescribing must be avoided[8].
- Doses must be taken on the same day each week.
- Patient must be supplied with the NPSA Patient-held blood monitoring and dosage record booklet and the manufacturers Patient Information Leaflet by the clinic when they are first prescribed methotrexate. If it is being used in an unlicensed indication this must be explained to patient.

### Oral methotrexate

- Only 2.5mg tablets should be prescribed and dispensed to avoid potentially fatal errors.
- Oral solutions available as specials as per BSPAR guidance. Tablets do disperse in water.

**Parenteral methotrexate**

Consider using methotrexate by s/c administration **only** on the advice of a specialist for:

- Patients with 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.

Parenteral methotrexate can:

- Improve the patients quality of life and satisfaction with treatment
- Ensure the maximum bioavailability
- Reduce symptomatic side effects for some patients, thus increases in the therapeutic dose are better tolerated
- Extend the time that disease is controlled before expensive anti-TNF therapies need to be introduced.

Subcutaneous Methotrexate

- As agreed by APCO only Metoject® subcutaneous methotrexate preparations should be used within Oxfordshire. All prescribing of methotrexate subcutaneous should be via brand name.
- Metoject® is licensed for active Rheumatoid Arthritis (RA), severe Psoriatic Arthritis, severe Recalcitrant Disabling Psoriasis and severe active Juvenile Idiopathic Arthritis (JIA).
- It is occasionally used in inflammatory bowel disease in patients with a short gut to maximise absorption.
- Metoject® is a single use pre-filled auto-injector pen (this replaced the pre-filled syringe presentation and has a different administration technique). It is available in 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg pens. Only these standard doses should be prescribed by GPs. Other strengths are difficult to obtain in the community.
- In order for a patient to use the product under the care of the GP, they must be able to administer the injection or have made alternative arrangements for relative / carer (or District Nurse/Community Childrens Nurse if patient and relative/carer are unable to administer) to do this for them. The patient will be counselled by the consultant **not** to start the injections before they have received training by the specialist nurse team (if injection is to be given by District Nurse or Community Childrens Nurse, the patient does not require training)
- For adults, the consultant will then request the GP to prescribe the initial dose and include all necessary information regarding the patients care for the GP's record. Once the patient has collected their first supply of medication, they can then phone the advice line to arrange an injection technique training appointment. The number is 01865 737656.
- For paediatric patients, the patient and parents/carers will be counselled by the consultant and will receive training from the specialist nurse team to administer the injections. If it is not possible for patient or parent/carer to administer the injections, alternative arrangements will be made by the Advanced Nurse Practitioners. The consultant will request the GP to prescribe the methotrexate and include all necessary information regarding the patients care for the GP's record.
- After 2 to 3 months of s/c injection the specialist will re-assess if the treatment is of benefit and whether it should be continued.

**Disposal of sharps**

- Cytotoxic sharps boxes (purple) will be provided by the hospital specialist nurse on initiation of treatment when attending for the self-administration training
- Once the sharps box is full and has been sealed it can be dropped off at the GP for disposal or collected by the local council in exchange for an empty one. This differs in areas so make sure the patient is aware of the correct process (the GP surgery should have these details).
- Only in exceptional pre-arranged circumstances should this exchange occur as part of a planned follow up clinical appointment at the outpatient department.

- Patients are advised to return their boxes for disposal and replacement when full or approximately every 3-6 months.
- For those receiving their treatment from the District Nursing or Community Children's Service, supply and collection of sharps box will be arranged by that service, either via the Council if available, or other local arrangement depending on the area – see GP, DN and CCN guidance document for more detail.

**PRE-TREATMENT ASSESSMENT BY THE SPECIALIST**

- FBC, LFT, U&E , CRP and eGFR.
- Chest X-ray if not done within the last 6 months (not necessary in children unless there is a specific indication)
- Lung function tests may be considered in smokers and patients with pre-existing lung disease.
- Procollagen 3 (P III NP) for patients with skin psoriasis.
- Varicella zoster serology in children to determine immune status to chickenpox. Consider vaccine if susceptible and if methotrexate can be delayed.
- In children and young people, live vaccines especially if part of an immunisation schedule, should be given at least 4 weeks before commencing methotrexate. If in doubt, seek advice from an Infectious Diseases specialist.

**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.

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|---|---|
| Respiratory, dermatology and neurology | FBC, CRP, LFTs, and U&Es every 2 weeks until dose remains unchanged for 6 weeks; thereafter every month until the patient has been stable for one year. Following that, based on clinical judgement, consider reducing frequency of monitoring to every 2 to 3 months. |
| Dermatology | In addition to above:<br>Procollagen 3 (P III NP) 3 monthly (specialist responsibility). |
| Inflammatory bowel disease | FBC, LFTs and U&Es every week until stabilized (first month). Thereafter bloods should be checked every 2 to 3 months unless there are clinical signs of over immunosuppression e.g. fever, sore throat |

**SIDE EFFECTS AND ACTIONS**

| SIDE EFFECTS | ACTION |
|---|---|
| WBC < $4x10^9$/l | Adults: Perform a differential and increase frequency of monitoring.<br>Paediatric: Withhold and discuss with specialist |
| WBC <3.5 x $10^9$/l | Withhold and discuss with specialist. Bone marrow suppression can occur abruptly. |
| Neutrophils <2 x $10^9$/l | Withhold and discuss with specialist. Bone marrow suppression can occur abruptly. |
| Platelets <150 x $10^9$/l | Withhold and discuss with specialist. Bone marrow suppression can occur abruptly. |
| MCV >105 - 110 fl<br><br>MCV >110 fl | Check folate, $B_{12}$ and TFT, and treat if appropriate. If WBC normal repeat in 4 weeks.<br>Stop methotrexate and seek advice. |
| **Adult** liver function<br>2 - 3 fold rise in ALT | Reduce the dose by 2.5 mg and repeat in 1 - 2 weeks.<br>In IBD review by specialist - LFTs can return to normal after stopping for 2 |

| | |
|---|---|
| >3 fold rise in ALT | weeks.<br><br>Withhold until discussed with specialist. |
| **Paediatric** liver function ALT or AST >120 | Withhold until discussed with specialist.<br>Transaminase increase 3 times the upper limit of normal is common within 2 days of drug administration and may be attributable to an asymptomatic viral infection. Consider rechecking ALT at trough level. (i.e. 0-2 days prior to injection) |
| Renal impairment | 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 ACEI and ARB. |
| Unexplained fall in albumin | Withhold and speak to specialist |
| Nausea and/or vomiting | Usually improves over time. If troublesome for **adults** consider:<br>• Increasing the dose of folic acid to 5 mg daily up to 6 days a week - omitting on the day methotrexate is taken.<br>• Splitting methotrexate dose over one evening and next morning.<br>• A short-term anti-emetic.<br>For **children** consider:<br>• Increase folic acid to 1-5mg, 3 days a week. Maximum increase to 5mg 6 days a week (omitting the day methotrexate is taken).<br>• Anti-emetic can be prescribed such as cyclizine or ondansetron<br>If unable to tolerate refer back to specialist for review. |
| Hair loss | Usually mild, rarely significant. Reversible on stopping drug. |
| Rash | Withhold treatment and discuss with specialist. |
| 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 (especially if accompanied by fever/sweats) | Methotrexate pneumonitis may occur. Withhold treatment, arrange chest X-ray and discuss urgently with consultant.<br><br>Pneumonitis is very rare in paediatric practice. Discuss with paediatric rheumatologist if an atypical presentation or persists > 2 weeks without preceding infection. |
| Abnormal bruising | Withhold until FBC result available. |
| Sore throat or other unusual infection | Urgent FBC and withhold until FBC result available. Susceptible to opportunistic infections such as viral wart, TB and pneumocystitis. |
| Lymprofilerative disorders | 2-5 fold increase |
| Cervical dysplasia | Regular cervical smears |
| Diarrhoea | Consider reducing dose |
| Fever, chills | Withhold until FBC result available |

*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* NPSA Patient-held blood monitoring and dosage record booklet. *G.Ps, specialists and pharmacists should monitor book whenever the meet patient.*

- One weekly dose of methotrexate can be withheld without inducing a flare. Patients are advised not to take the dose if more than 24-72 hours late (this depends on speciality so follow advice of specialist) but take as normal the following week.

- Folinic acid (given as calcium folinate) should be used for methotrexate induced myelosuppression, severe mucositis or methotrexate overdoses, in the initial dose 20 mg IV and followed by 15 mg qds orally until abnormalities improve.

**DRUG INTERACTIONS** – see BNF and SPC for complete list

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|---|---|
| Any anti-folates<br>Co-trimoxazole<br>Trimethoprim<br>Phenytoin<br>Sulphonamides<br>Fansidar® | Avoid co-prescribing: Increased anti-folate effect which may induce toxic effects of methotrexate on FBC. |
| Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin | Under specialist advice this combination is not contraindicated. NSAIDs and aspirin may reduce tubular excretion of methotrexate and enhance its toxicity. Over-the-counter products containing NSAIDs or aspirin are NOT recommended. Avoid in IBD as they can aggravate symptoms. |
| Ciclosporin | Patients co-prescribed ciclosporin with methotrexate should initially be re-stabilised by the specialist as it can increase methotrexate toxicity. |
| Immunisation with Live vaccines | Patients receiving methotrexate must NOT receive immunisation with LIVE vaccines (BCG, oral typhoid, oral cholera, measles, mumps, rubella, yellow fever, Sabin polio, Varicella/ Chickenpox, Rotavirus and Japanese Encephalitis). Inactivated polio is available although sub-optimal response may be seen.<br><br>Seasonal influenza vaccination is recommended. Remember for paediatric patients, Fluenz Tetra® (nasal flu vaccine) is live so must not be used.<br><br>Continue with standard vaccination strategy for any patient with IBD and Paediatric Rheumatology (check latest guidance) – H1N1, pneumococcal polysaccharide vaccine, HPV according to national guidance, hepatitis B for selected patients. |
| 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[7]. There can be increased risks of side effects (e.g. liver and haematological), but with careful monitoring experience suggests they may be used together. |
| Alcohol | Safe in moderation but may cause nausea. Stay below national guidance limits. |

**CONTACT INFORMATION**

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|---|---|---|
| Contact Details | Oxford University Hospitals NHS Trust | |
| Dermatology | Dermatologist | 01865 741155 ask for SR |

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| Respiratory Medicine | Dr Ling-Pei Ho (Respiratory Consultant):<br>Dr Rachel Hoyles (Respiratory Consultant):<br>Sarah Poole (Lead Respiratory Pharmacist): | 01865 225223<br><br>01865 225223<br><br>01865 741841; Bleep 4500 |
| Neurology | Dr David Hilton-Jones neurology consultant<br><br>Neurology Registrar on call | Tel 01865 231893<br><br>Hospital switchboard: 01865 741166<br>Bleep Registrar on call |
| Medicines Information | Tel 01865 221505 | |
| Gastroenterology (IBD) | Dr Simon Travis<br>Simon.travis@ndm.ox.ac.uk<br>Dr Oliver Brain<br>Oliver.brain@ouh.nhs.uk<br>IBD Advice line | 01865 228753<br><br><br><br>01865 228772 |

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