SHARED CARE ARRANGEMENT AND PRESCRIBING INFORMATION FOR ORAL METHOTREXATE (ADULTS)

This SCA is applicable for ALL conditions/specialities.

If methotrexate is being used as combination therapy, i.e. with leflunomide or sulfasalazine both SCAs must be referred to. The correct Monitoring Schedule for DMARDS, i.e. single agent or combination therapy should be followed.

Note: This document should be read in conjunction with the current Summary of Product Characteristics (SmPC).

Patient safety is paramount. The prescriber who prescribes the medicine legally assumes clinical responsibility for the drug and the consequences of its use.

GENERIC NAME (formulations and strength)

Name: Methotrexate

Formulation: Tablets

Strength: 2.5mg Prescribed as a ONCE WEEKLY dose.

NHS Grampian Policy; only the 2.5mg strength should be used to avoid the possibility of any confusion and potential unintentional overdose.

STATUS OF MEDICINE

Licence status: Licensed in the treatment of rheumatoid arthritis and psoriasis.
Used off-label in maintenance of remission in severe Crohn's disease after 16 weeks of subcutaneous (SC) methotrexate, steroid responsive inflammatory or autoimmune disorders and in the treatment of vasculitis.

Formulary status: Formulary – available for restricted use under specialist supervision

Black triangle medicine: NO

Risk minimisation materials: NO

CONDITION(S) TO BE TREATED UNDER THIS SCA

Oral methotrexate may be used in the following:

- Treatment of rheumatoid arthritis.
- Treatment of psoriasis.
- Maintenance of remission in severe Crohn's disease after 16 weeks of SC methotrexate.
- Treatment of vasculitis.
- Steroid responsive inflammatory or autoimmune disorders of the central and peripheral nervous system including myasthenia gravis, autoimmune encephalitis, neuromyelitis optica (NMO) spectrum disorder/myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), neurosarcoid, chronic inflammatory demyelinating polyneuropathy, and myositis.

TYPICAL DOSAGE REGIME	
Licensed dose	See Specialist service/SmPC for advice – variable according to condition being treated
Route of administration	Oral
Recommended starting dose	See Specialist service for advice – variable according to condition being treated
Titration dose/increment	See Specialist service for advice
Maximum dose	See Specialist service for advice
Situations requiring dose adjustment	See Specialist service for advice and Monitoring Schedule for DMARDs
Duration of treatment	See Specialist service for advice

RESPONSIBILITY OF ACUTE CARE/SPECIALIST SERVICE

- Baseline per Monitoring Schedule for DMARDs:
  - Full Blood Count (FBC), Liver Function Tests (LFTs), and Urea and Electrolytes (U&Es)
  - Chest x-ray
  - Dermatology only - Type III Procollagen Peptide (PIIINP test) to be undertaken once prior to treatment then repeated at four monthly intervals
- Copy of baseline results to be shared with primary care.
- Exclude pregnancy before starting therapy. Advise men and women:
  - Methotrexate is not compatible with pregnancy conception must be avoided during treatment.
  - Women on methotrexate at any dose should be advised to seek specialist advice prior to conception
  - Discuss the potential adverse effect of methotrexate on reproduction.
  - Ensure the patient understands the importance of reliable contraception

  The British Society for Rheumatology Guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids from April 2023 states that doses of methotrexate of 25mg or less per week should be stopped, at least 1 month or more pre-conception. Higher doses should be stopped for 6 months prior to conception.
  - Advise patient to contact their physician immediately should pregnancy occur
- Request for initiation of therapy and recommendations for dose increments to Primary Care.
- Provision of information regarding folic acid prescribing dose, frequency and timing to Primary Care. (Generally recommended 5mg daily, except on day of methotrexate treatment, to minimise nausea and improve methotrexate tolerability).
- Monitoring clinical response to treatment and advising on final dose required for the patient. Clinical decision regarding final dose required for patient.

- Pneumococcal polysaccharide vaccine (PPV), COVID-19 vaccine and annual influenza vaccine should be given as per Joint Committee of Vaccination and Immunisation(JCVI)/The Green Book recommendations. Shingles vaccine should be given to those individuals who are severely immunocompromised, or anticipating immunosuppressive therapy, and eligible in line with JCVI/The Green Book recommendations and Scottish Government vaccination programme. This may be dependent on the dose/therapy patients are receiving. Patients should be referred by specialist services to receive these vaccines in accordance with local protocol.

RESPONSIBILITY OF PRIMARY CARE/PRESCRIBING CLINICIAN

A Practice agreeing to prescribe oral methotrexate should:

- Prescribe medication under the guidance of the Consultant from the specialist service.
- Checking before prescribing each instalment of medication that the monitoring is up to date and results are within a satisfactory range.
- Note: for individuals referred for vaccinations by the specialist service it is ideal to wait for vaccinations before starting immunosuppressive treatments. However this risks not controlling the autoimmune condition quickly which can negatively affect long term prognosis. Therefore specialties do not insist on a delay in starting immunosuppressive treatment to allow for vaccinations and recommend vaccinations happen as soon as possible after starting immunosuppressive treatment.
- Prescribe methotrexate using the 2.5mg tablet strength only, as per board policy to minimise risk of confusion and unintended overdose.
- Ensure methotrexate is prescribed as a ONCE WEEKLY dose.
- Ensure that the relevant monitoring requirements have been undertaken at the correct frequency.
- The General Practitioner (GP) has primary responsibility for monitoring according to the Monitoring Schedule for DMARDs and review of results. Note also for dermatology the requirement for Type III Procollagen Peptide (PIIINP test) to be repeated at four monthly intervals.
- Only continue to prescribe medication if it is being satisfactorily monitored.
- Ensure the GP is aware that the drug can cause:
    - Leucopenia
    - Thrombocytopenia
    - Stomatitis and GI ulceration
    - Suppression of ovarian and testicular function
    - New or increasing fever, dyspnoea or cough or the presence of rash or oral ulceration
    - Renal or Hepatic damage.
- Folic acid 5mg (orally) should be prescribed as per specialist service recommendation. This is normally folic acid 5mg daily, except on day of methotrexate treatment, to minimize nausea and improve tolerability of methotrexate. It is not to be taken on the same day as methotrexate due to risk of reducing efficacy. Once established on treatment and if nausea subsides this may be reduced to a minimum of once weekly, usually given the 48 to 72 hours after methotrexate.
- Patients should be asked about the presence of infection, especially sore throat, cough or dyspnoea at each visit.

- Ensure when the patient has an inter-current illness FBC, U+E and LFTs are done and abnormal results are acted upon promptly. If an intercurrent illness occurs, when completing laboratory request always include details of the patient's medication.
- If bloods are taken due to intercurrent illness, ensure they are monitored and action taken as per the Monitoring Schedule for DMARDs.
- Infection - During a serious infection methotrexate should be temporarily discontinued until the patient has recovered from the infection and is off antibiotics for 2 weeks with no recurrence of infection.
  It can be considered appropriate to continue these drugs in patients with minor or uncomplicated viral infections or, if deemed clinically appropriate by the Specialist, in patients requiring long term antibiotic prophylaxis e.g. for prevention of recurrent UTIs.
- Contact the consultant in the event of a drug reaction, monitoring abnormality, or if you are concerned in any way regarding the current treatment regime.
- Be alert for any of the known adverse reactions.
- Ensure no interacting medications are prescribed in primary care.
- Monitor for concordance with therapy.
- The patient should be encouraged to ensure blood tests are undertaken at the correct intervals.
- It is responsibility of primary care to ensure that the medication is recorded on the patient's clinical medication record. This will facilitate central searches for annual vaccinations in order to ensure patients receiving DMARDs are called yearly by the HSCP teams for required vaccinations.
- Report any adverse events to consultant and the MHRA using the Yellow Card System.
- Post exposure prophylaxis (PEP) should be considered for non-immune individuals if exposed to shingles or chickenpox as per The Green Book. This may be dependent on the dose/therapy patients are receiving.
- If something unexpected occurs contact on call registrar or Consultant for the appropriate specialty.
- Notify the consultant if the drug is stopped.

MONITORING

Refer to the NHSG Guidelines For The Monitoring of Disease Modifying Anti-Rheumatic Drugs (DMARDs) For Healthcare Professionals. Results should be reviewed and action taken as per monitoring guidance.

If methotrexate is being used as combination therapy i.e. with leflunomide or sulfasalazine both SCAs must be referred to. The correct Monitoring Schedule for DMARDS i.e. single agent or combination therapy should be followed.

Primary Care are responsible to ensure results are reviewed and action taken as per monitoring guidance.

Note: In addition to absolute values for haematological or biochemical indices a rapid change or a consistent upward/downward trend in any value should prompt caution and extra vigilance.

RESPONSIBILITY OF THE PATIENT

- Take medication regularly as directed by the specialist/doctor.
- Attend hospital and GP clinic appointments as requested by specialist/GP practice. Failure to attend appointments may result in medication being reviewed/stopped.
- The patient should ensure all blood tests are taken at the correct intervals.
- Report any adverse effects/illness to the specialist/GP and present rapidly to specialist/GP should their condition significantly worsen.
- To minimise the risk of skin cancer, exposure to sunlight and Ultra Violet light should be limited by wearing protective clothing and using sunscreen with a high protection factor (minimum SPF 30).

PRESCRIBING INFORMATION

For specific product information consult the current summary of product characteristics (http://emc.medicines.org.uk/), the BNF/BNF for Children BNF (British National Formulary) | NICE

CONTRAINDICATIONS

For full detail please refer to the current Summary Product Characteristic (SPC) available at www.medicines.org.uk.

- NSAIDs/aspirin - can reduce excretion of methotrexate. However in the treatment of rheumatoid arthritis standard doses of NSAIDs may be continued. Due to the risk of toxicity monitoring is essential if a new prescription is added, checking all bloods monthly until stable, then returning to normal monitoring schedule. The use of Over the Counter (OTC) NSAIDs should be discouraged.
- Co-trimoxazole/Trimethoprim - Do not prescribe drugs with anti-folate properties such as co-trimoxazole as this can cause increase methotrexate toxicity.
- Hypersensitivity to the active substance or to any of the excipients.
- Severe/significantly impaired renal function.
- Significantly impaired hepatic function.
- Liver disease including fibrosis, cirrhosis, recent or active hepatitis.
- Severe or chronic infections and immunodeficiency syndrome.
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia.
- Alcoholism.
- Stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcer disease.
- Concurrent vaccination with live vaccines.
- Avoid concomitant use with drugs with antifolate properties.
- Pregnancy should be avoided by using an effective contraceptive method for at least 6 months after using methotrexate.
- Breastfeeding.
- Severe infections - during a serious infection methotrexate should be temporarily discontinued until the patient has recovered from the infection and is off antibiotics for 2 weeks with no recurrence of infection.

PREGNANCY

Not compatible with pregnancy discuss with specialist service.
Advise patient to contact their physician immediately should pregnancy occur.

Women on methotrexate at any dose should be advised to seek specialist advice prior to conception as methotrexate should be stopped and switched to another pregnancy compatible drug at least one month before planned conception.

The British Society for Rheumatology Guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids from April 2023 states that doses of methotrexate of 25mg or less per week should be stopped at least 1 month or more pre-conception. Higher doses should be stopped for 6 months prior to conception.

Men should also be advised that of doses of methotrexate of 25mg or less per week should be stopped at least 1 month or more pre-conception.

BREAST-FEEDING

Contraindicated, discussion is required with the specialist service.

COMMON SIDE EFFECTS

Blood and lymphatic system disorders	Leucopenia anaemia and thrombocytopenia
Nervous system disorders	Headache, drowsiness, dizziness and fatigue
Gastrointestinal disorders	Stomatitis, dyspepsia, nausea, vomiting, abdominal pain, oral ulcers and diarrhoea
Hepatobiliary disorders	Abnormal liver function tests (increased ALT, AST, alkaline phosphatase and bilirubin)
Skin and subcutaneous tissue disorders	Exanthema, erythema and alopecia

Action abnormal monitoring results are per NHSG Disease Modifying Anti-Rheumatic Drugs (DMARDs) Monitoring Guidance.

The specialist service should be contacted if there are any patient specific issues or concerns regarding side effects or abnormal results.

COMMON DRUG INTERACTIONS (for a full list see SmPC)

Advice should be obtained from the specialist service if required.

Some important interactions to consider include the following:

NSAID/aspirin	Can reduce excretion of methotrexate. **However low dose aspirin and standard doses of NSAIDs may be continued.** The use of over the counter (OTC) NSAIDs should be discouraged. Monitoring is essential if a new prescription is added, checking all bloods monthly until stable, then returning to normal monitoring schedule.
Co-trimoxazole/ Trimethoprim	Must not be co-administered with methotrexate as there is increased risk of haematological toxicity. Cases of severe bone marrow suppression have been reported.
Levetiracetam	Decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels.
Acidic drugs such as: phenylbutazone, phenytoin, tranquillisers, oral contraceptives, aminopyridine derivatives, thiazide diuretics, oral hypoglycaemics, tetracyclines, probenecid or sulfinpyrazone	Methotrexate is extensively protein bound and may displace, or be displaced by, other acidic drugs. The concurrent administration will increase methotrexate toxicity, concurrent use contra-indicated.
Nephro or heptotoxic agents	Avoid concurrent use with methotrexate
Mercaptopurine	Methotrexate increases plasma levels of mercaptopurine. Combinations of methotrexate and mercaptopurine may therefore require dose adjustment.
Live vaccines	Should be avoided. Refer to The Green book for further information as this may be dependent on the dose of methotrexate.

This information is not intended to be a complete list of interactions. For further information consider appropriate reference sources such as SmPC/Vision system.

ADVERSE DRUG REPORTING

If an adverse reaction should occur inform relevant medical practitioner as soon as possible.

Report to the MHRA using the Yellow Card System https://yellowcard.mhra.gov.uk/

REFERENCES

- https://www.medicines.org.uk/emc/product/511/smpc
- Methotrexate 10mg Tablets - Risk Management Materials - (emc) | 11723

ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION

In the event of a concern being raised, the primary care practitioner should contact the referring consultant via the hospital switchboard, via their secretary, by e-mail or letter, whichever is more appropriate. If the concern is urgent, and out of hours advice is required, the on call Renal Registrar may be contacted via switchboard.

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