National shared care protocol adapted for local use:

Rheumatological Conditions: Oral Methotrexate for patients in adult services (excluding cancer care)

The content of this shared care protocol was correct as of November 2023. As well these protocols, please ensure that summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites are reviewed for up-to-date information on any medicine.

Specialist Responsibilities

- Assess the patient and provide a diagnosis; ensure that this diagnosis is within the scope of this shared care protocol (section 2) and communicated to primary care.
- Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling (see section 11) to enable the patient to reach an informed decision. Obtain and document patient consent. Provide an appropriate patient information leaflet.
- Ensure the patient and/or carer understand and can follow the once-weekly dose regimen.
- Assess for contraindications and cautions (see section 4) and interactions (see section 7).
- Initiate and optimise treatment as outlined in section 5. Once the patient is known to be tolerating the medicine, transfer to shared care would normally take place. Before transfer to shared care, the patient is expected to have had at least one specialist review and be stable (no increase in mediation dose for at least 6 weeks alongside satisfactory investigation results). On transferring shared care, the specialist will provide at least 4 weeks medication to enable the practice to receive and process the shared care agreement and set up prescribing and ongoing monitoring. Any bloods required within the 4 weeks should be requested/organised and followed up by the specialist.
- If shared care is considered appropriate, and once treatment is optimised, write to the patient's GP practice and request shared care; detailing the diagnosis, current and ongoing dose of methotrexate and folic acid, any relevant test results, which day of the week the patient takes their methotrexate and folic acid, when the next monitoring is required, details of monitoring arrangements, details of current contraception if relevant, and other relevant treatments being received by the patient. Include the specialist service contact information (section 13).
- The specialist should also provide the details of the treatment to be undertaken by the GP, including the reasons for the choice of treatment, medicine combination, frequency of treatment, and the next review date by the specialist.
- Prescribe sufficient medication to enable transfer to primary care (usually 42 days). Further prescriptions will be issued where there are unforeseen delays to the transfer of care. The patient should not be put in a position where they are unsure where to obtain medication

supplies. The specialist team will be responsible for monitoring and prescribing the medicine during this initial period.

- Conduct the required monitoring in section 8 and communicate the results in writing to primary care within 14 days, where possible. After each review, provide primary care with a written summary within 14 days, advising whether treatment should be continued, confirming the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.
- Review treatment and reassume prescribing responsibility if a patient becomes or wishes to become pregnant.
- Provide advice to primary care on the management of adverse effects if required.
- Review patients annually. Review once every two years for patients under a Patient Initiated Follow-ups (PIFU) pathway.
- Provide patients taking methotrexate with a patient information leaflet and monitoring document. Counsel the patient particularly on contraception if appropriate (please see individual medication information sheet).
- Whenever the specialist sees the patient, they will record test results on the patient-held monitoring booklet and take any action necessary.
- Contact details for primary care prescribers will be made available.
- Details for fast-track referrals will be supplied.

Primary care responsibilities

- If shared care is not accepted, inform the specialist of the decision in writing within 14 days with reasons why shared care cannot be entered into. If shared care is accepted, ensure knowledge and understanding of the therapeutic issues relating to the patient's clinical condition. Undergo any additional training necessary to carry out the prescribing and monitoring requirements.
- Agree that, in their opinion, the patient should receive shared care for the diagnosed condition unless good reasons exist for the management to remain within the secondary care.
- If accepted, prescribe methotrexate and folic acid as detailed in the specialist's request and as per section 5, considering potential drug interactions in section 7.
- Adjust the dose of methotrexate and folic acid prescribed as advised by the specialist and communicate any changes made to the patient.
- Conduct the required monitoring as outlined in section 9. Communicate any abnormal results to the specialist. Discuss with the referring specialist team if there are any amendments to the suggested monitoring schedule.
- Ensure that the patient is given the appropriate appointments for follow-up and monitoring.
- If a patient fails to attend, contact the patient in a timely manner to arrange an alternative appointment. It is the GP's responsibility to decide whether to continue treatment in a patient who does not attend follow-up and monitoring appointments. If the patient regularly fails to attend the monitoring appointment, the GP may withhold the prescription and inform the consultant responsible for the patient's care.
- The primary care clinician conducting the investigations is responsible for completing the patient's monitoring record with the necessary information and up-to-date results of investigations. Manage adverse effects as detailed in section 10 and discuss them with the specialist team when required. Refer the patient back to the specialist team if further investigation is required.

- Stop methotrexate and discuss urgently with the specialist if the patient develops signs of severe infection, liver or respiratory disease, unexplained bleeding or bruising, becomes pregnant, or if immunosuppressed patients are exposed to chickenpox or shingles.
- Female patients must not become pregnant whilst taking this medication. Discuss with the specialist if the patient plans to become pregnant. Female patients must be advised to use effective contraception throughout the course of methotrexate therapy.
- Stop treatment as advised by the specialist.
- Offer patients vaccination in line with the current Joint Committee on Vaccination and Immunisation advice (Immunisation against infectious disease).

Patient and/or carer responsibilities

- Take or administer methotrexate as prescribed and avoid abrupt withdrawal unless advised by the primary care prescriber or specialist.
- Attend regularly for monitoring and review appointments with primary care and specialist and keep contact details up to date with both prescribers. If provided, they should bring their monitoring booklet to each appointment. Be aware that medicines may be stopped if they do not attend. If they are unable to attend any appointments, they should inform the relevant practitioner as soon as possible and arrange an alternative appointment.
- Report adverse effects to their primary care prescriber. Seek immediate medical attention if they develop any symptoms, as detailed in section 11.
- Report the use of any over the counter (OTC) medications to primary care and specialist and be aware that they should discuss the use of methotrexate and any current medication with their pharmacist before purchasing any OTC medicines.
- Avoid self-medication with over-the-counter aspirin or ibuprofen.
- Moderate their alcohol intake to no more than 14 units per week.
- Not to drive or operate heavy machinery if methotrexate affects their ability to do so safely.
- All patients should use appropriate contraception. Those of childbearing potential should take a pregnancy test if they think they could be pregnant and inform the specialist or GP immediately if they become pregnant or wish to become pregnant. See section 12.
- Store their medication securely away from children.
- Read the information supplied by their GP, specialist, and pharmacist, and contact the relevant practitioner if they do not understand any of the information given.
- Keep the patient-held monitoring booklet up to date with the results of investigations, dosage changes, and management alterations. Take any actions necessary.

Community pharmacist roles and responsibilities

- The community pharmacist will professionally check prescriptions to ensure they are safe for the patient and contact the GP if necessary.
- Fulfil the legal prescriptions for medication for the patient unless they are considered unsafe.
- The pharmacist will ask to see the patient's monitoring booklet, if provided, and check if any dose changes have been made since the last prescription issue.
- The pharmacist must ensure the strength of the tablet supplied to the patient is consistent to prevent any confusion about the number of tablets the patient must take. Confirm strength to be supplied with the prescription and the patient's monitoring booklet, if provided. If in any doubt, contact the prescriber for confirmation.

- To reduce dosing errors, **only methotrexate 2.5 mg tablets should be prescribed**. The dose should be taken **once weekly** on the same day each week, and that day should be clearly communicated to the patient and noted this day down in full on the prescription.
- Counsel the patient about their methotrexate, telling them about the dose in terms of quantity of tablets and (in most cases) weekly frequency, providing the patient with a monitoring booklet if they do not already have one.
- Ensure the patient can differentiate between their folic acid and methotrexate and know how to take them both.
- Be aware of patients who attend with symptoms such as breathlessness, persistent dry cough, vomiting or diarrhoea, as these can be signs of oral methotrexate toxicity or intolerance. Refer them back to the prescriber for further investigation. It is a good practice to maintain a record of any over-the-counter items supplied to the patient.

1. Background

Back to top

Methotrexate is a cytotoxic folic acid antagonist used to treat chronic inflammatory conditions and certain cancers. It inhibits the enzyme dihydrofolate reductase and inhibits the synthesis of DNA, RNA, and proteins.
Methotrexate is licensed for the treatment of certain cancers, as well as some chronic inflammatory disorders. It is not licensed for all the conditions it is used to treat. However, its use for the indications below is well-established and supported by clinical specialists.
Methotrexate is used to induce remission or partial remission in patients with inflammatory conditions, including arthritis, psoriasis, connective tissue disease and vasculitis. The clinical benefit may take up to 3 months. NSAIDs and simple analgesics may need to be continued. Patient-reported adverse effects usually occur early in therapy.
This shared care protocol does not cover the treatment of cancer or treatment of people less than 18 years old.

2. Indications

Back to top

The licensed indications for methotrexate include:

- Active rheumatoid arthritis
- Mild to moderate Crohn's disease in patient's refractory or intolerant to thiopurines (licensed indication of subcutaneous preparations)
- Severe psoriasis
- Severe psoriatic arthritis

Licensed indications vary with the brand. See the relevant summary of product characteristics for full details.

This shared care protocol includes treatment of chronic inflammatory conditions where off-label use of methotrexate is appropriate, including, but not limited to, the following conditions:

- Licensed: Rheumatoid arthritis and psoriatic arthritis
- Unlicensed: Connective tissue disease (e.g., Systemic Lupus Erythematosus (SLE), myositis, and vasculitis) – supported by the national guidance.

The specialist must specify the indication for each patient when initiating shared care and clearly state when the use is off label.

3. Locally agreed patient groups exclusion

Back to top

Patient receiving:

- Doses more frequently than once a week
- 10mg tablets
- Receiving subcutaneous therapy

are excluded from the shared care, i.e. classified as RED in the Nottinghamshire Joint Formulary

4. Contraindications and cautions

Back to top

This information does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it. Please see BNF & SPC for comprehensive information.

Contraindications:

- Hypersensitivity to methotrexate or any excipients.
- Significant hepatic impairment.
- Ascites or pleural effusion: drain prior to treatment to reduce the risk of methotrexate accumulation.
- Liver disease, including fibrosis, cirrhosis, and recent or active hepatitis, unless specified specifically by the secondary care team.
- Significant renal impairment – creatinine clearance (CrCl) less than 30 mL/min.
- Severe infections (acute or chronic) or immunodeficiency syndromes.
- Known active peptic ulceration.
- Pregnancy and breastfeeding.
- Vaccination with live vaccines during treatment with methotrexate at immunosuppressive doses. See section 7 for further detail.
- Concomitant use of medicines with anti-folate properties, e.g., trimethoprim, co-trimoxazole (see section 7).

Cautions:

- Renal impairment: dose reduction required (section 5).
- Alcohol dependence. Advise the patient to remain well within the national guidelines.
- Hepatic impairment, particularly if due to alcohol use.
- Pre-existing blood dyscrasias or disorders, including bone marrow hypoplasia, leucopoenia, thrombocytopenia, or significant anaemia. Confirm to primary care that any underlying dyscrasias have been considered and whether any change to standard monitoring in section 9 is required.
- Respiratory disease. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur, and deaths have been reported. Patients should be advised to contact their GP immediately should they develop persistent cough or dyspnoea.
- Concomitant use with hepatotoxic or haematotoxic medicines (see section 7).
- History of ulcers of the oral cavity, ulcerative stomatitis, gastrointestinal ulcers, or ulcerative colitis.
- History of chronic or recurrent infection (e.g., frequent infective COPD exacerbations, tuberculosis, or recurrent urinary tract infection). Localised or systemic infection including hepatitis B or C.
- Frail or elderly – consider reduced dose.

- Conditions which increase the risk of dehydration (e.g., vomiting) may increase the risk of toxicity. Consider interrupting treatment until symptoms cease.
- Patients who have no history of exposure to varicella zoster virus (VZV) i.e., chickenpox or herpes zoster (shingles), should avoid contact with individuals with chickenpox or herpes zoster. Contact the on-call microbiologist via the hospital switchboard for advice regarding those who have no antibodies to varicella–zoster virus and who have had significant exposure to chickenpox or herpes zoster. See The Green Book– chapter 34 for detailed guidance. If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.

5. Initiation and ongoing dose regimen

Back to top

- Once the patient is known to be tolerating the medicine, transfer to shared care would normally take place. Before transfer to shared care, the patient is expected to have had at least one specialist review and be stable (no increase in mediation dose for at least 6 weeks alongside satisfactory investigation results). On transferring shared care, the specialist will provide at least 4 weeks medication to enable the practice to receive and process the shared care agreement and set up prescribing and ongoing monitoring. Any bloods required within the 4 weeks should be requested/organised and followed up by the specialist.
- The duration of treatment & frequency of review will be determined by the specialist based on clinical response and tolerability.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed upon with the primary care clinician.
- Termination of treatment will be the responsibility of the specialist.

Initial stabilisation:

There is a wide dose range depending on the indication. The selected dose of methotrexate, and the folic acid regimen, will be tailored to the individual patient and decided by the specialist. The usual starting dose is 10 mg – 15 mg orally once weekly. **The dose titration period must be prescribed by the initiating specialist.**

To reduce dosing errors, **only the methotrexate 2.5 mg tablets should be prescribed**. The dose should be taken **once weekly** on the same day each week, and that day should be clearly communicated to the patient and noted this day down in full on the prescription.

Maintenance dose (following initial stabilisation):

Usual dose range**: 7.5 mg – 25 mg weekly given orally**, adjusted according to the response. The maximum licensed dose of methotrexate for rheumatoid arthritis is 25 mg per week.

Prescribers should be aware that patients often understand their dose by the number of tablets they take; avoid the use of **"as directed"** as an instruction. Therefore, **it should be clear which strength tablets the patient is taking.**

Example prescription: **Methotrexate 2.5 mg tablets, take six tablets (15 mg) once a week, on a Monday.**

Please note that for rheumatology conditions, a patient may be initiated on more than one DMARD.

All patients should be prescribed folic acid at a dose of 5 mg at least once weekly, to be taken on a different day than their methotrexate dose, to reduce the likelihood and severity of side effects associated with methotrexate and to improve continuation of therapy and compliance. The specialist should include clear details of the folic acid regimen in their communication with the patient and primary care.

The initial maintenance dose must be prescribed by the initiating specialist.

All DMARDs are long-term treatments. The clinical benefit may take up to 3 months. The duration of treatment will be determined by the specialist based on clinical response and tolerability.

Conditions requiring dose adjustment:

Renal impairment: in patients with CrCl less than 60 mL/min the dose should be reduced by 50%. If CrCl is less than 30mL/min discontinuation may be indicated. See section 10.

6. Pharmaceutical aspects

Back to top

Route of administration:	Oral tablets
Formulation:	**Methotrexate tablets** Other strengths are available, but to reduce dosing errors, **only 2.5 mg tablets should be prescribed**. The dose should be taken **once weekly** on the same day each week, and that day should be clearly communicated to the patient and noted down in full on the prescription.
Administration details:	Tablets should not be split or crushed for administration. Review formulation if the patient is unable to swallow tablets. Carers should wear single-use gloves to handle methotrexate tablets. Anyone handling the tablets should wash their hands immediately afterwards. Pregnant people, including patients and carers, should avoid handling methotrexate. If a dose of methotrexate is missed, it should be taken as soon as remembered, within one or two days. Doses which are three or more days late should be skipped entirely. Take the next dose as scheduled on the usual day. A double dose should not be taken to make up for a missed dose.
Other important information:	Methotrexate is taken once weekly, and there is a significant risk of toxicity if it is taken more frequently. Prescribers should follow the MHRA advice on preventing inadvertent daily dosing, including ensuring that the patient and/or carer understands the dosing schedule and is able to follow it.

	All patients should be prescribed folic acid at a dose of at least 5 mg once weekly, to be taken on a different day than their methotrexate dose. The specialist should include clear details of the folic acid regimen in their initial communication with primary care. In areas where methotrexate monitoring booklets are in use, the patient should receive a monitoring booklet from the specialist upon initiation of treatment. They should bring this booklet to all specialist and GP appointments where it will be updated by the health professional conducting the appointment. The patient should also produce the booklet to any health professional involved in other aspects of their care e.g., pharmacists and dentists.

7. Significant medicine interactions

Back to top

The following list is not exhaustive. Please see BNF or SPC for comprehensive information and recommended management.

Methotrexate is associated with a large number of interactions, some of which are significant enough to contraindicate concurrent use and require dose adjustment and/or additional monitoring (see section 4). Additional interactions which become relevant at higher doses (e.g., those used in oncology) are not included.

- **Trimethoprim and co-trimoxazole (Septrin®)**: Co-administration of medicinal products which cause folate deficiency (e.g., **trimethoprim** and **co-trimoxazole**) can lead to increased methotrexate toxicity and is contraindicated (see section 4). Particular caution should, therefore, also be exercised in the presence of existing folic acid deficiency.
- **Leflunomide**: increased risk of bone marrow and liver toxicity; increased monitoring and vigilance required.
- **Ciclosporin**: increased risk of nephrotoxicity and methotrexate toxicity.
- **Azathioprine and mercaptopurine**: not advised due to increased risk of toxicity.
- **Acitretin:** Avoid
- **Sulfasalazine**: may increase the risk of bone marrow and liver toxicity. However, this combination is used in clinical practice without incident. Be aware of trends in monitoring parameters.
- **Drugs with hepatotoxic, haematotoxic or nephrotoxic effects**: Increased frequency of monitoring may be recommended.
- **Live vaccines** (e.g., oral polio, oral typhoid, MMR, BCG, Zostavax®) are advised in line with the national schedule for all patients unless the patient is taking a dose of methotrexate or other immunosuppressive drugs that exceeds those specified in the Green Book. Doses below this level are not considered sufficiently immunosuppressive, and these patients can receive live vaccines. Clinician discretion is advised. Please refer to the Green Book Chapter 6 for current advice. N.B. Routine influenza and pneumococcal vaccinations are highly recommended.
- **Clozapine, cytotoxics and olanzapine:** increased risk of agranulocytosis. Avoid concomitant use.
- **Retinoids**: increased risk of hepatotoxicity and may increase plasma levels of methotrexate.
- **Levetiracetam**: may increase plasma levels of methotrexate.
- **Nitrous oxide and pyrimethamine**: increased antifolate effect of methotrexate.
- **Lomitapide**: increased risk of hepatotoxicity.
- **Probenecid**: excretion of methotrexate reduced.

- **Phenytoin:** possible increase of the antifolate effect of methotrexate leading to toxicity and decreased phenytoin effect. Increase the frequency of monitoring.
- **NSAIDs**, **COX-2 inhibitors, aspirin**: may reduce excretion of methotrexate, increasing the risk of toxicity. These drugs are frequently used with methotrexate without incident, and aspirin at antiplatelet doses is unlikely to interact to a significant degree. The type and dose of NSAID should not be altered during methotrexate therapy without prior consultation with the rheumatology specialist team. They should not be stopped just because the patient is starting methotrexate, as the medicine takes 1-2 months to exert an effect, and the patient is likely to need the NSAID in the long term. Be aware of trends in monitoring parameters.
- **Antibiotics** may alter methotrexate levels (excretion of methotrexate may be reduced – increased risk of toxicity). Methotrexate should be interrupted during periods of acute infection (see section 10).
- **Theophylline and other methylxanthines**: may reduce methotrexate efficacy. Methotrexate may reduce theophylline clearance.
- **Anticonvulsants**: may reduce methotrexate levels.
- **Colestyramine**: may increase the elimination of methotrexate.
- **Alcohol**: consumption of alcohol increases the risk of hepatotoxicity. Patients should moderate their alcohol intake to no more than 14 units per week.

8. Baseline investigations, initial monitoring, and ongoing monitoring to be undertaken by specialists

Back to top

Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in the immediate future will prescribing and monitoring be transferred to primary care.

Baseline investigations:

- Height and weight
- Blood pressure
- Full blood count (FBC)
- Urea and electrolytes (U&Es), including creatinine and creatinine clearance (CrCl)
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), and albumin
- Screening for HIV and hepatitis B and C should be undertaken at clinician discretion.
- Screening for lung disease, including interstitial lung disease and tuberculosis, should be undertaken at clinician discretion on a case-by-case basis.
- Provide or request appropriate vaccination prior to treatment initiation, according to local arrangements (e.g., pneumococcal, shingles, influenza, COVID-19)

Initial monitoring and at dose change:

To be repeated every 2 weeks until the dose has been stable for 6 weeks, then monthly for 3 months, and then 3 monthly thereafter.

- FBC
- U&Es, including creatinine and CrCl.
- ALT and/or AST, and albumin
- Rheumatology patients: CRP &/or ESR (may or may not monitor by the specialist. The decision to monitor is dependent on the patient's risk.)

Following a dose change repeat every 2 weeks until the dose has been stable for 6 weeks, then revert to previous schedule.

More frequent monitoring is appropriate in patients at higher risk of toxicity.

Ongoing monitoring:
The specialist will retain the responsibility for monitoring the patient's ongoing response to treatment and advise if a dose change or treatment cessation is appropriate. **This should usually be undertaken annually.**

When a patient is reviewed, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.

9. Ongoing monitoring requirements to be undertaken by primary care

Back to top

See section 10 for further guidance on the management of adverse effects/responding to monitoring results.

Monitoring	Frequency
• FBC • U&Es, including creatinine and CrCl. • ALT and/or AST and albumin	At least every 12 weeks, and more frequently in patients at higher risk of toxicity, as advised by the specialist team. Patients receiving methotrexate with leflunomide need to continue with monthly blood tests throughout their treatment. **The exact frequency of monitoring is to be communicated by the specialist in all cases**.
• Patients aged from 50 years who are severely immunosuppressed and have not received the shingles vaccine before will be eligible for the shingles vaccine (varicella zoster). This will be provided as two doses of the non-live vaccine. If patient is taking additional DMARDs, check advice for all drugs. Please refer to Green Book Chapter 6 and Chapter 28a (Shingles) for further details. • **Annual** influenza (The Green Book, Chapter 19) vaccinations are highly recommended. • COVID-19 vaccination (The Green Book, Chapter 14a) is safe and recommended.	• Shingles vaccination: Chapter 28a (Shingles). • Influenza vaccination: annual. It is advisable to add the patient to the influenza vaccine list. • Other vaccinations as per national schedule, e.g., pneumococcal vaccine, COVID-19.

• Repeat pneumococcal vaccine are highly recommended. See Green Book Chapter 25 for advice.	
(If relevant) If monitoring results are forwarded to the specialist team, please include clear clinical information on the reason for sending, to inform action to be taken by secondary care.	

10. Adverse effects and other management

Back to top

Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard
For a full list of side effects and information on incidence of ADRs, refer to the BNF or see relevant summaries of product characteristics
If you are in any doubt about any potential adverse reaction, please contact the rheumatology specialist team.

Result	Action for primary care
As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance. Other benchmark values may be set by secondary care in specific clinical circumstances. This will be communicated by the specialist.	
Full blood count: • White blood cells less than $3.5x10^9$/L • Lymphocytes less than $0.5x10^9$/L • Neutrophils less than $1.6x10^9$/L • Platelets less than $140x10^9$/L • Eosinophilia greater than $0.5x10^9$/L	Withhold and discuss with specialist team.
Macrocytosis • Mean cell volume greater than 105 fL	Consider interruption in treatment. Check serum folate, B12, alcohol history and TSH and treat any underlying abnormality. If results of these additional investigations are normal discuss with specialist team urgently.
Signs or symptoms of bone marrow suppression, e.g., unexplained bleeding or bruising with or without sore throat, purpura, mouth ulcers.	Check FBC immediately, withhold treatment while awaiting results, and discuss with the specialist team. See haematological monitoring above.
Infections: • Infection requiring antibiotics	Temporarily withhold methotrexate until the patient has recovered. Consider additional investigations (e.g., FBC), if clinically appropriate.
Liver function tests: • ALT or AST >100 units/L, or any sudden increases (e.g., double of baseline), **OR**	Withhold and discuss with specialist team.

• Unexplained fall in serum albumin <30g/L (in the absence of active disease) • Jaundice	Assess for other causes of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.
Renal function: Creatinine increase of greater than 30% from baseline in the last 12 months, or CrCl reduces to <60ml/min	Withhold and discuss with specialist team.
Gastrointestinal disorders: Nausea and vomiting	Review for reversible causes and treat as appropriate. Enquire which day of the week the patient takes their methotrexate, and which day(s) they take folic acid and confirm against the patient's records. Withhold and discuss with specialist team if persistent or severe.
Diarrhoea, ulcerative stomatitis, haematemesis, black or bloody stools, or suspected pancreatitis	Withhold and discuss with specialist team.
Symptoms of interstitial lung disease e.g., persistent cough, new or increasing dyspnoea, fever	If methotrexate-induced lung disease is suspected, discuss with specialist team urgently and withhold treatment. Treat with corticosteroids as directed by a specialist and do not restart methotrexate.
Photosensitivity	Continue methotrexate. Reinforce appropriate self-care e.g., sun avoidance and purchasing of a broad-spectrum sunscreen (at least SPF30).
Rash	Withhold until discussed with the rheumatology specialist team.
Pregnancy	In pregnant patients, stop methotrexate immediately and prescribe folic acid 5 mg/day. Discuss with specialist team urgently. See section 12. In pregnancies with paternal exposure, see section 12.

11. Advice to patients and carers

Back to top

The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.

The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:

- Symptoms of chickenpox or contact with a person with chickenpox or shingles.

- Persistent cough, shortness of breath, or any other problems with breathing.
- Sore throat, mouth ulcers, high temperature, skin rash, swollen glands, or any other signs or symptoms of infection
- Signs or symptoms of liver problems, such as yellow skin or eyes (jaundice), itching all over, nausea, vomiting, abdominal discomfort, or dark urine.
- Swelling of the hands, feet, or ankles
- Unexplained bleeding or bruising, black stools, or blood in the vomit or stools.
- Suspected or confirmed pregnancy.

The patient and/or carer should be advised:

- Patients must be given a pre-treatment information leaflet and a patient held monitoring and dosing booklet by rheumatology when they start methotrexate treatment if available.
- What shared care means for their treatment, what to expect, and their responsibilities under shared care.
- The patient will also be given an approved information leaflet from Versus Arthritis. Further copies are available here.
- Methotrexate is taken **once weekly** and taking it more frequently can be dangerous. If a patient thinks they have taken too much methotrexate they should immediately seek advice from their prescriber, or NHS 111.
- For patients taking tablets, that they will only ever be prescribed methotrexate 2.5 mg tablets. **Patients who receive 10 mg tablets should always question the discrepancy**.
- Which day or days they should take their folic acid, with emphasis that methotrexate and folic acid should not be taken on the same day.
- Moderate their alcohol intake to no more than 14 units per week while taking methotrexate. More information can be found at https://www.nhs.uk/live-well/alcohol-support/calculating-alcohol-units/. Taking alcohol and methotrexate together increases the risk of liver injury.
- Tell anyone who prescribes them a medicine that they are taking methotrexate. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe.
- Skin may be more sensitive to exposure to UV light while taking methotrexate. If this occurs use appropriate self-care: e.g., sun avoidance, protective clothing, avoiding tanning (including tanning beds) and to purchase and use a broad-spectrum sunscreen (at least SPF30).
- To use effective contraception, and to take a pregnancy test if they think they could be pregnant. Patients should inform the specialist or GP immediately if they become pregnant. All patients, both men and women, should inform their specialist well in advance if they are planning a pregnancy so that changes can be made to their treatment regime.
- Not to drive or operate heavy machinery if methotrexate affects their ability to do so safely, e.g., due to fatigue or dizziness.
- That vaccination in line with current national advice (e.g., for COVID-19, influenza) is safe and recommended.
- Avoid contact with people with chicken pox or shingles and report any such contact urgently to their primary care prescriber. If the patient is exposed, and they have no prior history of exposure, contact the specialist for advice. For detailed advice on risk assessment and post exposure prophylaxis following exposure to chicken pox and shingles, see:
    - the Green Book (Chapter 34)
    - UKSHA guidance: Guidelines on post-exposure prophylaxis (PEP) for

varicella/shingles April 2022

Patient information:

- VersusArthritis Methotrexate

12. Pregnancy, paternal exposure, and breast feeding

Back to top

It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist.

All patients should be informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The specialist team should be contacted if a patient becomes pregnant or is planning to become pregnant or breastfeed.

Pregnancy:

Methotrexate is contraindicated in pregnancy. It is cytotoxic and is used for termination of pregnancy and to treat ectopic pregnancy. Pregnancy should be excluded prior to starting treatment. Patients of childbearing potential should use effective contraception during treatment and for 3 months afterwards.

If a patient becomes pregnant within 3 months of treatment with methotrexate, folic acid 5 mg daily must be continued throughout the pregnancy. If a patient becomes pregnant whilst on methotrexate the methotrexate must be stopped immediately and folic acid 5mg prescribed.

Contact the Rheumatology team and refer urgently to early pregnancy unit if a patient becomes pregnant.

If a patient is considering conception, this should be discussed with the Rheumatology team at least 3 months in advance to discuss the possibility of switching to an alternative medicine.

Information for healthcare professionals: Methotrexate in pregnancy (UKTIS)
Information for patients and carers: Methotrexate in pregnancy (Bumps)

Breastfeeding:

The manufacturers contraindicate use of methotrexate while breastfeeding. The UK Drugs in Lactation Advisory Service recommends caution and advises that breastfeeding should be avoided until at least 24 hours after a weekly dose not exceeding 25 mg. Infant blood counts should be monitored. Limited evidence indicates that small amounts are found in breast milk after weekly administration.

Information for healthcare professionals: https://www.sps.nhs.uk/medicines/methotrexate/

Paternal exposure:

There are hypothetical risks of genetic abnormalities in sperm which could potentially affect offspring conceived during treatment. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less

than 30 mg/week). Where a couple wishes to attempt conception and the male partner's condition is well-controlled with methotrexate, the UK Teratology Information Service recommends an assessment and discussion of the potential benefits and risks of continuing paternal treatment vs. discontinuation. This should be undertaken by the specialist, using a shared decision-making approach. The risks to the foetus are theoretical rather than established.

Paternal methotrexate use at the time of conception is not an indication for additional foetal monitoring. However, other risk factors may be present in individual cases which may independently increase the risk of adverse pregnancy outcome. Clinicians are reminded of the importance of consideration of such factors when performing case-specific risk assessments.

Information for healthcare professionals: Paternal Exposure Methotrexate

Fertility:

Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases.

13. Specialist contact information

Back to top

Name: **Named Rheumatology Consultant as per clinic letter**

Role and specialty: **Consultant Rheumatologist**

Daytime telephone number: **NUH: 0115 919 4477 Secretaries Extension: 78947**
SFH: 01623 676002 then choose option 2

Email address: **NUH:** Nuhnt.ntcrheumatologysecretaries@nhs.net
SFH: sfh-tr.rheumqueries@nhs.net

14. Additional information

Back to top

Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed. Ensure that the specialist is informed in writing of any changes to the patient's GP or their contact details.

15. References

Back to top

- eBNF. Methotrexate. Accessed via https://bnf.nice.org.uk/drug/methotrexate.html on 26/06/23.
- Methotrexate 2.5 mg tablets (Maxtrex®). Date of revision of the text 16/03/22. Accessed via https://www.medicines.org.uk/emc/product/1376/ on 22/06/23.
- British Society of Rheumatology and British Health Professionals in Rheumatology. 2017. Guidelines for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Accessed via https://academic.oup.com/rheumatology/article/56/6/865/3053478.

- British Society of Rheumatology and British Health Professionals in Rheumatology. 2016. Guideline on prescribing drugs in pregnancy and breastfeeding – Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Accessed via https://academic.oup.com/rheumatology/article/55/9/1693/1744535. MHRA Drug Safety Update. Methotrexate once weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing. June 2023. Accessed via https://www.gov.uk/drug-safety-update/methotrexate-once-weekly-for-autoimmune-diseases-new-measures-to-reduce-risk-of-fatal-overdose-due-to-inadvertent-daily-instead-of-weekly-dosing.

16. Other relevant national guidance

Back to top

- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

17. Local arrangements for referral

Back to top

Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.

- The request for shared care should be accompanied by individual patient information, outlining all relevant aspects of the patient's care and which includes direction to the information sheets at the APC website.
- The specialist will request shared care with the GP in writing.
- If the GP doesn't agree to shared care, they should inform the specialist of their decision in writing within 14 days, outlining the reason for the decline. The agreement can be assumed if the GP does not provide a written decline.
- In cases where shared care arrangements are not in place or where problems have arisen within the agreement, and patient care may be affected, the responsibility for the patient's management, including prescribing, reverts to the specialist.
- Should the patient's condition change, the GP should contact the relevant specialist using the details provided with the shared care request letter.