Methotrexate (oral and subcutaneous) for patients in adult services (excluding cancer care) - Sheffield.

Adapted from national shared care protocol, published 4 July 2022, Version 1

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Specialist responsibilities

- Assess the patient and provide diagnosis; ensure that this diagnosis is within 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 and monitoring booklet, where appropriate.
- Ensure the patient and/or carer understands and can follow the once-weekly dose regimen.
- If prescribing subcutaneous methotrexate ensure the patient/carer is trained to administer safely. Ensure that there are local arrangements for safe supply and disposal of ancillary products.
- Assess for contraindications and cautions (see section 4) and interactions (see section 7).
- Initiate and optimise treatment as outlined in section 5. Transfer to primary care is normally after the patient has been treated for 3 months and with satisfactory investigation results for at least 4 weeks.

- Once treatment is optimised, complete the shared care documentation and send to patient's GP practice 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, and when the next monitoring is required. Include contact information (section 13). If subcutaneous methotrexate is prescribed, include the brand.
- Prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care.
- Conduct the required monitoring in section 8 and communicate the results to primary care. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate. Please note that dermatology will continue to monitor procollagen 3 N-terminal peptide (PIIINP) at 6 monthly intervals.
- 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.

Primary care responsibilities

- Respond to the request from the specialist for shared care in writing. It is asked that this be undertaken within 14 days of the request being received by the GP practice, where possible.
- If accepted, prescribe methotrexate (stating day of week to be taken) and folic acid as detailed in the specialists request and as per section 5, taking into any account potential drug interactions in section 7.
- Only methotrexate as the 2.5 mg tablets or if subcutaneous injection, as Metoject® or Nordimet® brands, should be prescribed.
- For patients receiving subcutaneous methotrexate, waste management products and collection of cytotoxic waste can be arranged through the GP practice (GP is responsible for prescribing suitable sized purple lidded cytotoxic waste bins e.g. 3 or 5L and accepting returns of full bins from patients). Waste bin can be prescribed or maybe cheaper to purchase from a community pharmacy if the patient pays prescription charges. Also, see **Recommendations for the storage, administration and disposal of subcutaneous methotrexate in the community** for more details.
- Adjust the dose of methotrexate and folic acid prescribed as advised by the specialist.
- Conduct the required monitoring as outlined in section 9. Communicate any abnormal results to the specialist.
- Manage adverse effects as detailed in section 10 and discuss with specialist team when 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.
- Discuss with the specialist if the patient plans to become pregnant. See section 12.
- Stop treatment as advised by the specialist.

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.
- 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 they should discuss the use of methotrexate with their pharmacist before purchasing any OTC medicines.
- 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.

1. Background

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Methotrexate is a cytotoxic folic acid antagonist used to treat chronic inflammatory conditions and certain cancers. It inhibits the enzyme dihydrofolate reductase and inhibits 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 are well established and supported by clinical specialists.

This shared care protocol does not cover treatment of cancer, or treatment of people less than 18 years old.

2. Indications

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The licensed indications for methotrexate include:

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

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

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

- Rheumatology (e.g., inflammatory arthritis, connective tissue disease, vasculitis)
- Dermatology (e.g., severe eczema, bullous conditions)
- Gastroenterology (e.g., severe Crohn's disease or other inflammatory bowel disease)
- Neurology (e.g., myasthenia gravis, inflammatory neuropathies)
- Ophthalmology (e.g., uveitis, scleritis)

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

This shared care protocol applies to adults aged 18 and over. It does not include use of methotrexate for cancer indications.

3. Locally agreed off-label use Back to top

See section 2.

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.
- Significant renal impairment –eGFR <**30** ml/min/1.73m^2
- Severe infections (acute or chronic) or immunodeficiency syndromes.
- Known active peptic ulceration.
- Pregnancy and breast-feeding section 12
- 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.
- Hepatic impairment, particularly if due to alcohol use.
- Pre-existing blood dyscrasias or disorders, including bone marrow hypoplasia, leucopenia, thrombocytopenia, or significant anaemia. Specialist to 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.
- 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, or recurrent urinary tract infection).
- 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.

* The national methotrexate shared care protocol recommends calculating CrCL however because CrCL requires a calculation and because locally in Sheffield, the chemical pathology laboratory reports on eGFR results, this measure has been adopted within the SCP.

- Using e GFR doesn't pose a clinical risk to the cohorts covered by this SCP.
- eGFR is an easier clinical measure for clinicians to use.

5. Initiation and ongoing dose regimen

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- Transfer of monitoring and prescribing to primary care is normally after the patient has been treated for at least 3 months, and the dose has been optimised, and with satisfactory investigation results for at least 4 weeks.
- 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 specialist unless directions have been discussed and agreed 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 dose titration period must be prescribed by the initiating specialist.

Maintenance dose (following initial stabilisation):

Usual dose range**: 7.5 mg – 25 mg weekly**, adjusted according to response. Please note for rheumatology conditions a patient may be initiated on more than one DMARD. To reduce dosing errors **only the 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.

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. 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.

Transfer of monitoring and prescribing to primary care is usually after 3 months. The duration of treatment will be determined by the specialist based on clinical response and tolerability.

Conditions requiring dose adjustment:

- See section 10.

6. Pharmaceutical aspects

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Route of administration:	Oral tablets, or subcutaneous injections
Formulation:	**Methotrexate tablets**

	Other strengths are available but, to reduce dosing errors, **only the 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. Methotrexate 2.5 mg tablets **Methotrexate subcutaneous injection** Solution for injection available in 2.5 mg increments ranging from 7.5 mg – 30 mg and varying with brand: • 50 mg/mL in pre-filled pen (Metoject®): 7.5 mg to 30 mg • 25 mg/mL in pre-filled pen (Nordimet®): 7.5 mg to 25 mg If subcutaneous methotrexate is prescribed, secondary care must specify the brand and the patient should be maintained on that brand due to device familiarity. Brand should be specified on clinical systems. See SPCs for full details of available products. Local, pre-existing arrangements for the supply of methotrexate injection and ancillary products, and for the disposal of cytotoxic waste, should be observed. See: **Recommendations for the storage, administration and disposal of subcutaneous methotrexate in the community** and Primary care responsibilities When deciding which formulation to prescribe, the specialist should consider the patient's circumstances and overall polypharmacy burden, especially for patients with a high pill burden. See MHRA advice on preventing inadvertent daily dosing. Converting from an oral to a subcutaneous dosage form may be appropriate where patients experience intolerable gastrointestinal adverse effects and should only be undertaken by a specialist.
Administration details:	Tablets should not be split or crushed for administration. Review formulation if 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. Avoid skin or mucosa contact with methotrexate solution for injection. Spillage kits should be available for patients on subcutaneous 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

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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, 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.

- 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.
- **Sulfasalazine**: may increase 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 drug 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.
- Avoid concomitant use of **cytotoxics, clozapine, and olanzapine:** increased risk of agranulocytosis.
- **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 increased methotrexate toxicity, and decreased phenytoin effect.
- **NSAIDs**, **COX-2 inhibitors, aspirin:** may reduce excretion of methotrexate, increasing 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. Be aware of trends in monitoring parameters.
- **Antibiotics** may alter methotrexate levels. 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 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 specialist

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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 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 eGFR
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total protein, bilirubin, alkaline phosphatase and gamma-glutamyl transferase (GGT) (extended LFTs)
- Screening for HIV and hepatitis B and C
- 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)
- Psoriasis patients: serum procollagen 3 N-terminal peptide (PIIINP)

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. After which, the transfer of prescribing to primary care should normally only take place when the patient has received a stable dose for at least 4 weeks and their blood and physical tests results have been satisfactory.
- FBC
- U&Es, including creatinine and eGFR
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total protein, bilirubin, alkaline phosphatase and gamma-glutamyl transferase (GGT)) (extended LFTs)
- Rheumatology patients: CRP &/or ESR
- Psoriasis patients: serum PIIINP

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.

At initiation of shared care, communication to primary care should include current and ongoing dose, any relevant test results, and date the next monitoring is required. 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

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

Monitoring	Frequency
• FBC • U&Es including creatinine and eGFR • Alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total protein, bilirubin, alkaline phosphatase and gamma-glutamyl transferase (GGT) (extended LFTs) • Rheumatology patients: CRP &/or ESR; specialist to confirm.	At least every 12 weeks, and more frequently in patients at higher risk of toxicity, as advised by the specialist team.
• Patients aged 60-79 years old could be eligible for the shingles vaccine (herpes zoster). Also Shingrix® - non-live has - replaced Zostavax® as vaccine of choice. Severely immunosuppressed qualify from age 50 years, Refer to Green Book Chapter 6 (Contraindications and special considerations) and Green Book Chapter 28a (Shingles) for further details. • **Annual** influenza (The Green Book, Chapter 19) vaccinations are recommended. • COVID-19 vaccination (The Green Book, Chapter 14a) is safe and recommended.	• Shingles vaccination: one-off. • Influenza vaccination: annual. It is advisable to add the patient to the influenza vaccine list. • Other vaccinations as per national schedule.

• Repeat pneumococcal vaccine may be indicated. 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

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Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard

For information on incidence of ADRs see relevant summaries of product characteristics

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. *If clinically concerned, withhold and discuss with specialist team.*	
• 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.
Mean cell volume >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 Unexplained fall in serum albumin <30g/L Jaundice	Withhold and discuss with specialist team. 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. • If eGFR <50 (but above 40) ml/min/1.73m^2 , • In the small number of rheumatology patients with known and stable eGFR < 40 ml/min/1.73 m^2 and methotrexate dose 10 mg or less per week,	Withhold and discuss with specialist team. • can continue methotrexate but tests to be repeated within 2-3 weeks and then seek advice from department initiating methotrexate if the abnormality is persistent • can continue methotrexate but stop and check with specialist if eGFR falls < 30/ml/min/ 1.73m^2
Gastrointestinal disorders: Nausea	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. Discuss with specialist team if persistent or severe. Switch to subcutaneous therapy may be indicated, under specialist advice.
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, 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).
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

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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 or vomiting.
- 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:

- What shared care means for their treatment, what to expect, and their responsibilities under shared care.
- 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.
- For patients taking 20mg/week or more: to avoid contact with people with chickenpox or shingles and report any such contact urgently to their primary care prescriber. If the patient is exposed, primary care clinician to contact the specialist for advice. For detailed advice on risk assessment and post exposure prophylaxis following exposure to chickenpox and shingles, see:
    - the Green Book (Chapter 34)
    - UKSHA guidance: Guidelines on post-exposure prophylaxis (PEP) for varicella/shingles April 2022

Patient information:

General information: https://www.nhs.uk/medicines/methotrexate/

12. Pregnancy, paternal exposure and breast feeding

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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.

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.

- Methotrexate at any dose should be avoided in pregnancy and stopped at least one month in advance of planned conception, when it should be switched to another pregnancy-compatible drug to ensure maintenance of maternal disease suppression.
- In women treated with low-dose (≤25 mg/week) methotrexate within one month prior to conception, folic acid supplementation (5 mg/day) should be continued up to 12 weeks of pregnancy.

- In unintended pregnancy on low-dose methotrexate (≤25 mg/week), there is minimal risk to the foetus; the drug should be stopped immediately, folic acid supplementation (5 mg/day) continued, and a careful evaluation of foetal risk with early referral to a foetal medicine department considered.

Those who wish to become pregnant should speak to their specialist to discuss the possibility of switching to an alternative medicine.

Information for healthcare professionals:
https://uktis.org/monographs/use-of-methotrexate-in-pregnancy/
Information for patients and carers: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Methotrexate/

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 fetus are theoretical rather than established.
Paternal methotrexate use at the time of conception is not an indication for additional fetal 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:
https://uktis.org/monographs/paternal-use-of-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

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Name: Dr Tom King
Role and specialty: Dermatology: Consultant Dermatologist
Daytime telephone number: *secretary: 0114 2711832 Office: 0114 2713039*
Email address: tom.king2@nhs.net
Out of hours contact details: *Ring switchboard at NGH for medical consultant on call (01142434343)*

Name: Kerry Robinson
Role and specialty: Gastroenterology: IBD Clinical nurse specialist
Daytime telephone number: *0114 2668705*
Email address: kerry.robinson6@nhs.net
Alternative contact: *IBD nurse team sth.ibdnurseadmin@nhs.net*
Out of hours contact details: *Ring switchboard at NGH for medical consultant on call (01142434343)*

Name: Dr Thean Chew
Role and specialty: Gastroenterology: Consultant Gastroenterologist
Daytime telephone number: *0114 2261087*
Email address: theanchew@nhs.net
Out of hours contact details: *Ring Switchboard at NGH for Medical Consultant on call (0114 2434343)*

Name: *Dr Channa*
Role and specialty: Neurology: Consultant Neurologist
Daytime telephone number: *0114 271 3708*
Email address: Hewamadduma- c.hewamadduma@nhs.net
Out of hours contact details: *Ring switchboard at NGH for medical consultant on call (01142434343)*

Name: Dr Katharine Sears
Role and specialty: Ophthalmology: Consultant Ophthalmologist
Uveitis Specialist nurses email: sth.uveitisnurses@nhs.net
Uveitis Specialist nurses telephone number: 0114 2712947
Email address: katharine.sears@nhs.net
Daytime telephone number: 0114 2713619
Out of hours contact details: *Ring switchboard at NGH for medical consultant on call (01142434343)*

Name: Julie Cole

Role and specialty: Rheumatology: Clinical Nurse Specialist,

Rheumatology Daytime telephone number: 0114 2713086

Email addresses:

For routine primary care queries e.g. abnormal blood monitoring results not covered by the SCP please email : sth.rheumatologygpcorrespondence@nhs.net – usual response time is within two working days.

If patient acutely unwell and this is thought related to methotrexate, **GP** only, to contact Rheumatology on call, hours 9 am to 5 pm only - via STH switchboard

For patient queries: sth.ropd@nhs.net

14. Additional information

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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

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- eBNF. Methotrexate. Accessed via https://bnf.nice.org.uk/drug/methotrexate.html on 13/08/2021.
- Methotrexate 2.5 mg tablets (Maxtrex®). Date of revision of the text 12/2020. Accessed via https://www.medicines.org.uk/emc/product/1376/ on 13/08/21.
- Methotrexate 10 mg solution for injection in pre-filled injector (Methofill®). Date of revision of the text 01/03/21. Accessed via https://www.medicines.org.uk/emc/product/9057/smpc on 13/08/21.
- Methotrexate 10 mg solution for injection in pre-filled pen (Metoject®). Date of revision of the text 07/2020. Accessed via https://www.medicines.org.uk/emc/product/11351/ on 13/08/21.
- Methotrexate 10 mg solution for injection in pre-filled pen (Nordimet®). Date of revision of the text Dec 2020. Accessed via https://www.medicines.org.uk/emc/product/7721/ on 13/08/21.
- Methotrexate 10 mg solution for injection in pre-filled pen (Zlatal®). Date of revision of the text 25/09/2020. Accessed via https://www.medicines.org.uk/emc/product/7270/ on 13/08/21.
- Methotrexate 2 mg/mL oral solution (Jylamvo®). Date of r/evision of the text 01/01/2021. Accessed via https://www.medicines.org.uk/emc/product/8599/ on 13/08/21.
- 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 Dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease 2016. Accessed via https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.14816.
- British Society of Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids 2022 https://academic.oup.com/rheumatology/article/62/4/e48/6783012?login=true
- 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.

September 2020. 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.

- SPS Methotrexate monitoring guidance

16. Other relevant national guidance

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- Shared Care for Medicines Guidance – A Standard Approach (RMOC). Available from https://www.sps.nhs.uk/articles/rmoc-shared-care-guidance/
- 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

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

Each speciality may have different criteria for referral. Seek advice where necessary.

Each directorate has their own arrangements / paperwork for transferring care to primary care, the National Shared Care Transfer Forms are available here if needed.

Amendment April 2024

Revised the Primary care responsibilities section to improve arrangements around safe disposal of subcutaneous methotrexate injections and minor amendments made to Safe handling of subcutaneous injections.

Amendment July 2025

Added in references to measuring eGFR rather than CrCL, amended contact details of rheumatology department and added SPS methotrexate monitoring guidance.