

National shared care protocol adapted for local use:

Inflammatory Bowel Disease: Oral Methotrexate for patients in adult services (excluding cancer care)

The content of this shared care protocol was correct as of September 2024. As well as 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 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 ([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. It is expected that at least one hospital review will occur before transfer to shared care occurs. 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.
- 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 current contraception if relevant, and other relevant treatments being received by the patient. Include 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 28 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, including the review of the blood results from the previous 12 months](#), 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, confirm the ongoing dose, and whether the ongoing monitoring outlined in [section 9](#) remains appropriate.

- Enquire about any history of varicella-zoster and test the patient for varicella-zoster if there is no known history. There is no need for a test if there is a previous history. The patient should be offered vaccination if there are no antibodies.
- Offer HIV and Hepatitis B and C testing.
- 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 if patients are under a [Patient Initiated Follow-ups \(PIFU\) pathway](#).
- Provide training to primary care prescribers, if necessary, to support the shared care agreement.
- Provide patients taking methotrexate with a patient information leaflet and monitoring document. Counsel the patient particularly on contraception if appropriate.
- Whenever the specialist sees the patient, they will record test results on the patient-held monitoring booklet, if provided, and take any action necessary.

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](#), taking into any account potential drug interactions in [section 7](#).
- Adjust the dose of methotrexate and folic acid prescribed as advised by the specialist and communicate 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, if provided, 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.
- Contact details for primary care prescribers will be made available.
- 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, routine influenza and pneumococcal vaccinations 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. If unable to attend any appointments, they should inform the relevant practitioner as soon as possible and arrange an alternative 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.
- 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](#).
- Ensure not to run out of their medications. Request a supply of maintenance therapy in a timely manner and 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.
- 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

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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 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, and the clinical benefit may take up to 3 months. Patient-reported adverse effects usually occur early in therapy.

Methotrexate is positioned as a second-line immunosuppressive agent in patient resistant or intolerant of azathioprine or mercaptopurine.

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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Licensed indications vary with brand. See the relevant [SPC](#) for full details.

The licensed indications for methotrexate include:

- Mild to moderate Crohn's disease in patient's refractory or intolerant to thiopurines.

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

- Maintenance and remission of adult patients with inflammatory bowel disease

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.

3. Locally agreed patient groups exclusion

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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

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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 and excessive alcohol consumption.
- Ascites or pleural effusion: drain prior to treatment to reduce the risk of methotrexate accumulation.
- Significant renal impairment – creatinine clearance (CrCl) less than 30 mL/min.
- Severe infections (acute or chronic) or immunodeficiency syndromes and malignancies.
- Known active peptic ulceration.
- Pregnancy and breast-feeding.
- 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, leucopenia, 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.
- Photosensitivity.
- 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, history of 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

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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, 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 initiating 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 usual starting dose is 2.5 – 10mg 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. The prescriber should decide with the patient which day of the week the patient will take their methotrexate and specify the day of intake on the prescription.

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

Maintenance dose (following initial stabilisation):

Usual dose range: **10 mg – 25 mg once weekly** given orally, adjusted according to the response.

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

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. This is 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.

There is no set duration of treatment with methotrexate, as evidence in the area is lacking. Patients usually will be on treatment for up to 5 years but occasionally this can be longer – prolonged use may be considered if needed. 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

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Route of administration:	Oral tablets
Formulation:	<u>Methotrexate tablets</u> Other strengths are available but, to reduce dosing errors, <u>only the 2.5 mg tablets should be prescribed</u> . The dose should be taken <u>once weekly</u> 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. <u>A double dose should not be taken to make up for a missed dose.</u>
Other important information:	Methotrexate is taken <u>once weekly</u> , 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.

- **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 (severe bone marrow depression has been reported).

- **Leflunomide:** increased risk of bone marrow and liver toxicity; increased monitoring and vigilance required.
- **Acitretin and ciclosporin:** avoid concomitant use due to 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 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 due to antifolate effect. Caution in use. Increase monitoring frequency.
- **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. 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 the elimination of methotrexate.
- **Proton Pump Inhibitors:** concomitant use with high dose methotrexate (>500mg/m²) should be avoided, especially in patients with renal impairment.
- **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 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
- Screening for lung disease, including interstitial lung disease and tuberculosis, e.g., chest x-ray 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 – check more frequently if there is suspicion of renal function deterioration.
- ALT and/or AST, and albumin

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

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.

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
<ul style="list-style-type: none">FBCU&Es including creatinine and CrClALT 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. The exact frequency of monitoring is to be communicated by the specialist in all cases.
<ul style="list-style-type: none">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.Pneumococcal vaccines are highly recommended. See Green Book Chapter 25 for advice.	<ul style="list-style-type: none">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.

(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 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 GASTROENTEROLOGY SPECIALIST TEAM.

Result	Action for primary care
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<p>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.</p> <p>Other benchmark values may be set by secondary care in specific clinical circumstances. This will be communicated by the specialist.</p>	
<p>Full blood count:</p> <ul style="list-style-type: none"> • White blood cells less than $3.5 \times 10^9/L$ • Lymphocytes less than $0.5 \times 10^9/L$ • Neutrophils less than $1.6 \times 10^9/L$ • Platelets less than $140 \times 10^9/L$ • Eosinophilia greater than $0.5 \times 10^9/L$ (unexplained) 	Withhold and discuss with specialist team.
<p>Macrocytosis</p> <ul style="list-style-type: none"> • Mean cell volume >105 fl 	<p>Consider interruption in treatment.</p> <p>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.</p>
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.
<p>Infections:</p> <p>Infection requiring antibiotics</p>	Temporarily withhold methotrexate until the patient has recovered. Consider additional investigations (e.g., FBC), if clinically appropriate.
<p>Liver function tests:</p> <ul style="list-style-type: none"> • ALT or AST >100 units/L, or any sudden increases (e.g., double of baseline), OR • Unexplained fall in serum albumin $<30g/L$ (in the absence of active disease), or • ALP $> \times 2$ upper limit of reference range and the ALT: AST ratio is greater than 0.8. • Jaundice 	<p>Withhold and discuss with specialist team.</p> <p>Assess for other causes of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.</p>
<p>Renal function:</p> <p>Creatinine increases of greater than 30% from baseline in the last 12 months, or CrCl reduces to $<60ml/min$</p>	Withhold and discuss with specialist team for a possible 50% dose reduction. Do not use if CrCl $< 30ml/min$.
<p>Gastrointestinal disorders:</p> <p>Nausea and vomiting</p>	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 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

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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, 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:

- The patient must be given a pre-treatment information leaflet and a patient held monitoring and dosing booklet (if available) by gastroenterology team when they start methotrexate treatment.
- 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, one-off pneumococcal vaccinations) 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:

- [Crohn's and Colitis UK](#)

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. Men and women of childbearing potential should use effective contraception during treatment and for 6 months afterwards.

If a patient becomes pregnant within 6 months of treatment with methotrexate, folic acid 5 mg daily should 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 gastroenterology team and refer urgently to the early pregnancy unit if a patient becomes pregnant.

Those who wish to become pregnant should speak to their prescriber 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](#)

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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Please contact the appropriate IBD Nurse Specialist if you require any advice about treatment or disease management.

Nottingham University Hospitals NHS Trust Contacts:

Switchboard **0115 9249924 ext. 78715**

IBD Direct line **0115 9709324**

Sherwood Forest NHS Foundation Trust Contacts

Kings Mill Hospital 01623 622515

IBD Nurse Specialists **Ext 4277**

Out of hours

A consultant, specialist registrar or pharmacist may be contacted via the appropriate hospital switchboard.

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 11/09/2023.
- Methotrexate 2.5 mg tablets (Maxtrex®). Date of revision of the text 08/2023. Accessed via <https://www.medicines.org.uk/emc/product/1376/> on 11/09/2023.
- 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>.
- Lamb, CA., Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1-s106
- Hausmann J, Zabel K, Herrmann E, et al. Methotrexate for maintenance of remission in chronic active Crohn's disease: Long-term single-center experience and meta-analysis of observational studies. Inflamm Bowel Dis 010; 16:1195e202.

16. Other relevant national guidance

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- 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.

- 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 shared care protocols on the [APC website](#).
- Prescribing and monitoring responsibility will only be transferred when it is agreed by the specialist and the patient's primary care prescriber that the patient is stabilised on their medication regimen without adverse effect and with benefits demonstrated.
- 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 back 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.

Methotrexate SCP

Version	Author(s)	Date	Changes
V1.0	NNICB Interface team	Sept 2024	<p>Adopted from the National template published by NHS England in July 2022. The information is cross-referenced between the national template and the local shared care guidelines.</p> <p>Additional information included to reflect the locally agreed shared care protocol.</p> <p>VZV exposure information updated to reflect local processes</p> <p>Consultations:</p> <ul style="list-style-type: none"> ▪ Dr Sunil Samuel Head of Service Gastroenterology NUH ▪ Azma Malik Advanced Pharmacist Practitioner Gastroenterology NUH ▪ Dr Caroline Sharratt Consultant Gastroenterologist SFH <p>VZV exposure guidance updated to local process – contact on-call microbiologist.</p> <p>Link to RMO Shared care for medicines guidance removed, as no longer available</p>