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National shared care protocol:

# Methotrexate (oral and subcutaneous) for patients in adult services (excluding cancer care) note: Subcutaneous methotrexate shared care is not commissioned in Ipswich and East Suffolk

4 July 2022, Version 1

Review date – January 2025

**The content of this shared care protocol was correct as of January 2022. 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 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.
- 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, or liaise with primary care to arrange safe administration by a healthcare professional. 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.
- 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 made, where possible.
- If accepted, prescribe methotrexate and folic acid as detailed in the specialists 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.
- 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.
- 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)
- Respiratory disease (e.g. sarcoidosis, interstitial lung 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.

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

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**To be agreed and completed locally (include supporting information)**

## 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.
- 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.
- 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.
- 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.
- 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.

## 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 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 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:**

- 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, or subcutaneous injections |
| Formulation: | **Methotrexate tablets**<br>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.<br>Methotrexate 2.5 mg tablets<br><br>**Methotrexate subcutaneous injection**<br>Solution for injection available in 2.5 mg increments ranging from 7.5 mg – 30 mg and varying with brand:<br>• 50 mg/mL in pre-filled injector or syringe (Methofill®): 7.5 mg to 30 mg<br>• 50 mg/mL in pre-filled pen (Metoject®): 7.5 mg to 30 mg<br>• 25 mg/mL in pre-filled pen (Nordimet®): 7.5 mg to 25 mg<br>• 25 mg/mL in pre-filled syringe (Zlatal®): 7.5 mg to 25 mg<br>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. |

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| | 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.<br>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.<br>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.<br>Pregnant people, including patients and carers, should avoid handling methotrexate.<br>Avoid skin or mucosa contact with methotrexate solution for injection. Spillage kits should be available for patients on subcutaneous methotrexate.<br>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.<br>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.<br>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 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, 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 CrCl
- ALT and/or AST, and albumin
- 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<br>• U&Es including creatinine and CrCl<br>• ALT and/or AST and albumin<br>• Rheumatology patients: CRP &/or ESR; specialist to confirm (both are not routinely required)<br>• Psoriasis patients: serum PIIINP | At least every 12 weeks, and more frequently in patients at higher risk of toxicity, as advised by the specialist team.<br>**The exact frequency of monitoring to be communicated by the specialist in all cases**. |
| • Patients aged 70-79 years old could be eligible for the shingles vaccine (herpes zoster). For patients on immunosuppressive therapy, a non-live vaccine may be indicated and specialist input may be required. Refer to Green Book Chapter 6 (Contraindications and special considerations) and Green Book Chapter 28a (Shingles) for further details.<br>• **Annual** influenza (The Green Book, Chapter 19) vaccinations are recommended.<br>• COVID-19 vaccination (The Green Book, Chapter 14a) is safe and recommended.<br>• Repeat pneumococcal vaccine may be indicated. See Green Book Chapter 25 for advice. | • Shingles vaccination: one-off.<br>• Influenza vaccination: annual. It is advisable to add the patient to the influenza vaccine list.<br>• Other vaccinations as per national schedule. |
| **(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** | |
| • Full blood count:<br>• White blood cells less than $3.5x10^9$/L<br>• Lymphocytes less than $0.5x10^9$/L<br>• Neutrophils less than $1.6x10^9$/L<br>• Platelets less than $140x10^9$/L<br>• Eosinophilia greater than $0.5x10^9$/L | Withhold and discuss with specialist team. |
| Mean cell volume >105 fL | Consider interruption in treatment.<br>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:**<br>Infection requiring antibiotics | Temporarily withhold methotrexate until the patient has recovered. Consider additional investigations (e.g. FBC), if clinically appropriate. |
| **Liver function tests:**<br>ALT or AST >100 units/L, or any sudden increases (e.g. double of baseline), OR<br>Unexplained fall in serum albumin <30g/L<br>Jaundice | Withhold and discuss with specialist team.<br>Assess for other causes of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication. |

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| **PIIINP** (psoriasis only)<br>Levels greater than:<br>• 10 mg/L on one occasion<br>• 8.0 mg/L on two occasions<br>• 4.2 mg/L on three occasions in a 12 month period | Discuss with specialist team, with urgency dictated by clinical condition and liver function test results. |
| **Renal function**:<br>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:**<br>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**<br>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.<br>• 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 chicken pox or shingles and report any such contact urgently to their primary care prescriber. If the patient is

exposed, 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:

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.

Patients of child bearing 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 should be continued throughout the pregnancy. 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: https://www.medicinesinpregnancy.org/bumps/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://www.medicinesinpregnancy.org/bumps/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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| Speciality | Contact name | Contact Details |
|---|---|---|
| Neurology | **ESNEFT Ipswich Site** | |
| | Dr Simon Kerrigan<br>Dr Petr Pokorny<br>Dr Mortada Elyas<br>Dr Clare Galton<br>Dr Andrew Graham | Email Secretaries:<br>neurologyipswich@esneft.nhs.uk<br>Tel: 01473 704044 / 01473 704041 |
| | **ESNEFT Colchester Site** | |
| | Dr Imtiaz Ahmed<br>Dr Dr Natalia Salari<br>Dr Mohammed Sharief<br>Epilepsy Nurse Specialist | Telephone Secretaries: 01206 742243<br>Email Secretaries:<br>ch.neurology@esneft.nhs.uk<br><br>Tel Epilepsy Nurse Specialist: 01206 746472 |
| Gastroenterology | **ESNEFT Ipswich Site** | |
| | Dr Simon Williams<br>Dr Louise Scovell<br>Dr Yin Miao<br>Dr Abdul Mohsen<br>Dr Hermant Laxaman<br>Dr Adnan Rislan<br>IBD Nurse Specialist | Tel: 01473 703519<br>Tel: 01473 702535<br>Tel: 01473 703188<br>Tel: 01473 703505<br>Tel: 01473 702114<br><br>Tel: 01473 702865<br>Email: gastrosecs@esneft.nhs.uk<br>Advice and guidance on NHS e-referrals |
| | **ESNEFT Colchester Site** | |

| | | |
|---|---|---|
| | Dr Ian Gooding<br>Dr Donagh O'Riordan<br>Dr Mary McStay<br>Dr Achuth Shenoy<br>Dr Simon Ralphs<br><br>IBD Nurse Specialist | Email secretaries: chu-ftr.gastroenterologysecretaries@esneft.nhs.uk<br><br><br><br>01206 744231<br>Email: colchesteribdadviceline@esneft.nhs.uk |
| **Dermatology** | **ESNEFT Ipswich Site** | |
| | Shuk Yates, Clinical Nurse Specialist Dermatology<br>Jodie Newman, Clinical Nurse Specialist Dermatology<br>Dr Liberta Labinoti | Consultant (via secretaries): 01473 704042<br>Specialist nurse: 01473 706877<br>Email: IPS.derm@esneft.nhs.uk<br>Advice and guidance on NHS e-referrals |
| | **ESNEFT Colchester Site** | |
| | Dr Farooq<br>Dr Asfar<br>Dr Galahitiyawa,<br>Kerry Penfold, Clinical Nurse Specialist Dermatology<br>Soumya Sunny, Clinical Nurse Specialist Dermatology<br>Dr Khalid Mahmood<br>Susan Robertson, Clinical Nurse Specialist Dermatology | Email: dermatologycolchester@esneft.nhs.uk<br>Specalist Nurse: 01206 487 216 |
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| **Rheumatology** | **ESNEFT Ipswich Site** | |
| | Dr Lane / Dr Watts:<br>Dr Weerakoon / Dr Shand<br>Dr Abdulkader/Dr Ntatsaki | Tel: 01473 702362<br>Tel: 01473 702039<br>Tel: 01473 707324<br>Email: ihn-tr.rheum-sharedcare@nhs.net<br>Advice and guidance on NHS e-referrals |
| | **ESNEFT Colchester Site** | |

| | | |
|---|---|---|
| | Dr Paul Byrne<br>Dr Tom Walton<br>Dr Rachel Davies<br>Dr Lauren Steel<br>Clinical Nurse Specialist May Clark<br>Clinical Nurse Specialist Lucy Mascurine | Tel Department: (01206) 742165/742279<br>Email Nurses:<br>rheumatology.nurseadvice@esneft.nhs.uk |
| **Respiratory** | **ESNEFT Ipswich Site** | |
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| | **ESNEFT Colchester Site** | |
| | Respiratory Dr Rekha Badiger<br>Dr Samantha Cooper<br>Dr Peter Hawkins<br>Dr Misha Sidhu<br>Dr Mphatso Wirima<br>Dr Emma Boynton<br>Dr Safin Rahman | Email Secretaries:<br>respsecretaries@esneft.nhs.uk<br>Tel: 01206 742612 |

## 14. Additional information

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It is anticipated that each area will continue to adhere to pre-existing local arrangements for the supply of methotrexate injection and ancillary products, and for the disposal of cytotoxic waste.

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.
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- 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 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. 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.


## 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.

**To be agreed and completed locally**

Subcutaneous methotrexate is not commissioned for shared care in Ipswich and East Suffolk. Please note that for Ipswich and East Suffolk subcutaneous methotrexate is a red hospital only drug.

SNEE Integrated Medicines Optimisation Committee approved 10/10/2022 ESNEFT MGG approved 24/10/2023

## Appendix 1: Shared Care Request letter (Specialist to Primary Care Prescriber)

Dear *[insert Primary Care Prescriber's name]*

Patient name: *[insert patient's name]*
Date of birth: *[insert date of birth]*
NHS Number*:* *[insert NHS Number]*
Diagnosis: *[insert diagnosis]*

As per the agreed *[insert APC name]*shared care protocol for *[insert medicine name]* for the treatment of *[insert indication],* this patient is now suitable for prescribing to move to primary care.

The patient fulfils criteria for shared care and I am therefore requesting your agreement to participate in shared care. Where baseline investigations are set out in the shared care protocol, I have carried these out.

I can confirm that the following has happened with regard to this treatment:

| | **Specialist to complete** |
|---|---|
| *The patient has been initiated on this therapy and has been on an optimised dose for the following period of time:* | |
| *Baseline investigation and monitoring as set out in the shared care documents have been completed and were satisfactory* | *Yes / No* |
| *The condition being treated has a predictable course of progression and the patient can be suitably maintained by primary care* | *Yes / No* |
| *The risks and benefits of treatment have been explained to the patient* | *Yes / No* |
| *The roles of the specialist/specialist team/ Primary Care Prescriber / Patient and pharmacist have been explained and agreed* | *Yes / No* |
| *The patient has agreed to this shared care arrangement, understands the need for ongoing monitoring, and has agreed to attend all necessary appointments* | *Yes / No* |
| *I have enclosed a copy of the shared care protocol which covers this treatment/the SCP can be found here (insert electronic/ web link)* | *Yes / No* |
| *I have included with the letter copies of the information the patient has received* | *Yes / No* |
| *I have provided the patient with sufficient medication to last until* | |
| *I have arranged a follow up with this patient in the following timescale* | |

Treatment was started on *[insert date started]* and the current dose is *[insert dose and frequency]*.

If you are in agreement, please undertake monitoring and treatment from *[insert date]*
NB: date must be at least 1 month from initiation of treatment.

The next blood monitoring is due on *[insert date]* and should be continued in line with the shared care guideline.

Please respond to this request for shared care, in writing, within 14 days of the request being made where possible.

## Appendix 2: Shared Care Agreement Letter (Primary Care Prescriber to Specialist)

**Primary Care Prescriber Response**

Dear *[insert Doctor's name]*
Patient *[insert Patient's name]*
NHS Number *[insert NHS Number]*
Identifier *[insert patient's date of birth and/oraddress]*

Thank you for your request for me to accept prescribing responsibility for this patient under a shared care agreement and to provide the following treatment

| Medicine | Route | Dose & frequency |
|---|---|---|
| | | |

I can confirm that I am willing to take on this responsibility from *[insert date]* and will complete the monitoring as set out in the shared care protocol for this medicine/condition.

Primary Care Prescriber signature: _____Date: _____

Primary Care Prescriber address/practice stamp

## Appendix 3: Shared Care Refusal Letter (Primary Care Prescriber to Specialist)

**Re:**

Patient *[insert Patient's name]*

NHS Number *[insert NHS Number]*

Identifier *[insert patient's date of birth and/oraddress]*

Thank you for your request for me to accept prescribing responsibility for this patient.

In the interest of patient safety NHS *[insert CCG name]***,** in conjunction with local acute trusts have classified *[insert medicine name]*as a Shared Care drug, and requires a number of conditions to be met before transfer can be made to primary care.

**I regret to inform you that in this instance I am unable to take on responsibility due to the following:**

| | | **Tick which apply** |
|---|---|---|
| **1.** | **The prescriber does not feel clinically confident in managing this individual patient's condition, and there is a sound clinical basis for refusing to accept shared care**<br><br>As the patients primary care prescriber I do not feel clinically confident to manage this patient's condition because *[insert reason]*. I have consulted with other primary care prescribers in my practice who support my decision. This is not an issue which would be resolved through adequate and appropriate training of prescribers within my practice.<br><br>**I have discussed my decision with the patient and request that prescribing for this individual remain with you as the specialist, due to the sound clinical basis given above.** | |
| **2.** | **The medicine or condition does not fall within the criteria defining suitability for inclusion in a shared care arrangement**<br><br>As the medicine requested to be prescribed is not included on the national list of shared care drugs as identified by RMOC or is not a locally agreed shared care medicine I am unable to accept clinical responsibility for prescribing this medication at this time.<br><br>**Until this medicine is identified either nationally or locally as requiring shared care the responsibility for providing this patient with their medication remains with you** | |

| | | |
|---|---|---|
| **3.** | **A minimum duration of supply by the initiating clinician**<br><br>As the patient has not had the minimum supply of medication to be provided by the initiating specialist I am unable to take clinical responsibility for prescribing this medication at this time. Therefore can you please contact the patient as soon as possible in order to provide them with the medication that you have recommended.<br><br>***Until the patient has had the appropriate length of supply the responsibility for providing the patient with their medication remains with you.*** | |
| **4.** | **Initiation and optimisation by the initiating specialist**<br><br>As the patient has not been optimised on this medication I am unable to take clinical responsibility for prescribing this medication at this time. Therefore can you please contact the patient as soon as possible in order to provide them with the medication that you have recommended.<br><br>***Until the patient is optimised on this medication the responsibility for providing the patient with their medication remains with you.*** | |
| **5.** | **Shared Care Protocol not received**<br><br>As legal responsibility for clinical care lies with the clinician who signs the prescription, I need to ensure that I am in possession of sufficient clinical information for me to be confident to prescribe this treatment for my patient and it is clear where each of our responsibilities lie to ensure the patient is safely managed***.***<br><br>For this reason I am unable to take clinical responsibility for prescribing this medication at this time, therefore would you please contact the patient as soon as possible in order to provide them with the medication that you have recommended.<br><br>***Until I receive the appropriate SCP, responsibility for providing the patient with their medication remains with you.*** | |
| **6.** | **Other (Primary Care Prescriber to complete if there are other reasons why shared care cannot be accepted)** | |

I would be willing to consider prescribing for this patient once the above criteria have been met for this treatment.

NHS England ‘Responsibility for prescribing between Primary & Secondary/Tertiary care’ guidance (2018) states that “when decisions are made to transfer clinical and prescribing responsibility for a patient between care settings, it is of the utmost importance that the GP feels clinically competent to prescribe the necessary medicines. It is therefore essential that a transfer involving medicines with which GPs would not normally be familiar should not take place without full local agreement, and

the dissemination of sufficient, up-to-date information to individual GPs.” In this case we would also see the term GP being interchangeable with the term Primary Care Prescriber.

Please do not hesitate to contact me if you wish to discuss any aspect of my letter in more detail and I hope to receive more information regarding this shared care agreement as soon as possible

Yours sincerely

**Primary Care Prescriber signature:** _____

**Date:** _____

**Primary Care Prescriber address/practice stamp**