## Methotrexate (oral and subcutaneous) for patients in adult services (excluding cancer care)

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| Clinical content last reviewed: | November 2023 | Next review date: | November 2025 |

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| **Version** | **Date published** | **Changes since previous version** |
| RDTC v1.0 | 10/04/24 | Hyperlinks and references updated to latest versions. Safety advice reinforced throughout  Section 5: advice added on monitoring for patients taking methotrexate with leflunomide, and when higher doses of folic acid may be needed  Section 6: advice on shingles vaccination updated to align with new national schedule  Section 11: links added to MHRA advice on sun exposure  Section 12: Information on use in pregnancy updated to reflect UKTIS advice |
| RDTC v1.1 | 26th November 2024 | Advice on shingles vaccine clarified to reflect potential eligibility of patients aged 50 years or older taking immunosuppressive therapy |

**Local review and adoption**

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| **Local approval** | **Date** |
| Local content added |  |
| Approved for use by xx ICB |  |
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Clinical content has been reviewed and updated by the RDTC on the date indicated above. Every effort is made to keep the content up to date. These templates are provided to the North West and North East and Yorkshire ICBs for localisation and approval through standard ICB processes. The most recent version is available on the RDTC website at <https://rdtc.nhs.uk/prescribing-support-document/shared-care-protocol-methotrexate-in-adults/>.

Information requiring local completion is highlighted.

This document is intended for use by NHS healthcare professionals and cannot be used for commercial or marketing purposes.

**Shared Care Protocol**

## Methotrexate (oral and subcutaneous) for patients in adult services (excluding cancer care)

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| Background | 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 routinely prescribed with folic acid supplements, to reduce methotrexate toxicity.  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. |
| Licensed and agreed off-label indications | 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 unresponsive to conventional therapies * 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. 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. |
| Locally agreed indications | *To be completed locally* |
| Initiation and ongoing dose regime | Transfer of monitoring and prescribing to primary care is normally after at least 12 weeks, and when the patient’s dose has been optimised and with satisfactory investigation results for at least 12 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 dose can be increased to 10mg if the person experiences adverse effects to methotrexate; 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.**  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 creatinine clearance (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](#ten_ADRs).  Dose reduction should be considered in elderly patients, due to diminished hepatic and renal function and decreased folate stores. |
| Baseline investigations, initial monitoring, and ongoing monitoring to be undertaken by specialist | 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 viral infections as per local policy, e.g. HIV, hepatitis B and C, varicella zoster, Epstein Barr virus, cytomegalovirus * 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.  Patients taking concomitant methotrexate and leflunomide require longer term monthly monitoring. Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis.  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 6](#six_monitoring) remains appropriate. |

## Ongoing monitoring requirements to be undertaken by primary care

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.

| **Monitoring** | **Frequency** |
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| * FBC * U&Es including creatinine and CrCl * ALT and/or AST and albumin * Rheumatology patients: CRP &/or ESR; specialist to confirm * 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.  **The exact frequency of monitoring to be communicated by the specialist in all cases**. |
| * Patients aged 60-79 years old are eligible for the shingles vaccine (herpes zoster). Patients aged 50 years or older and taking immunosuppressive therapy may also be eligible. Specialist input may be required. Refer to [Green Book Chapter 6 (Contraindications and special considerations)](https://www.gov.uk/government/publications/contraindications-and-special-considerations-the-green-book-chapter-6) and [Green Book Chapter 28a (Shingles)](https://www.gov.uk/government/publications/shingles-herpes-zoster-the-green-book-chapter-28a) for further details. * **Annual** influenza ([The Green Book, Chapter 19](https://www.gov.uk/government/publications/influenza-the-green-book-chapter-19)) vaccinations are recommended. * COVID-19 vaccination ([The Green Book, Chapter 14a](https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a)) is safe and recommended. * Repeat pneumococcal vaccine may be indicated. See [Green Book Chapter 25](https://www.gov.uk/government/publications/pneumococcal-the-green-book-chapter-25) for advice. | * Shingles vaccination: single course (two doses). * Influenza vaccination: annual. It is advisable to add the patient to the influenza vaccine list. * Other vaccinations as per national schedule. |

## Pharmaceutical aspects

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| Route of administration: | Oral tablets, or subcutaneous injections |
| Formulation: | **Methotrexate tablets**  Methotrexate 2.5 mg tablets  Other strengths are available but, to reduce dosing errors, **only the 2.5 mg tablets should be prescribed**. The dose should be taken **once weekly** on the same day each week, and that day should be clearly communicated to the patient.  **Methotrexate subcutaneous injection**  Solution for injection available in 2.5 mg increments ranging from 7.5 mg – 30 mg and varying with brand:   * 50 mg/mL in pre-filled injector or syringe (Methofill®): 7.5 mg to 30 mg * 50 mg/mL in pre-filled pen (Metoject®): 7.5 mg to 30 mg * 25 mg/mL in pre-filled pen (Nordimet®): 7.5 mg to 25 mg * 25 mg/mL in pre-filled syringe (Zlatal®): 7.5 mg to 25 mg   If subcutaneous methotrexate is prescribed, secondary care must specify the brand and the patient should be maintained on that brand due to device familiarity. Brand should be specified on clinical systems.  See [SPCs](https://www.medicines.org.uk/emc/search?q=methotrexate) 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.  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](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).  Converting from an oral to a subcutaneous dosage form may be appropriate where patients experience intolerable adverse effects and should only be undertaken by a specialist. |
| Administration details: | Tablets should not be split or crushed for administration. Review formulation if patient is unable to swallow tablets. Carers should wear single-use gloves to handle methotrexate tablets. Anyone handling the tablets should wash their hands immediately afterwards.  Pregnant people, including patients and carers, should avoid handling methotrexate.  Avoid skin or mucosa contact with methotrexate solution for injection. Spillage kits should be available for patients on subcutaneous methotrexate.  If a dose of methotrexate is missed it should be taken as soon as remembered, within one or two days, and not on the same day as folic acid. 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](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), 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. |

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| Cautions and contraindications | This information does not replace the Summary of Product Characteristics (SPC), and should be read in conjunction with it. Please see [BNF](https://bnf.nice.org.uk/drugs/methotrexate/) & [SPC](https://www.medicines.org.uk/emc/search?q=methotrexate) 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 gastrointestinal ulceration, stomatitis, or ulcers of the oral cavity. * Pregnancy and breast-feeding. * Vaccination with live vaccines during treatment with methotrexate at immunosuppressive doses. See [section 9](#nine_interactions) for further detail. * Concomitant use of medicines with anti-folate properties, e.g. trimethoprim, co-trimoxazole (see [section 9](#nine_interactions)).  Cautions:  * Renal impairment: dose reduction required ([section 4](#four_dosing)). * 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 6](#six_monitoring) is required. * Respiratory disease. * Concomitant use with hepatotoxic or haematotoxic medicines (see [section 9](#nine_interactions)). * 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. * Psychiatric disorders |
| Significant drug interactions | The following list is not exhaustive. Please see [BNF](https://bnf.nice.org.uk/drugs/methotrexate/) & [SPC](https://www.medicines.org.uk/emc/search?q=methotrexate) 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 8**](#eight_cautions_cx)**). 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 8](#eight_cautions_cx)). 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. If this combination is used, dose adjustment of the thiopurine may be required. * **Sulfasalazine**: may increase risk of bone marrow and renal 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 typhoid, MMR, BCG,) 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](https://www.gov.uk/government/collections/immunisation-against-infectious-disease-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](https://www.gov.uk/government/publications/contraindications-and-special-considerations-the-green-book-chapter-6) for current advice. * Avoid concomitant use of **cytotoxics** or **clozapine**,: increased risk of adverse reactions. * **Retinoids**: increased risk of hepatotoxicity, and may increase plasma levels of methotrexate. * **Levetiracetam**: may increase plasma levels of methotrexate; manufacturers recommend careful monitoring of methotrexate and levetiracetam levels. * **Nitrous oxide** and **pyrimethamine**: increased risk of methotrexate toxicity. Manufacturer advises avoiding concomitant nitrous oxide and 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](#ten_ADRs)). * **Theophylline and other methylxanthines**: may reduce methotrexate efficacy. Methotrexate may reduce theophylline clearance. Manufacturers advise theophylline monitoring and avoiding excessive caffeine consumption. * **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. |

## Adverse effects and management

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**.** For information on incidence of ADRs see relevant SPCs.

**Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit** [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

Advice based on shared care guidelines published by NHS England, and checked against current guidance.

| **Adverse effect** | **Management** |
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| * Full blood count: * White blood cells less than 3.5x109/L * Lymphocytes less than 0.5x109/L * Neutrophils less than 1.6x109/L * Platelets less than 140x109/L * Eosinophilia greater than 0.5x109/L | Withhold and discuss with specialist team. |
| Mean cell volume greater than 105 fL | Consider interruption in treatment.  Check serum folate, B12, alcohol history and TSH and treat any underlying abnormality. If results of these additional investigations are normal discuss with specialist team urgently. |
| Signs or symptoms of bone marrow suppression, e.g. unexplained bleeding or bruising with or without sore throat, purpura, mouth ulcers. | Check FBC immediately, withhold treatment while awaiting results, and discuss with the specialist team. See haematological monitoring above. |
| **Infections:**  Infection requiring antibiotics | Temporarily withhold methotrexate until the patient has recovered and the antibiotic course is complete. Consider additional investigations (e.g. FBC), if clinically appropriate. |
| **Liver function tests:**  ALT or AST greater than 100 units/L, or any sudden increases (e.g. double of baseline), OR  Unexplained fall in serum albumin to less than 30g/L  Jaundice | Withhold and discuss with specialist team.  Assess for other causes of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication. |
| **PIIINP** (psoriasis only)  Levels greater than:   * 10 mg/L on one occasion * 8.0 mg/L on two occasions * 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**:  Creatinine increase of greater than 30% from baseline in the last 12 months, or CrCl reduces to less than 60ml/min | Withhold and discuss with specialist team. |
| **Gastrointestinal disorders:**  Nausea | Review for reversible causes and treat as appropriate. Enquire which day of the week the patient takes their methotrexate, and which day(s) they take folic acid and confirm against the patient’s records. Discuss with specialist team if persistent or severe. Switch to subcutaneous therapy may be indicated, under specialist advice. |
| Diarrhoea, ulcerative stomatitis, haematemesis, black or bloody stools, or suspected pancreatitis | Withhold and discuss with specialist team. |
| **Symptoms of interstitial lung disease**  e.g. persistent cough, dyspnoea, fever | If methotrexate-induced lung disease is suspected, discuss with specialist team urgently and withhold treatment. Treat with corticosteroids as directed by a specialist and do not restart methotrexate. |
| **Photosensitivity** | Continue methotrexate. Reinforce appropriate self-care e.g. sun avoidance and purchasing of a broad spectrum sunscreen (at least SPF30). See [MHRA advice](https://www.gov.uk/drug-safety-update/methotrexate-advise-patients-to-take-precautions-in-the-sun-to-avoid-photosensitivity-reactions). |
| **Pregnancy** | * In pregnant patients, stop methotrexate immediately and prescribe folic acid 5 mg/day. Discuss with specialist team urgently. See [section 12](#twelve_pregnancy). * In pregnancies with paternal exposure, see [section 12](#twelve_pregnancy). |

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| Advice to patients and carers 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 drugs. | **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. * Any unusual swelling * 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. Use appropriate self-care: e.g. avoid exposure to intense sunlight (especially between 11am and 3pm) or to UV rays (e.g. sunbeds or tanning equipment), use a sun protection product with a high protection factor (at least SPF30)., wear a hat and clothes that cover your arms and legs when in the sun. Talk to a healthcare professional if you are worried about a skin reaction you have had while taking methotrexate. See [MHRA advice](https://www.gov.uk/drug-safety-update/methotrexate-advise-patients-to-take-precautions-in-the-sun-to-avoid-photosensitivity-reactions). * To use effective contraception while taking methotrexate and for three months after stopping. To take a pregnancy test if they think they could be pregnant. Patients should inform the specialist or GP immediately if they become pregnant, so that their treatment can be urgently reviewed. Patients should not stop taking methotrexate without speaking to their specialist or GP first. * 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)](https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34)   + UKSHA guidance: [Guidelines on post-exposure prophylaxis (PEP) for varicella/shingles Jan](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1073013/UKHSA_guidelines_on_VZ_post_exposure_prophylaxis.pdf) 2023   Patient information:  General information: [NHS.uk](https://www.nhs.uk/medicines/methotrexate/) |
| Pregnancy, paternal exposure and breastfeeding | **Pregnancy:**  Methotrexate is cytotoxic and is contraindicated in pregnancy. High dose methotrexate is used 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 at least a month afterwards. Patients who become pregnant whilst taking methotrexate should be referred to their local Fetal Medicine Unit for fetal assessment and counselling.  Folic acid 5 mg daily should be taken throughout pregnancy for those who either conceive on methotrexate, or who conceive within three months of stopping methotrexate, to counter any effect on folate deficiency that may have arisen during treatment. Those who wish to become pregnant should speak to their prescriber to discuss the possibility of switching to alternative medication.  Information for healthcare professionals: [UK Teratology Information Service (UKTIS)](https://uktis.org/monographs/use-of-methotrexate-in-pregnancy/)  Information for patients and carers: [Best Use of Medicines in Pregnancy (BUMPs)](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, and the infant should be monitored for signs of immunosuppression and gastrointestinal disturbances. Very limited evidence indicates that negligible amounts are found in breast milk after weekly administration.  Information for healthcare professionals: [UK Drugs in Lactation Advisory Service (UKDiLAS)](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. However, 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. Manufacturers advise that male patients or their female partners use effective contraception for 3 months after stopping methotrexate. Men should not donate semen during treatment or for 3 months following discontinuation.  Paternal methotrexate use at the time of conception is not an indication for additional fetal monitoring  Information for healthcare professionals: [UKTIS - paternal use of methotrexate](https://uktis.org/monographs/paternal-use-of-methotrexate/)  Information for patients: [BUMPS – methotrexate use in men attempting to father a child](https://www.medicinesinpregnancy.org/Medicine--pregnancy/Methotrexate-paternal/)  **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. |
| Specialist contact information and arrangements for referral | *To be completed locally* |
| Additional information | 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. |
| References | 1. British National Formulary. Methotrexate. Accessed via <https://bnf.nice.org.uk/drug/methotrexate.html> on 23/11/23. 2. 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 23/11/23. 3. Methotrexate 2.5 mg tablets Patient Information Leaflet (Maxtrex®). Last revised 08/2023. Accessed via <https://www.medicines.org.uk/emc/files/pil.1376.pdf> on 28/03/24. 4. Methotrexate 10 mg solution for injection in pre-filled injector (Methofill®). Date of revision of the text 01/03/21. <https://products.mhra.gov.uk/> on 23/11/23. 5. Methotrexate 10 mg solution for injection in pre-filled pen (Metoject®). Date of revision of the text 09/2023. Accessed via <https://www.medicines.org.uk/emc/product/11351/> on 23/11/23. 6. Methotrexate 10 mg solution for injection in pre-filled pen (Nordimet®). Date of revision of the text 03/11/23. Accessed via <https://www.medicines.org.uk/emc/product/7721/> on 23/11/23. 7. Methotrexate 10 mg solution for injection in pre-filled pen (Zlatal®). Date of revision of the text 20/04/23. Accessed via <https://www.medicines.org.uk/emc/product/7270/> on 23/11/23. 8. Methotrexate 2 mg/mL oral solution (Jylamvo®). Date of revision of the text 10/2023. Accessed via <https://www.medicines.org.uk/emc/product/8599/> on 23/11/23. 9. 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>. 10. 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>. 11. British Society for Rheumatology 2023. Guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Accessed via <https://academic.oup.com/rheumatology/article/62/4/e48/6783012>. 12. Renal Drug Database. Methotrexate. Reviewed 02/22/18. Accessed via <https://renaldrugdatabase.com/> on 23/11/23. 13. 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>. 14. MHRA Drug Safety Update: Methotrexate: advise patients to take precautions in the sun to avoid photosensitivity reactions. August 2023. Accessed via <https://www.gov.uk/drug-safety-update/methotrexate-advise-patients-to-take-precautions-in-the-sun-to-avoid-photosensitivity-reactions>. 15. Specialist Pharmacy Service. Using folic acid with methotrexate in rheumatoid arthritis. 20th February 2023. Accessed via <https://www.sps.nhs.uk/articles/using-folic-acid-with-methotrexate-in-rheumatoid-arthritis/> on 16/11/23. |
| To be read in conjunction with the following documents | * 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/>. |