NORTH AND EAST DEVON HEALTHCARE COMMUNITY
SHARED CARE PRESCRIBING GUIDELINE

Weekly oral and subcutaneous methotrexate

Treatment of rheumatological and autoimmune diseases

Specialist: Please complete letter on page 10 before sending guideline to GP

GP: Please indicate whether you wish to share patient's care by completing letter on page 10 and return to specialist

Aim of treatment

Methotrexate is a folic acid antagonist and is classified as an antimetabolite cytotoxic agent. The National Patient Safety Agency (NPSA) has highlighted the risks when prescribing methotrexate including failings from poor monitoring of therapy which have led to fatalities. This guideline incorporates their recommendations.

Indication: Treatment of adults with inflammatory joint disease and autoimmune disease.

Methotrexate requires careful monitoring to avoid toxicity. The prescription and supply of subcutaneous (sc) methotrexate will be organised by the rheumatology consultant but monitoring will still be required by the GP. This administration route is used if:

1. There has been a good response to oral methotrexate but patients suffer severe GI side effects
2. Poor response to oral preparation due to suspected reduced absorption.

A summary of prescribing information is provided on page 7.

Specialist responsibilities

- Initiate **oral methotrexate**, supply 28 days' medication. Refer to MHRA Drug safety update, Sept 2020: Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing (see "supporting information" section below).
- For female patients of child-bearing age – exclude pregnancy before initiating treatment.
- Discuss benefits and side effects of treatment with patient or patient's carers including, where appropriate, for female and male patients the risks associated with pregnancy and need for reliable method of contraception.
- Refer patient to specialist nurse service where appropriate (eg. new patient) for advice on taking the drug, its cautions, side effects associated with treatment, monitoring requirements and the timing of re-assessment and by whom.
- Ascertain immune status by enquiring about history of chickenpox. Measurement of antibodies to varicella-zoster is not recommended.
- Issue a patient information leaflet and booklet for recording test results. Ensure that patient understands that they should bring the booklet to each hospital or GP practice appointment and that they are responsible for entering tests results. Discuss options with patient or carer for those who are not able to record results in booklet.
- Conduct baseline tests – full blood count, liver function tests, U&Es, creatinine, folate, vitamin B12 and chest x-ray. Copy results to GP.
- To generate prescriptions for **subcutaneous methotrexate**. Review results of monitoring before issuing each prescription.
- Inform the GP that monitoring will be required for patients receiving subcutaneous methotrexate.

- Specify review dates.
- Prompt verbal communication followed up in writing to GP (and responsible nurse in case of patients unable to self-administer) of changes in treatment or monitoring requirements, results of monitoring, assessment of adverse events or when to stop treatment. Urgent changes to treatment should be communicated by telephone to GP.
- Reporting adverse events to MHRA.

General practitioner responsibilities

If GP has agreed to share care:

- Continue to prescribe **oral methotrexate** in accordance with these guidelines. Refer to MHRA Drug safety update, Sept 2020: Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing (see "supporting information" section below).

PRESCRIBE METHOTREXATE TABLETS IN MULTIPLES OF 2.5mg ONCE WEEKLY (TO BE TAKEN ON THE SAME DAY EACH WEEK)

- Prescribe oral folic acid 5mg at least once weekly (usual recommended dose is 5mg once daily on the six days of the week that the patient does not take methotrexate). The dose to be taken at least 24 hours after methotrexate dose.
- For oral or sc methotrexate, conduct monitoring during treatment as specified below. Review results and take any necessary action.
- Where GP computer systems allow, for patients receiving injectable methotrexate this drug should be added to the list of drugs prescribed on the computer record to alert to interactions and increase patient safety. Add methotrexate sc to the patient record as a new drug and enter 'Information only: Issued and supplied by hospital' in the directions for use or dose field. Detailed guidance on how to add medicines prescribed by other sources to patient records is available from PCT prescribing and medicines management teams.
- Ensure that the GP computer system has an alert flag in accordance with NPSA guidance.
- Record results of monitoring in GP system.
- Agree system for communicating results of monitoring to patient.
- Communicate results of monitoring to responsible nurse in case of patients unable to self-administer sc doses.
- Take appropriate action if patient reports sign(s) or symptom(s) specified under Monitoring.
- Be aware of criteria for referral to Rheumatology team.
- There are significant interactions with methotrexate. Ensure there are no drug interactions with existing drugs and be alert to the possibility of interactions when initiating drugs.
- Respond to advice from secondary care on dose changes and frequency of monitoring.
- Report to and seek advice from specialist on any aspect of patient care of concern to GP which may affect treatment. Prompt referral to specialist if there is a change in patient's health status.
- Report adverse events to specialist.
- Stop treatment in case of a severe adverse event or as per shared care guideline.
- Offer influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check that the patient has had one dose of pneumococcal vaccine (revaccination is not recommended, except every five years in patients whose antibody levels are likely to have declined more rapidly e.g. asplenia) – see BNF or Green Book

Monitoring

1. Prior to starting therapy: rheumatology team

- Measure baseline height & weight, blood pressure, full blood count, U&Es, creatinine, LFTs, folate and vitamin B12
- Conduct chest-x-ray
- Consider patient risk factors for viral infections and screen for occult viral infections (hepatitis B and C and HIV) where appropriate
- Pregnancy test in women of childbearing age (unless pregnancy has been unequivocally excluded). Consider contraception as appropriate

2. Monitoring during treatment: general practice

Laboratory tests and blood pressure

It is recommended that all blood counts are monitored and recorded in the patient record to comply with NPSA and GMS.

<table>
<tr><th>Tests</th><th>Frequency of monitoring</th><th>Guidance</th><th>Action to be taken by GP</th></tr>
<tr><td>FBC</td><td rowspan="3">Every two weeks until on stable dose for 6 weeks, then every month for 3 months, then at least every 12 weeks*.
Following dose increases, monitor every 2 weeks until on a stable dose for 6 weeks, then as above.

Patient factors where continued monthly monitoring is recommended (unless otherwise specified):
• Previous toxicity or deranged FBC or LFTs while on DMARDs
• Chronic kidney disease (CKD 3 or worse)
• Pre-existing liver disease

Additional urgent monitoring tests should be carried out within 24 hours for any patient with acute kidney injury (AKI).</td><td>WCC < 3.5 x 10^9/L
Neutrophils < 1.6 x 10^9/L
Eosinophils >0.5 x 10^9/L
Platelets < 140 x 10^9/L
MCV > 108fl</td><td rowspan="3">If results meet specified criteria, stop treatment and refer to specialist.
If isolated MCV rise, check for other causes (B12, folate, thyroid function and alcohol consumption). If results are normal, refer to specialist.
If concerned about sequential drops in FBC indices (possibly still within normal range), consider an early re-test/seek specialist advice.
If deterioration in renal function, dose adjustment may be necessary; if toxicity suspected or dosing advice required refer to specialist team.</td></tr>
<tr><td>Creatinine / eGFR</td><td>Creatinine increase >30% over 12 months and/or eGFR <60ml/min/1.73m^2</td></tr>
<tr><td>ALT and/or AST and albumin</td><td>ALT and/or AST >100 U/L

Albumin unexplained reduction to <30g/L</td></tr>
<tr><td colspan="4">* For patients on a combination of methotrexate and leflunomide, extend monthly monitoring for at least 12 months before considering reduced frequency on an individual patient basis (specialist to advise). Refer also to N&E Devon leflunomide shared care guideline (https://onedevon.org.uk/download/leflunomide-rheumatology-shared-care-guideline-north-and-east-devon)
Other factors that may increase risk of toxicity include moderate renal impairment, extremes of body weight, polypharmacy (especially other haematotoxic/ hepatotoxic/ nephrotoxic drugs), comorbidities, age > 80 years. Where more frequent ongoing monitoring is required due to a combination of patient factors this will be advised by the specialist prescriber.</td></tr>
</table>

Signs and symptoms

Patients MUST report mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding, shortness of breath and/or dry cough, and any unexplained illness/infection.

Action to be taken by GP:

- **Review patient with any of the signs or symptoms listed above within 24 hours** for clinical assessment, full blood count and liver function tests. Signpost patient to alternative provider if this is not possible e.g. weekend/bank holiday
- **Stop treatment and refer if:**
    - Abnormal bruising
    - Severe sore throat
    - Rash
    - Severe oral ulceration
    - Unexplained illness including severe nausea, vomiting or diarrhoea
- **If pulmonary symptoms are reported** including new or increasing dyspnoea or dry cough. Stop treatment and refer. Patients should be investigated urgently with a chest x-ray to exclude pneumonitis. GP to arrange chest x-ray.

During a **serious** infection **STOP** treatment. During minor infections (e.g. uncomplicated UTI treated with a short antibiotic course) treatment can be continued.

Do not stop treatment prior to surgery unless significant risk of infection.

Contact Microbiology if a patient, not known to be immune to chickenpox, comes into contact with shingles or chickenpox, for advice on whether zoster immune globulin or other treatment is indicated.

In patients suffering from chickenpox or active skin lesions from shingles, withhold. Patients with chickenpox: contact microbiologist for consideration of admission to hospital for IV antivirals. Patients with shingles: if any vesicles are still present (regardless of the time of onset), treat with aciclovir (800mg five times a day for 7 days).

Patient/carer responsibilities

Patients (and/or their carers):

- Take methotrexate as prescribed ONCE A WEEK on the SAME DAY EACH WEEK
- MUST report mouth ulcers, sore throat, fever, epistaxis, rash, unexpected bruising or bleeding, new or increasing breathlessness and dry cough, and any unexplained illness/infection to their GP and/or specialist (or out of hours service e.g. NHS 111 if their GP practice is closed for weekend/bank holiday).
- Ensure they record the results of any monitoring in their booklet
- Be aware that taking OTC NSAIDs in addition to methotrexate may interfere with treatment
- Report any other adverse effect to their GP and/or specialist whilst being treated with methotrexate.
- Ensure that they have a clear understanding of their treatment.
- Ensure they attend for monitoring requirements.
- Be aware that treatment will be stopped if patient does not attend for monitoring.
- Promptly seek medical advice if they think they have taken too much methotrexate

Back-up advice and support

Contact details	Telephone No	E-mail address
Dr R Haigh	(01392) 403705	richardhaigh@nhs.net
Dr S Earl	(01392) 406351	Susannah.earl@nhs.net
Dr M Brown	(01392) 403567	mary.brown11@rnhs.net
Dr R Mascarenhas	(01392) 406355	r.mascarenhas@nhs.net
Dr M Abusalameh	(01392) 403772	m.abusalameh@nhs.net
Dr M Cates	(01392) 403707	matthewcates1@nhs.net
Dr S Kyle	(01271) 311571	stuartkyle@nhs.net
Dr R Manhas	(01271) 311571	roopemanhas@nhs.net
Dr V Arya	(01271) 311571	vivek.arya2@nhs.net
RD&E rheumatology dept		rde-tr.rheumatology@nhs.net
NDHT rheumatology dept		ndht.rheumatology@nhs.net

Please do not use rheumatology department emails for enquiries relating to patients receiving DMARDs under the care of other specialties e.g. dermatology, gastroenterology etc.

Supporting Information

This guideline highlights significant prescribing issues, not all prescribing information and potential adverse effects are listed. Please refer to SPC/data sheet for full prescribing data.

Patient Safety Agency has highlighted the risks when prescribing methotrexate including failings from poor monitoring of therapy which have led to fatalities. This guideline incorporates their recommendations.

Why do health professionals make mistakes?

A once weekly dosage is very unusual. Only a tiny proportion of medicines administered in the UK are taken at this frequency. Whilst drug packaging has reminders of the correct dose, in practice these are not sufficiently eye-catching to prevent mistakes. Also, the packaging for the 10mg strength tablet looks very similar to the 2.5mg strength tablet.

Why do carers make mistakes?

The drug is packaged in packs of 28 or 100. When patients are prescribed smaller quantities, the dose warning information is often separated from the tablets. In addition folic acid is often prescribed with methotrexate; these are taken daily and can add to the confusion. There is evidence that even when patients are given clear written information that they should take this drug on a weekly basis, they can assume that this must be incorrect. For this reason verbal communication with patients is essential. Methotrexate is a powerful drug. Patients and carers are not always sufficiently informed of the symptoms they should look out for that would indicate toxicity.

Patient information

Patients should be given information about methotrexate, including written information in the form of the methotrexate booklet, and allowed time to understand it or discuss it with their families before starting treatment. The weekly dosing and the importance of monitoring must be stressed.

MHRA Drug Safety Update (September 2020): Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing

Advice for prescribers:

- before prescribing methotrexate, make sure that the patient is able to understand and comply with once-weekly dosing
- consider the patient's overall polypharmacy burden when deciding which formulation to prescribe, especially for a patient with a high pill burden
- decide with the patient which day of the week they will take their methotrexate and note this day down in full on the prescription
- inform the patient and their caregivers of the potentially fatal risk of accidental overdose if methotrexate is taken more frequently than once a week; specifically, that it should not be taken daily
- advise patients of the need to promptly seek medical advice if they think they have taken too much
- Refer to the MHRA Drug Safety Update for more information

Dose

Refer to MHRA Drug safety update, September 2020: Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing (see “supporting information” section above)

Dose: For both oral and SC methotrexate, the usual dose range is 2.5mg-20mg ONCE WEEKLY on the SAME DAY EACH WEEK.

Oral: **oral methotrexate should be prescribed as multiples of 2.5mg tablets.**

- Methotrexate is also available as tablets containing 10mg of methotrexate. The 10mg tablets of methotrexate are to be used only in oncology and in haematology for patients with malignant disease. The prescriptions must be endorsed as such by the prescriber in secondary care. **There should be no prescribing of 10mg tablets in primary care**.

Subcutaneous: The consultant rheumatologist prescribes sc methotrexate with the dose individualised for each patient.

To limit the side effects of methotrexate, all patients should receive folic acid 5mg orally at least once weekly at least 24 hours after taking methotrexate (usual recommended dose is 5mg once daily on the six days of the week that the patient does not take methotrexate).

Special patient groups: Dose reduction is required for elderly patients and for patients with hepatic or renal impairment.

All prescriptions should avoid the use of “as directed” in prescribing; a specific dose must be put on each prescription. Patients often understand their dose by number of tablets rather than “mg”. Quantity and frequency of dose should be regularly discussed with the patient.

Repeat prescriptions should be retained separately for prescriber review prior to authorising.

The label on prescribed/dispensed methotrexate tablets should state the instructions clearly, for example: ‘methotrexate 2.5mg tablets: (number of tablets) to be taken as a single dose ONCE A WEEK on XXXDAY’.

Contraindications

- Hypersensitivity to methotrexate
- Severe hepatic or renal impairment
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia
- Serious acute or chronic infections or evidence of immunodeficiency syndrome
- Concurrent administration of drugs with antifolate properties e.g. co-trimoxazole, trimethoprim and sulphonamides
- Ulcers of the oral cavity and known active gastrointestinal ulcer disease
- Pregnancy – methotrexate is teratogenic and can affect male and female fertility. Men and women of child-bearing age should use a reliable method of contraception during treatment and at least four months thereafter. When planning a pregnancy, it is important that both men and women on this drug discuss medication with the Rheumatology team (at least three months before conception). See section on pregnancy for further information.
- Lactation
- Live vaccines

Precautions

- Risk of hepatotoxicity: Closer monitoring of LFTs required for patients taking other hepatotoxic medicines (e.g. leflunomide). See below for recommendation on alcohol.
- Alcohol consumption increases the risk of liver fibrosis. Ideally not more than 1 unit/day should be consumed. Discuss with doctor and limit to minimum acceptable amount.
- Methotrexate causes bone marrow depression. Closer monitoring of the full blood count and platelets is required for patients taking other haematotoxic medicines (e.g. leflunomide)
- Renal impairment – more frequent monitoring required as methotrexate is eliminated mainly by the renal route. Care is required with the elderly and patients taking nephrotoxic drugs.
- Acute or chronic interstitial pneumonitis often associated with eosinophilia has been reported.
- Possible activation of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C).
- Malignant lymphomas may occur in patients receiving low dose methotrexate in which case stop treatment.
- Diarrhoea and ulcerative stomatitis can be toxic effects and require interruption of therapy as haemorrhagic enteritis and intestinal perforation may result.

Side effects

Common/uncommon:

- Stomatitis, dyspepsia, nausea, reduced appetite, oral ulcers, diarrhoea, pharyngitis, enteritis, vomiting
- Exanthema, erythema, pruritus, photosensitisation, loss of hair, increase in rheumatic nodules, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticaria
- Injection site reactions
- Precipitation of diabetes
- Headache, tiredness, drowsiness, dizziness, confusion, depression, cognitive dysfunction
- Elevated transaminases, cirrhosis, liver atrophy, periportal fibrosis and fatty degeneration of liver
- Pneumonia, interstitial alveolitis/ pneumonitis
- Leukopenia, anaemia, thrombocytopenia, pancytopenia
- Inflammation and ulceration of urinary bladder or vagina, renal impairment, disturbed micturition
- Arthralgia, myalgia, osteoporosis

Interactions

Caution with concurrent use of hepatotoxic, nephrotoxic or haematostatic drugs.

- Analgesics: NSAIDs (including aspirin) - increased risk of toxicity with concurrent use.
- Antibacterials: increased risk of haematological toxicity with concurrent use of co-trimoxazole and trimethoprim. Increased risk of toxicity when methotrexate given with doxycycline, penicillins, sulfonamides, tetracycline and possibly with ciprofloxacin and neomycin.
- Antiepileptics: antifolate effect of methotrexate increased by phenytoin; excretion of methotrexate has been reported as being decreased by levetiracetam leading to potentially toxic levels. Advice when administered with levetiracetam is to monitor blood levels of both drugs.
- Antimalarials: antifolate effect of methotrexate increased by pyrimethamine
- Antipsychotics: avoid concomitant use of clozapine due to increased risk of agranulocytosis
- Cardiac glycosides: methotrexate possibly reduces absorption of digoxin tablets
- Ciclosporin: risk of toxicity when methotrexate given with ciclosporin
- Diuretics: excretion of methotrexate increased by acetazolamide
- Leflunomide: concurrent use increases incidence of pancytopenia and hepatotoxicity
- Probenecid: risk of methotrexate toxicity as excretion reduced by probenecid

- Retinoids: concurrent use of acitretin or etretinate increase risk of hepatotoxicity
- Theophylline: methotrexate possibly increases plasma concentration of theophylline.
- Ulcer-healing drugs: excretion of methotrexate possibly reduced by omeprazole (increased risk of toxicity).
- Vaccines – see below

Vaccines

- Use of live vaccines is contraindicated. Live vaccines and live attenuated vaccines include: measles, mumps and rubella; BCG; poliomyelitis – oral Sabin vaccine; yellow fever; typhoid – oral.
- Flu and pneumococcal vaccines may be given (see GP responsibilities).
- Shingles vaccination should **not** be given to patients on the combination of methotrexate and leflunomide, or on more than 25mg methotrexate weekly
- Shingles vaccination **can** be given to eligible patients on up to 25mg weekly methotrexate (as monotherapy, or in combination with non-biologic DMARDs ***except mycophenolate mofetil or leflunomide***). Specialist advice should be sought if uncertain.
- Passive immunisation should be carried out using Varicella Zoster Immunoglobulin (VZIG) in non-immune patients if exposed to chickenpox or shingles. See local guidance page 3.

For additional information refer to the British Society of Rheumatology guidance on vaccinations for immuno-suppressed patients at:
http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/v/vaccinations_in_the_immunocompromised_person.pdf

Pregnancy and lactation

See Contraindications section and SPC for further information

Methotrexate is teratogenic and can affect male and female fertility. Women of child-bearing age should use a reliable method of contraception during treatment and at least four months after stopping methotrexate treatment.

Refer also to MHRA Drug Safety Update (2019): “Medicines with teratogenic potential: what is effective contraception and how often is pregnancy testing needed?”

When planning a pregnancy it is important to discuss medication with the Rheumatology team.

There is limited evidence that methotrexate at low doses (20mg/week or below) in male patients may be compatible with paternal exposure. However, male patients who are not planning a family should use contraception and discuss conception with the Rheumatology team when planning a pregnancy.

Methotrexate is not recommended in breast-feeding women.

Ability to drive or operate machinery

Methotrexate can cause dizziness, fatigue, blurred vision and eye-irritation which may affect the ability to drive or operate machinery.

Date ratified by Effective Practice Committee: April 2011
Partially updated: October 2019

Shared Care Agreement Letter - Consultant Request

To: Dr……..

Practice Address: ……

……

……

Patient Name:
Hospital number:
Date of birth:
Address:

DIAGNOSED CONDITION: **……..**

I recommend treatment with the following drug: **……**

I request your agreement to sharing the care of this patient according to the North and East Devon Health Community Shared Care Prescribing Guidelines for this drug.

Principles of shared care:
GPs are invited to participate. If GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug the GP should reply to this request as soon as practical. Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them.

The doctor who prescribes the medication has the clinical and legal responsibility for the drug and the consequences of its use.

Signed:		**Date:**	
Consultant name:			
Consultant email:			
Department email:			
Contact telephone:			

GP RESPONSE
I agree/ do not agree* to share the care of this patient in accordance with the Shared Care Guideline.

Signed: …….. **Date: ……**

GP name: …….. ***Delete as appropriate**