This guideline is currently under review. In the interim, the guideline remains valid; if GPs have any specific concerns or questions, they should seek advice from the specialist with whom they have agreed to share care.

NORTH AND EAST DEVON HEALTHCARE COMMUNITY SHARED CARE PRESCRIBING GUIDELINE

http://www.devonpct.nhs.uk/Treatments/NE_Devon_Shared_Care_Guidelines.aspx#A

Weekly oral and subcutaneous methotrexate

Treatment of inflammatory bowel disease

Specialist: Please complete letter on page 9 before sending guideline to GP

GP: Please indicate whether you wish to share patient's care by completing letter on page 9 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 bowel disease and autoimmune disease. Methotrexate requires careful monitoring to avoid toxicity. It is recommended that oral methotrexate be initiated in secondary care after consultant recommendation and under consultant supervision. The prescription and supply of subcutaneous (sc) methotrexate will be organised by the gastroenterology 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 5.

Specialist responsibilities

- Decision to prescribe methotrexate. 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 CHM.

General practitioner responsibilities

If GP has agreed to share care:

- Prescribing of **oral methotrexate** after communication with specialists regarding the need for treatment.

PRESCRIBE METHOTREXATE TABLETS IN MULTIPLES OF 2.5mg ONCE WEEKLY

- Prescribe oral folic acid 5mg at least once weekly. The dose to be taken at least 24 hours after methotrexate dose. The regimen will depend on the side effects of methotrexate – more folic acid can help.
- 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.
- For oral or sc methotrexate, conduct monitoring of full blood count, U&Es, creatinine, LFTs and CRP as specified. Review results and take any necessary action.
- Record results of monitoring in GP system.
- Agree system for communicating results of monitoring to patients.
- 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 Gastroenterology 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.

Monitoring

1. Prior to starting therapy: gastroenterology team

- Measure baseline full blood count, U&Es, creatinine, LFTs, folate and vitamin B12
- Conduct chest-x-ray

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.

The frequency of monitoring of FBC, LFTs and renal function is based on the recommendations of the British Society of Rheumatology (2009) and differs from the CHM recommendations reproduced in the BNF (2010; vol 60).

Tests	Frequency of monitoring	Guidance	Action to be taken by GP
Full blood count	-Every two weeks for three months, and monthly thereafter	**If WCC** falls on three successive occasions **or** <3.5 x 10^9/l **If neutrophils** fall on 3 successive occasions **or** <2.0 x 10^9/l **If platelet** count falls on 3 successive occasions **or** <150 x 10^9/l **If MCV** >105fl	If concerned about sequential drops in FBC indices (possibly still within the normal range) consider an early retest **If count(s) meet specified criteria, stop treatment and refer to Gastoenterology team** If an isolated MCV rise – check for other causes (B12, folate and alcohol consumption). **If results normal, refer to Gastroenterology team**
U&Es and creatinine	- After dose increase, weekly for four weeks	If deterioration in renal function	Adjust dose or contact Gastroenterology team (see guidance for dose adjustment)
LFTs		**If AST or ALT** > 2 times ULN **Albumin** – unexplained fall (in absence of active disease)	If small rise in AST or ALT, early next test. **If >3 times rise, stop treatment and refer to Gastroenterology team.** **Stop treatment and refer to Gastroenterology team**
CRP	Every three months	If CRP high consider infection	-

Signs and symptoms

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

Action to be taken by GP:

- **See patient with any of the signs or symptoms listed above within 24 hours** for full blood count and liver function tests.
- **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.

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.

Patient responsibilities

Patients:

- MUST report mouth ulcers, sore throat, fever, epistaxis, rash, unexpected bruising or bleeding, and any unexplained illness/infection to their GP and/or specialist.
- 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.

Back-up advice and support

Contact details	Telephone No	E-mail address
Dr T. Daneshmend	01392 402803	tawfique.daneshmend@nhs.net
Dr R. Ayres	01392 402818	reuben.ayres@nhs.net
Dr J. Christie	01392 402791	john.christie@nhs.net
Dr T. Shirazi	01392 406220	tarek.shirazi@nhs.net
Dr T. Ahmad	01392 406218	tariq.ahmad1@nhs.net
Dr A. Moran	01271 322734	alex.moran@ndevon.swest.nhs.uk
Dr A Davis	01271 322447	andrew.davis@ndevon.swest.nhs.uk
Nurse specialists (RD&E)		
Fiona Fry	01392 402728	F.fry@nhs.net
Clare Holding	01392 402728	Clare.holding@nhs.net
Laura. Strang	01392 402728	Laura.strang@nhs.net

Guideline updated by Clinical Effectiveness Team, Public Health, NHS Devon in consultation with local specialists and GPs

For non-clinical enquiries: clinicaleffectiveness.devonpct@nhs.net

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.

Dose

Dose: For oral and SC methotrexate, the usual dose range is 2.5mg-20mg once weekly. Weekly IM methotrexate 25mg may be used in secondary care.
Oral methotrexate should be prescribed as multiples of 2.5mg tablets.
Subcutaneous: The consultant gastroenterologist 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 once weekly at least 24 hours after taking methotrexate.

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

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 sulfonamides
- 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 gastroenterology team (at least three months before conception)..
- Lactation
- Live vaccines

Precautions

- Risk of hepatotoxicity: Closer monitoring of LFTs required for patients taking other hepatotoxic medicines. 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.
- 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
- 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 contra-indicated. Live vaccines and live attenuated vaccines include: measles, mumps and rubella; BCG; poliomyelitis – oral Sabin vaccine; yellow fever; typhoid – oral.
- Flu and pneumococcal vaccines are recommended.
- 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.

Pregnancy and lactation

See Contraindications section and SPC for further information

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.

Product information

Methotrexate tablets 2.5mg tablets. Cost per 28 days treatment at 7.5mg/day: £11.77
Methotrexate pre-filled syringes – individualised dosages available as licensed and unlicensed preparations.

Date ratified by Effective Practice Committee: April 2011
Review date: November 2013

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Shared Care Agreement Letter - Consultant Request

To: Dr.....

Practice Address: .....

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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:		
Contact telephone number:		

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