Working in partnership

SHARED CARE PRESCRIBING GUIDELINE
For Methotrexate Therapy in Inflammatory Bowel Disease (IBD)

NOTES to the GP

The expectation is that these guidelines should provide sufficient information to enable GPs to be confident to take clinical and legal responsibility for prescribing this drug.
The questions below will help you confirm this:

- Is the patient's condition predictable or stable?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care prescribing guideline?
- Have you been provided with relevant clinical details including monitoring data?

If you can answer YES to all these questions (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility.

If the answer is NO to any of these questions, you should not accept prescribing responsibility. You should write to the consultant within 14 days, outlining your reasons for NOT prescribing. If you do not have the confidence to prescribe, we suggest you discuss this with the appropriate Milton Keynes Hospital specialist service, who will be willing to provide training and support.

The patient's best interests are always paramount

Date prepared: April 2016	**Date approved:** July 2016
Approved by: Milton Keynes Prescribing Advisory Group	**Review date:** July 2018 (Unless clinical evidence changes)

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Review Author: Quynh-Anh Nguyen - Principal Pharmacist, MKUH – Medicine

Introduction and reason for shared care

This guideline has been developed in order to assist General Practitioners, Gastroenterologists and IBD Specialist Nursing staff and other members of the multi-disciplinary team involved in the patients care. The aim of the shared care protocol is to ensure evidence based care is delivered to patients requiring methotrexate for IBD. It intends to support healthcare professionals involved in this care by providing up-to-date guidance for use of methotrexate. It will provide agreed indications for use, the initial and ongoing monitoring requirements and detail current side effects profile, potential complications and possible drug interactions.
This shared care protocol outlines suggested ways to which the responsibilities for managing the prescribing and monitoring of Methotrexate with patients who have inflammatory bowel disease can be shared between the hospital specialist team and general practitioner (GP).

Shared Care Guidelines for Methotrexate Therapy in Inflammatory Bowel Disease (IBD)

Circumstances When Shared Care Is Appropriate

- Prescribing responsibility will only be transferred when the consultant and the GP are in agreement that the patient's condition is stable or predictable.
- Patients will only be referred to the GP once the GP has agreed in each individual case and the hospital will continue to provide prescriptions until successful transfer of responsibilities as outlined below.

1. Areas of Responsibility

Consultant

- The specialist will confirm the working diagnosis to the patient and/or carer as appropriate.
- Discuss treatment and monitoring with the patient, provide patient with patient information leaflet prior to commencement of therapy.
- The specialist and patient to complete patient education checklist.
- Perform baseline tests, including pregnancy test and chest x-ray, and monitoring during the first 12 weeks of treatment
- **Prescribe intramuscular methotrexate and oral folic acid tablets for the first 12 weeks of treatment.**
- **Initiate oral therapy.** The specialist will provide the initial prescription for 28 days' supply.
- To complete the patient-held monitoring booklet if patient requests or if they are seen by or are going to see out of area specialists (e.g. Oxford) who are unable to see ICE results.
- Discuss rationale for commencement of therapy, risk v benefit approach, potential side effects including need to report untoward side effects.
- The specialist will suggest that shared care may be appropriate for the patient's condition.
- Request to GP via prescribing agreement form at the end of this document to continue treatment. Send hard copy of shared care guideline, including all completed information to GP.
- Annual review of the patient (minimum), the frequency may vary dependant on individual need.

IBD Nurse

- Educate on medication pre commencement to ensure informed decision regarding commencement of Methotrexate is established.
- Potential calls via the telephone helpline may be in relation to side effects and can be dealt with over the telephone a record of this information must be imported into the electronic patient record.
- All the correspondence in relation to outlining target dose, advice on frequency increase and other advice specific to Methotrexate are recorded accurately.
- Adhere to suggestions as discussed in this document when giving patient advice in relation to adverse effects.
- Clarify with the patient, to ensure they are aware of the regime, contraception, blood monitoring and document in clinic letter when therapy commenced.
- If the patient is pregnant or planning to become, discontinue medication and facilitate an urgent outpatient appointment in the consultant clinic.
- Review blood monitoring results via telephone and advise accordingly, liaise with the IBD team as clinical need dictates.
- Any dosage adjustments made by the hospital specialist team will be recorded in the electronic medical notes and full details sent to the GP.
- All patients are counselled that joint aches, nausea, and flu like symptoms may occur, it is important to determine if they are tolerable or whether administration by injection may be better tolerated.
- Support GPs, provide copy of all documents in shared care guideline, provide blood results and

share information regarding patient treatment.
- Go through the Methotrexate patient information leaflet and patient record sheet to confirm retention of information and understanding.
- Complete and send GP invite letter.
- Liaise with medicines information department as the need dictates.

GP

- Ensuring that he/she has the knowledge and information to understand the therapeutic issues in relation to the patient's clinical condition.
- Agreeing that the patient should receive shared care for the diagnosed condition unless there is a specific rationale for the patient management to remain within secondary care.
- Report to and seek advice on any aspect of the patient care that is of concern to the GP and may affect treatment.
- Ensure blood test results are checked prior to issuing a prescription for the medication.
- Continue to prescribe oral therapy in accordance with the written instructions within the GP letter.
- To complete the patient-held monitoring booklet if patient requests or if they are seen by or are going to see out of area specialists (e.g. Oxford) who are unable to see ICE results.
- Report any adverse effects of the treatment to the specialist hospital team.
- The GP will ensure the patient is monitored as described in this protocol, and will take advice from the hospital specialist team if there are any amendments to the suggested monitoring schedule.
- Refer patients considering pregnancy to the hospital specialist team. Advise to continue contraception in interim.
- The GP will ensure the patient is given appropriate appointments for follow up and monitoring. It is the GP's responsibility to decide to discontinue treatment in a non-compliant patient for follow up and monitoring. As a guide:
    - 1-2 weeks late-written or telephone reminder
    - 4 weeks late-telephone reminder
    - 6 weeks late-a written letter stating medication will be stopped and hospital specialist team informed.
- GPs should contact the hospital specialist team if any dose adjustments are required or if the need to discontinue the medication arises.

Patient
- To attend for regular blood tests.
- To report any side effects.
- To take their medication as agreed, unless otherwise advised by an appropriate health professional.
- Attend follow up appointments. If unable then inform health care professional to enable an alternative appointment to be scheduled.
- The patient will store medication securely.
- Read information provided by health care professional, and contact the relevant professional if they do not understand information provided.

2. COMMUNICATION AND SUPPORT

Hospital contacts: (the referral letter will indicate named consultant) **Milton Keynes University Hospital NHS Foundation Trust**	 01908 660033

Standing Way, Eaglestone, Milton Keynes, MK6 5LD Out of hours – contact Medical Registrar via switchboard	
Dr. George MacFaul, Consultant Physician and Gastroenterologist	01908 997109
Dr. Sandro Lanzon-Miller, Consultant Physician and Gastroenterologist	01908 997060
Dr Ravi Madhotra, Consultant Physician and Gastroenterologist	01908 997103
Inflammatory Bowel Disease Nursing Team	01908 996955 Email: IBDNursingTeam@mkhospital.nhs.uk

Specialist support / resources available to GP including patient information:

This shared care guideline is available online at www.formularymk.nhs.uk then click on shared care guidelines.

A detailed guidance on prescribing and monitoring Methotrexate in Inflammatory Bowel Disease is available on the Hospital Trust website.

Blood test results taken by the specialist hospital team will be available on the ICE system, if the GP cannot access blood test results via ICE, it should be agreed that the hospital specialist team will send a paper copy of the blood test results to the GP in a timely manner.

The dosage regime and frequency of blood test monitoring should be clearly explained to the patient.

3 CLINICAL INFORMATION

Indication(s):	[Unlicensed] Maintenance therapy in steroid-dependent and steroid refractory patients with Crohn's Disease
Place in Therapy:	Methotrexate is utilised to avoid prolonged steroid use by maintaining patients in remission who have had an adverse reaction to either Azathioprine or 6-mercaptopurine. Sometimes it is used to reduce immunogenicity of biologic agents, although there is no supportive evidence.
Therapeutic summary:	Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis.
Dose & route of administration:	**Acute disease:** 25mg once a week for 12 weeks intramuscular administration. **Maintenance:** 15mg once a week as **an oral tablet**. *The dose should be adjusted in renal impairment as follows:* ***Creatinine clearance (ml/min)*** / ***Dose*** *> 50* / *100 %* *20 – 50* / *50 %* *< 20* / *must not be used* **Folic acid** 5mg PO should be prescribed for use three days post

	administration. This helps reduce anaemia, nausea & vomiting side effects. This should NOT be taken on the same day as the methotrexate treatment. Folic Acid will be supplied by the Consultant whilst the patient is on Intramuscular injection. It should then be supplied by the GP once the patient has switched to oral maintenance therapy.
Duration of treatment:	There is no current evidence to suggest any specific length of treatment with Methotrexate. The decision needs to be based on the patient's condition, patient's acceptance and response to treatment. Treatment will only be discontinued following consultant review.
Preparations available:	Methotrexate is available as 2.5mg and 10mg tablets. NOTE. It is advisable that only one strength of methotrexate is prescribed and dispensed to avoid errors

Summary of adverse effects: (See summary of product characteristics (SPC) for full list http://www.medicines.org.uk/emc/medicine/21378)

Adverse effect (frequency)	**Management**
WBC (uncommon)	<4.0X10^9/l Contact the hospital specialist team.
Neutropenia (uncommon)	If the neutrophils <2 x 10^9/L contact the hospital specialist. If neutrophils <1.5 x 10^9/L, stop medication and contact hospital specialist.
Platelets (uncommon)	Reduce dose by 25% and recheck bloods If <150 x 10^9/L contact hospital specialist.
Lymphocytes (uncommon)	<0.5 x 10^9/L contact hospital specialist.
Varicella (Unknown)	If in contact with the virus, non-immune patients require two weeks of oral Aciclovir 800mg 5 times daily and inform hospital specialist.
Nausea, vomiting or diarrhoea (common)	Can be improved by dividing or reducing the dose, or increasing the dose of folic acid.
Abnormal bruising /bleeding/ fever/severe sore throat (uncommon)	Stop – discuss with hospital specialist team; check FBC immediately and withhold until the result of FBC is available.
Significant reduction in renal function (uncommon)	Any abnormality, attempt to identify alternative cause. Repeat bloods and contact hospital specialist. If grossly abnormal (twice the normal range) Withhold and contact hospital specialist immediately for advice.
Flu like illness/ general aches and pains/general malaise (unknown)	This could possibly part of a hypersensitivity reaction. Discuss with the gastroenterology specialist team.
Severe or persistent infection-pneumonitis –unexplained respiratory symptoms such as dyspnoea and dry cough, especially with fever & sweats. (Uncommon/Very rare)	Stop medication, take FBC, CRP and contact hospital specialist.
Macrocytosis (MCV>ULN) (unknown)	This typically does not signify a medical concern. Check serum folate and B12 & TSH. Treat any underlying abnormality. If results are within normal parameters discuss with hospital specialist team.

Rash (common) **Oral Ulceration** (unknown)	If rash is a significant new rash, stop treatment until resolved and check FBC. If FBC abnormal, contact hospital specialist. Wait until rash resolved and consider restarting at reducing dose provided no blood dyscrasias.
Liver impairment (common) Abnormal LFTs (ALT or ALT > x2 ULN Threefold rise in transaminase	Any abnormality, attempt to identify alternative cause. Repeat bloods and contact hospital specialist. Reduce dose by 25%, consider withholding and contact hospital specialist immediately for advice. Isolation of GGT does not require alteration of dose. Stop medication and contact hospital specialist.
Hair loss (common)	Discuss with hospital specialist team.
Lymphomas (uncommon)	Stop medication and contact the hospital specialist team.
Ulcerative stomatitis (common)	May respond to increasing the dose of folic acid, contact hospital specialist team.
Monitoring Requirements by specialist: Pre-treatment assessment will include:	• Annual influenza vaccination should be administered or advised. • Chest X-ray- to exclude pneumonitis & as comparison should subsequent pulmonary side effects occur. • Pregnancy test and date of last menstrual period for women of childbearing potential. • Liver biopsy should be considered if heavy alcohol consumption, chronic hepatitis B or C or abnormal LFT's. • FBC, U&Es, LFTs, CRP prior to starting methotrexate.
Monitoring Requirements by GP:	Careful monitoring is essential during treatment, as this is an immunosuppressive drug. See table below for regimen

Time period of treatment	***Frequency of monitoring***	***Monitoring to be carried out by***	***Test to be done***			
			FBC	**LFTs**	**CRP**	**U&Es**
0-8 weeks	*Weekly*	*Consultant*	✓	✓	✓	✓
8 weeks-3months	*Fortnightly*	*Consultant*	✓	✓	✓	✓
>3 months and stable dose for 6 weeks	*Monthly*	*GP*	✓	✓	✓	✓
>6 months and dose stable	*3 monthly*	*GP*	✓	✓	✓	✓
Any dose adjustment	*2 weeks post dose change then monthly*	*Consultant or GP following discussion*	✓	✓	✓	✓
All patients	*6 monthly*	*GP*	✓	✓	✓	✓

Increased frequency of blood monitoring should be effectively communicated. Situations where increased frequency of blood monitoring may be required:

- Downward trend in WBC or neutrophil count
- Renal impairment
- Following a dose change
- Mild to moderate hepatic impairment
- Concomitant drug therapy

Explicit criteria for review and discontinuation of the medicine
Other benchmark values may be set by secondary care in specific clinical circumstances. This will be

communicated by secondary care	
Clinically relevant drug interactions: For more detailed information please refer to current BNF and product SPC.	**Drug interactions** • sulphonamides (including hypoglycaemics) – possible increase in methotrexate levels • co-trimoxazole / trimethoprim - Close monitoring of FBC is required, as it increases the risk of hematological toxicity. • NSAIDS – increases methotrexate toxicity • Probenecid – significantly increases methotrexate levels • oral salycilates (low dose aspirin probably OK) • theophylline – reduced theophylline clearance • diuretics – thiazides including bendroflumethiazide • Acitretin - ↑incidence of liver toxicity Other considerations • Alcohol – possible increased risk of hepatic cirrhosis/fibrosis • Avoid folic acid / folinic acid administration on same day as methotrexate In some instances, concomitant medication will be clinically justified. Please check with Medicines information before commencing concomitant methotrexate. Close monitoring of FBC is required with concomitant use.
Clinically relevant Precautions and Contraindications:	**Live vaccines** are contraindicated during and up to 3 months after treatment. If possible, vaccinate non-immune patients prior to immuno-suppressive treatment dependent on the results of the examinations. This will be performed by the specialist. **Renal impairment** As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal impairment, which may result in severe undesirable effects. Where renal function may be compromised, monitoring should take place more frequently. This applies in particular, when medicinal products are administered concomitantly, which affect the elimination of methotrexate, cause kidney damage or which can potentially lead to impairment of blood formation. Dehydration may also intensify the toxicity of methotrexate. **Liver function tests** Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the consultant gastroenterologist
Pregnancy and lactation	• Methotrexate is teratogenic and embryotoxic and is unsuitable for those of child-bearing age. • Women should stop 3-6 months before conception, men at least 4 months beforehand (allowing for 6 week washout of toxic metabolites and 2.5 months for spermatogenesis). • Healthy pregnancies have occurred in women taking methotrexate so abortion is not mandatory, but should be discussed.

	• If pregnancy is to continue, stop Methotrexate and provide high dose folic acid (15mg daily) for a minimum of 6 weeks. • Methotrexate should be avoided in breastfeeding
	Special warnings Patients must be clearly informed that the therapy has to be administered **once a week**, not every day. Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore treatment with methotrexate should only be initiated and supervised by physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed by the physician of the risks involved and the recommended safety measures.
Treatment of overdose:	If the error is not considered serious, check bloods and miss next dose. If it is serious, urgent treatment with calcium leucovorin or calcium folinate may be required in hospital. Contact A & E department immediately. Calcium Leucovorin (calcium folinate) is the antidote often referred to as folinic acid for neutralising immediate toxic effects of methotrexate.
Practical issues:	It is advised that only one strength of methotrexate tablets is dispensed (either 2.5mg OR 10mg) to make up doses to avoid error
Supply of ancillary equipment	N/A
Key references:	IBD Standards Group, 2009. Quality Care - Service standards for the healthcare of people who have Inflammatory Bowel Disease (IBD). Available online: http://www.bsg.org.uk/attachments/160_IBDstandards.pdf Further information sources: ECCO 2009 Guidelines on prevention, diagnosis and management of opportunistic infections in IBD

Appendix 1: Methotrexate Letter to GP

Department of Gastroenterology
Inflammatory Bowel Disease
Dr S Lanzon-Miller
Dr R Madhotra
Dr G MacFaul

Surname:

Forename:

DOB:

Hospital No:

Date:
Diagnosis:
Re: Methotrexate Monitoring

Dear Dr.
The above patient was seen in the Gastroenterology clinic today and treatment with **Methotrexate** has been initiated. I am writing to invite you to participate in the shared care management of this patient. Please refer to the shared care guideline enclosed. You can also access an electronic copy of the SCG at: http://www.formularymk.nhs.uk/Shared-Care-Guidelines/

The patient has been on mg once weekly administered intramuscularly for the first twelve weeks of treatment, and is due to complete this course on / / . The patient will require mg oral methotrexate for the remainder of treatment to commence on / / .
We have provided 4 weeks supply of methotrexate and folic acid. We would be grateful if you can continue the prescribing. Clinical response can usually be expected by 6-12 weeks.

Folic acid 5mg PO, should also be prescribed for use three days after methotrexate administration. This helps reduce anaemia, nausea & vomiting side effects. This should NOT be taken on the same day as the methotrexate treatment.

Please note that although methotrexate is not licensed for use in IBD, this regimen is in line with national guidelines. Further information can be found in the link above.
The risks and benefits of treatment have been discussed with the patient and counselling given regarding the importance of compliance with the blood monitoring programme during treatment. Treatment will be discontinued if not compliant with monitoring.

We are grateful for your help in prescribing of the oral treatment and monitoring this patient. Thank you for your help in advance.
Yours sincerely
Print name: ……..Designation:…….……

Contact details:
Should you have any further questions or need advice, consult the specific health professional using the contact numbers below:

Inflammatory Bowel Disease Nursing team	Telephone: 01908 996955, Monday – Friday Email: IBDNursingTeam@mkhospital.nhs.uk
Dr Sandro Lanzon-Miller MD FRCP, Consultant Physician / Gastroenterologist	Telephone/ facsimile: 01908 243867 (Secretary 8.00am to 4.00pm)
Dr Ravi Madhotra MD FRCP, Consultant Physician / Gastroenterologist	Telephone / facsimile: 01908 243751 (Secretary 8.00am to 4.00pm)
Dr George MacFaul MD FRCP, Consultant Physician / Gastroenterologist	Telephone / facsimile: 01908 243308 (Secretary 8.00am to 4.00pm)

To be completed by the GP and returned to the hospital consultant above

Please sign and return your agreement to shared care within 14 days of receiving this request (tick which applies)
□ I accept sharing care as per shared care prescribing guideline and above instructions
□ I would like further information. Please contact me on:……
□ I am not willing to undertake shared care for this patient for the following reason:
……

GP name: ……GP signature: ……
Date: ……../……../……..