Methotrexate

Traffic light classification- Amber 1
Information sheet for Primary Care Prescribers
Part of the Shared Care Protocol: Management of Inflammatory Bowel Disease IN ADULTS with AZATHIOPRINE, 6-MERCAPTOPURINE or METHOTREXATE

Indications:
Maintenance of remission of adult patients with inflammatory bowel disease – unlicensed but in line with national guidelines[1].

Any patients to be excluded from shared care:
Patients receiving;
- doses more frequently than once a week,
- 10mg tablets,
- subcutaneous therapy,

are excluded from shared care i.e. classified as RED on the Nottinghamshire joint Formulary (www.nottinghamshireformulary.nhs.uk)

Therapeutic Summary
Methotrexate acts in an anti-inflammatory manner, probably through inhibition of cytokine and eicosanoid synthesis. Currently methotrexate is positioned as a second-line immunosuppressive agent in patient resistant or intolerant of azathioprine or mercaptopurine.
Patient reported adverse effects usually occur early in therapy, but please see explicit criteria for review below.

Products available
Methotrexate 2.5mg tablets ONLY

Dosages and route of administration
Methotrexate is given orally **once per week**. The patient is advised to take the treatment on the same day each week and the day of the week is defined in the NPSA booklet to avoid confusion. The initial dose and subsequent dosing will be determined by secondary care and recorded within the NPSA monitoring booklet and by written communication.

Methotrexate will be prescribed a dose of 10mg up to 25mg weekly for maintenance treatment in this patient group.[5]

The prescriber should decide with the patient which day of the week the patient will take their methotrexate and specify the day of intake on the prescription.[3]

Methotrexate is the subject of a National Patient Safety Agency (NPSA) alert available from: www.npsa.nhs.uk. This alert recommends that all prescribers must avoid the use of 'as directed' in the dosage instructions box. Prescribers should be aware that patients often understand their dose by the number of tablets they take; therefore **it should be clear which strength tablets the patient is taking**.

Example prescription: Methotrexate **2.5mg tablets,** take **six tablets (15mg)** once a week**.**

Folic acid 5 mg should be prescribed concurrently to reduce likelihood and severity of side-effects associated with methotrexate and improves continuation of therapy and compliance. The dosing will be specified by letter from the Gastroenterology team and in the NPSA booklet.

Duration of treatment
There is no set duration of treatment with methotrexate, as evidence in the area is lacking. Patients usually will be on treatment for up to 5 years but occasionally this can be longer - prolonged use may be considered if needed. Potential risks and benefits should be discussed on an individual basis.

Monitoring Requirements and Responsibilities

Pre-treatment assessment to be performed by specialist and will include:

- FBC, LFT, U&E and chest X-ray[1,2]

On-going monitoring: [2]

Time period in treatment	Frequency of monitoring	Tests to be done		
		FBC	LFT	U&E
0-6 weeks	Fortnightly	✓	✓	✓
6 weeks – 3 months	Monthly	✓	✓	✓
>3 months and stable dose for 6 weeks	3 monthly*	✓	✓	✓
Any dose increase	2 weekly post dose increase then revert to above protocol	✓	✓	✓
* The Gastroenterology Specialist team may advise more frequent monitoring if patients at higher risk of toxicity as appropriate				

- Patient to report any rash, oral ulceration, sore throat, abnormal bruising or bleeding.
- No additional monitoring requirements are required in primary care for patients receiving additional biological therapy including anti-TNF therapy.
- **Routine influenza and pneumococcal vaccinations are highly recommended**.

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.[2]

Adverse Event	Action
Nausea and vomiting or diarrhoea	Withhold until discussed with gastroenterology specialist team.
WBC <3.5x10^9/l	Withhold until discussed with gastroenterology specialist team.
Neutrophils <1.6x10^9/l	Withhold until discussed with gastroenterology specialist team.
Platelets <140x10^9/l	Withhold until discussed with gastroenterology specialist team.
AST / ALT > twice upper limit of reference range AND the ALT:AST ratio is greater than 0.8	Withhold until discussed with gastroenterology specialist team.
Rash or oral ulceration	Withhold until discussed with gastroenterology specialist team.
New or increasing dyspnoea or dry cough	Withhold until discussed with gastroenterology specialist team.
Macrocytosis (MCV>upper limit of **reference range**)	Withhold[3] and check serum folate and B12 & TFT. Treat any underlying abnormality. If results are normal, interrupt treatment until discussed with gastroenterology specialist team.
Unexplained eosinophilia >0.5 x 10^9/l	Withhold until discussed with gastroenterology specialist team
Abnormal bruising / fever /severe sore throat	Immediate FBC. Withhold until results available and discuss with gastroenterology specialist team.
Albumin- unexplained fall (in absence of active disease)	Withhold until discussed with gastroenterology specialist team.
Mild to moderate renal impairment (CrCl 30-59 ml/min)	Withhold until discussed with gastroenterology specialist team for possible 50% dose reduction. Must not be used if CrCl <30 ml/min.[3]

In addition to absolute values for haematological or biochemical indices a rapid fall or rise or consistent downward or upward trend in any value should prompt caution and extra vigilance

For a full list of Side Effects refer to the BNF or Summary of Product Characteristics.

IF YOU ARE IN ANY DOUBT ABOUT ANY POTENTIAL ADVERSE REACTION, PLEASE CONTACT THE GASTROENTEROLOGY SPECIALIST TEAM.

Relevant Contraindications

- **TRIMETHOPRIM, Co-TRIMOXAZOLE and other anti-folate drugs – see interactions**
- Hypersensitivity to methotrexate or to any of the excipients
  Pregnancy (see below) and breast feeding
- Significant hepatic impairment and excessive alcohol consumption
- Liver disease including fibrosis, cirrhosis, recent or active hepatitis unless specified specifically by the secondary care team.
- Severe / significant renal impairment (i.e. CrCl <10ml/min)
- Severe acute or chronic infections, immunodeficiency syndromes and malignancies
- Pre-existing blood dyscrasias (i.e. bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia)
- Underlying lung disease
- Stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcer disease
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at www.dh.gov.uk): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. N.B. Routine influenza and pneumococcal vaccinations are highly recommended.

Relevant Precautions

- Localised or systemic infection including hepatitis B or C and history of tuberculosis.
- Severe / significant renal failure (dose reductions may be required when CrCl <60ml/min).
- Blood disorders
- Alcohol – advise patient to remain well within national guidelines.
- Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Patients should be advised to contact their GP immediately should they develop persistent cough or dyspnoea.
- Patients who have no history of exposure to varicella zoster virus (VZV) i.e. chickenpox or herpes zoster (shingles), should avoid contact with individuals with chickenpox or herpes zoster. Varicella–zoster immunoglobulin (VZIG) is recommended for individuals who are at increased risk of severe varicella (including patients taking immunosuppressant medicines e.g. azathioprine, ciclosporin, methotrexate, leflunomide) and who have no antibodies to varicella–zoster virus and who have significant exposure to chickenpox or herpes zoster. See https://www.gov.uk/government/publications for detailed guidance. If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.

Pregnancy

Methotrexate is teratogenic and embryotoxic, henceforth, patients ***must not become pregnant*** whilst taking this drug. Women need to stop the drug for 6 months before attempting to become pregnant.[1, 3] The same advice applies to men wishing to start a family.

In the event of a woman falling pregnant whilst taking methotrexate, the drug should be discontinued immediately and high dose folic acid (15mg daily) provided for at least 6 weeks.[1] Please access urgent advice from the local fetomaternal medicine / obstetric unit.

Clinically relevant medicine interactions and their management

- **TRIMETHOPRIM – do not give concurrently with methotrexate.**
- Co-trimoxazole (Septrin®): Avoid concomitant use – due to anti-folate properties (severe bone marrow depression has been reported).
- Nitrous oxide: Concomitant use should be used with caution
- Aspirin and Non-steroidal anti-inflammatory drugs (NSAIDs): Aspirin or other NSAIDs are thought to increase the potential toxicity of methotrexate, and therefore, the type and dose of NSAID should not be altered during methotrexate therapy without prior consultation with the gastroenterology specialist team. However, they should not be stopped just because the patient is starting methotrexate as the drug takes 1-2 months to exert an effect and the patient is likely to need the NSAID in the long-term.
- Phenytoin and levetiracetam: antifolate effect of Methotrexate increased (increase toxicity) – caution in use, increase frequency of monitoring.

- Proton Pump Inhibitors (e.g. omeprazole, lansoprazole, pantoprazole): prolongs the elimination of methotrexate via the kidneys. Stop 4 to 5 days before initiation and consider alternatives such as H2-receptor antagonists.[6]
- Antibacterials *other than* trimethoprim and co-trimoxazole: Excretion of methotrexate may be reduced (increased risk of toxicity) – caution in use, increase frequency of monitoring.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book': Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. Inactivated polio is available although suboptimal response may be seen.
- Clozapine – increased risk of agranulocytosis
- Probenecid - reduces the excretion of methotrexate increasing its toxicity
- Acitretin: Avoid concomitant use – increased Methotrexate concentration and hepatotoxicity.

For a full list of contraindications, precautions and drug interactions refer to the BNF or Summary of Product Characteristics.

Information given to patient

- Patients must be given an NPSA pre-treatment information leaflet and a patient held monitoring and dosing booklet by gastroenterology when they start methotrexate treatment.
- The patient must be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, fever, bruising, bleeding, unusual weakness and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, diarrhoea and dark urine), and respiratory effects (e.g. shortness of breath or dry cough) to the GP.[8]
- Patients should be advised to avoid contact between themselves and individuals with chickenpox or shingles if they have no prior history of exposure. Any exposure of patients with no varicella–zoster virus antibodies to chickenpox and shingles sufferers should be reported to the GP for assessment and possible treatment.
- Female patients will be advised of the need to avoid pregnancy during therapy and for 6 months after stopping methotrexate.
- A patient information leaflet is available from Crohn's and Colitis UK.

Community Pharmacist's Role[7]

For patients taking methotrexate:

1. The pharmacist will ask to see the patient's monitoring booklet and check if any dose changes have been made since the last prescription issue.
2. The pharmacist must ensure the strength of the tablet supplied to the patient is consistent to prevent any confusion about the number of tablets the patient must take. Confirm strength to be supplied with the prescription and the patient's monitoring booklet. If in any doubt, contact the prescriber for confirmation.
3. Counsel the patient about their methotrexate, telling them the dose in terms of quantity of tablets and (in the vast majority of cases) weekly frequency, providing the patient with a monitoring booklet if they do not already have one.
4. Ensure the patient can differentiate between their folic acid and methotrexate and know how to take them both.
5. Be aware of patients who attend with symptoms such as breathlessness, dry persistent cough, vomiting or diarrhoea, as these can be signs of oral methotrexate toxicity or intolerance. Refer them back to the prescriber for further investigation. It is good practice to maintain a record of any over-the-counter items supplied to the patient.

Patient's Role

- The patient should take the methotrexate medicine on the same day every week.[8]
- Inform all healthcare professionals of their current medication prior to receiving any new prescribed or over-the-counter medication.
- Read the information supplied by their GP, specialist and pharmacist and contact the relevant practitioner if they do not understand any of the information given.
- The patient will report any suspected adverse reactions (as above) to the GP for assessment.
- The patient will report to their GP or specialist any new onset breathlessness, dry persistent cough, vomiting or diarrhoea, fever or sore throat, mouth ulcers, skin rashes, bleeding or unusual weakness, as these can be signs of toxicity or intolerance of methotrexate.

- Patients who are taking methotrexate will ensure they have a patient information leaflet and monitoring document, and bring it to all appointments with healthcare professionals, including GPs, consultants, pharmacists, dentists etc.
- Patients are advised to avoid self-medication with over-the-counter aspirin or Ibuprofen.
- Always attend your scheduled clinic visits and blood test appointments.[8]
- Attend routine influenza and pneumococcal vaccinations.
- Request supply of maintenance therapy in a timely manner, and store medication securely away from children.

References

1. Lamb, CA., Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut2019;68:s1-s106
2. Ledingham, J., Gullick, N. et al. (2017) BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology **56**(6), 865-868.
3. Summary of Product Characteristics for Methotrexate [28/02/2019], accessed 28/08/2020, link
4. Hausmann J, Zabel K, Herrmann E, et al. Methotrexate for maintenance of remission in chronic active Crohn's disease: Long-term single-center experience and meta-analysis of observational studies. Inflamm Bowel Dis 010; 16:1195e202.
5. BNF. Publication last updated on 11/08/2020. (online), viawww.medicinescomplete.com , accessed 28/08/20
6. Baxter K (ed), *Stockley's Drug Interactions*. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com (accessed 28/08/2020).
7. NPSA patient safety alert #13; Improving compliance with oral methotrexate guidelines [accessed 28/08/2020].
8. European Medicines Agency. 2019. New measures to avoid potentially fatal dosing errors with methotrexate for inflammatory disease. [Online] available at www.ema.europa.eu (accessed 28/08/2020). link

There are no current NICE guidelines on the use of azathioprine, mercaptopurine or methotrexate for Inflammatory Bowel Disease further than reference in Crohn's and UC guidelines.

Version Control- **Methotrexate: Inflammatory Bowel Disease in Adults**			
Version	Author(s)	Date	Changes
2.1	Shary Walker	19/11/20	1. Added the new measure to avoid potentially fatal dosing error: "Prescribers should specify the day of the methotrexate intake on the prescription". 2. Updated the on-going monitoring and explicit criteria. 3. Relevant contraindications updated. 4. New updates: "In the event of a woman falling pregnant whilst taking methotrexate, the drug should be discontinued immediately and high dose folic acid (15mg daily) provided for at least 6 weeks". And also, the interval of stopping methotrexate for women trying to be pregnant was extended from 3 months to 6 months. 5. Relevant interactions updated. Interaction with proton pump inhibitors added. Consider H2 antagonists as the alternative. 6. Added more patients' roles and responsibilities