Methotrexate orally for Crohn's disease in Adults

It is vital for safe and appropriate patient care that there is a clear understanding of where clinical and prescribing responsibility rests between Consultants and General Practitioners (GPs).
This guideline reinforces the basic premise that:
When clinical and / or prescribing responsibility for a patient is transferred from hospital to GP, the GP should have full confidence to prescribe the necessary medicines. Therefore, it is essential that a transfer of care involving medicines that a GP would not normally be familiar with, should not take place without the "sharing of information with the individual GP and their mutual agreement to the transfer of care."
These are not rigid guidelines. On occasions, Consultants and GPs may agree to work outside of this guidance. As always, the doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Indications: Maintenance of remission of Crohn's disease if this was induced by intramuscular methotrexate.	**Dosage and administration:** 15mg orally ONCE PER WEEK Doses should be lowered for patients with renal impairment. Folic acid 5mg daily to be co-prescribed except for the day of methotrexate administration.

Additional Information: Excess alcohol must be avoided. Safe limits are viewed as the national guidelines i.e. no greater than 14 units per week.
All patients, male and female, should be advised against conception and pregnancy during treatment with methotrexate as it is an abortifacient as well as a teratogenic drug. Patients should be advised to continue contraception for at least 3 months after stopping methotrexate.
Patients should be advised to report all symptoms and signs suggestive of infection, especially sore throat.

Monitoring requirements:

Before treatment:

- Full blood count (FBC), urea and electrolytes (U&Es), creatinine and liver function tests (LFTs)
- Chest X Ray (unless done within previous 6 months) Screen with Varicella Zoster Virus (VZV) serology, Hepatitis B surface Antigen, HIV serology
- Pneumococcal and annual seasonal influenza vaccinations are recommended for all. Consider Varicella and Hepatitis B vaccination in non-immune patients prior to treatment.

During treatment:
FBC, LFTs, U/Es and creatinine every 2 weeks until dose and results stable for 6 weeks; monthly thereafter. If patient's results remain stable, monitoring can be reduced to every 2-3 months.
If dose is increased, repeat FBC, LFTs, U&Es & creatinine weekly for one month then return to monthly.
The hospital will be responsible for prescribing the first 4 weeks of oral methotrexate.

Action to be taken if abnormal results/adverse effects:

WBC < 3.5 x 10^9/l or Neutrophils < 2.0 x 10^9/l or Platelets < 150 x 10^9/l	Withhold treatment and recheck in 1 week, discuss with consultant in charge.
MCV > 105fl	Check serum B12, folate & TFT and discuss with consultant in charge.

AST, ALT > 2 fold rise (from the upper limit of the reference range) **Stop if bilirubin >85.5 micromol/L**	Consider for liver biopsy when persistent elevation occurs - Discontinue treatment in patients with abnormal LFTs who decline liver biopsy.
Hypoalbuminaemia – Unexplained fall in the absence of active disease	Monitor closely and consider need for liver biopsy.
Nausea	Nausea occurs commonly and may be reduced by changing timing of dose (before bedtime), ensure adequate intake of folic acid, and consider anti-emetic at time of weekly dose.
Rashes **Oral ulceration** **Vomiting and diarrhoea**	Withhold treatment and reassess in 1 week, discuss with consultant in charge.
Renal function – significant deterioration compared to baseline or upper limit of normal of reference range	Withhold treatment and recheck immediately, discuss with consultant in charge.
Severe sore throat **Abnormal bruising**	Immediate FBC and withhold treatment until the result of FBC is available.
New or increasing dyspnoea or dry cough	Withhold treatment, arrange CXR and pulmonary function tests, discuss with consultant in charge.

Contraindications:

- Significant chronic liver disease
- Pregnancy (see additional information)
- Breastfeeding
- Pre-existing blood dyscrasias, such as significant marrow hypoplasia, leukopenia, thrombocytopenia or anaemia
- Active Infections
- Live vaccines are contra-indicated on theoretical grounds.
- Hypersensitivity to methotrexate and/or excipients.
- Significant pleural effusion
- Severe renal impairment (<20ml/min)
- Alcohol excess/abuse

Significant Drug interactions: (For full information see current edition of the British National Formulary (BNF))

- Avoid concomitant administration of co-trimoxazole or trimethoprim with methotrexate – can cause severe bone marrow suppression.
- Probenecid and penicillins reduce methotrexate excretion (increased risk of toxicity) – for patients in whom it is unavoidable to co-prescribe penicillins and methotrexate closer monitoring is recommended.
- Non-steroidal anti-inflammatory drugs (NSAIDs) also reduce excretion of methotrexate. However, NSAIDs in addition to methotrexate are not contra-indicated.
- Other significant drug interaction: ciclosporin, antimalarials (pyrimethamine), Antiepileptics (phenytoin, levetiracetam), Leflunomide, Retinoids (acitretin)

Cautions:

- Peptic ulceration
- Ulcerative colitis
- Ulcerative stomatitis
- Risk of accumulation in ascites or pleural effusion – drain before treatment
- Acute porphyria
- Significantly impaired hepatic function
- **Inactive chronic infections (herpes zoster, TB, hepatitis B and C) due to possible activation)**

Adverse Effects:

Cardiovascular	Pericarditis
Eye	Visual disturbances
Fertility	Defective oogenesis & spermatogenesis, impaired fertility, menstrual disturbances, teratogenic
Gastrointestinal	Nausea & vomiting, dyspepsia, diarrhoea, mucosal ulceration of intestinal & oral epithelium, stomatitis, toxic megacolon
Haematological	Leucopenia, infection, septicaemia, chills & fever, thrombocytopenia, anaemia
Kidney	Renal toxicity, inflammation & ulceration of urinary bladder, dysuria
Liver	Rise in serum transaminases, cirrhosis, fibrosis & fatty degeneration of liver
Musculoskeletal	Vasculitis, arthralgia myalgia •
Nervous system	Headache, tiredness, drowsiness, neurotoxicity
Respiratory	Pneumonia, interstitial alveolitis / pneumonitis often associated with eosinophilia, pulmonary fibrosis. Symptoms indicating potentially severe lung injury are dyspnoea, dry non-productive cough and fever
Skin	Changes in skin and nail pigmentation, erythema, pruritus, urticarial, herpetiform eruptions of skin, herpes zoster, vasculitis, photosensitisation, exanthema, rheumatoid nodulosis, Stevens-Johnson syndrome, epidermal necrolysis

For more information see the relevant summary of product characteristics

Specialist responsibilities:

- Obtain baseline blood results for FBC, LFTs and U&Es.
- Discuss with the patient, the benefits and side effects of treatment.
- If the patient is a woman of child bearing potential or male – ensure that they are aware of the importance of effective contraception and the need to discuss with their consultant if they wish to become pregnant.
- Issue and explain the NPSA methotrexate patient information and patient-held blood monitoring and dosage record booklet.
- Discuss how the patient / carer can be aware of possible signs methotrexate toxicity or intolerance.
- Ensure that the patient understands and accepts their responsibilities (see section below).
- Seek consent for treatment and document in the patient's notes.
- Explain the weekly dosage regimen.
- Discontinue methotrexate if no response, or if significant adverse event occurs.
- Update the patient's NPSA booklet with any dose changes.

- Promptly communicate with the GP via a clinic letter any changes in treatment, results of monitoring undertaken, and assessment of adverse events. The clinic letter should clearly state if the dose has remained the same or if a dose adjustment had been made – specifically highlighting the new dose in comparison with the preceding one.
- Advise GPs when to stop treatment.
- Report serious adverse events (e.g. those requiring hospitalisation) to the Medicines and Healthcare Regulatory Agencies (MHRA) or the Committee on Safety of Medicines (CSM).
- Provide clear arrangements for back-up, advice and support.

GP's responsibilities:

- Monitor the FBC, LFTs and U&Es as per recommended schedule and document in the patient's **monitoring booklet.**
- **Once the specialist has recommended continuation following the trial period provide the patient with monthly repeat prescriptions of methotrexate, stating the total once weekly oral dose. The patient should allow at least 48 hours for the GP to generate a prescription.**
- Ensure patient's NPSA booklet and practice computer systems are updated with any dose **changes.**
- Refer promptly to the specialist if there is a change in the patient's status or concerns **regarding compliance. In most cases, do not stop treatment without discussion with the Inflammatory Bowel Disease (IBD) Helpline on 0151 678 5111.**
- **If patient fails to attend more than 2 monitoring visits it is not safe to continue treatment – contact the IBD Helpline for advice.**
- **Report serious adverse events to the specialist and CSM.**
- **Administer Pneumococcal Vaccine/ Pneumovax® II and annual influenza vaccines.**
- **Consider passive immunisation with Varicella zoster immunoglobulin in non-immune patients exposed to chicken pox or shingles**.

Patient's responsibilities:

- Read the written patient information provided about the drug and have a clear understanding of the risks / benefits of subcutaneous methotrexate treatment.
- Attend for blood tests.
- Limit intake of alcohol to the national safe weekly limits.
- Report any adverse effects to their GP and/or specialist whilst treated with methotrexate.
- Take monitoring booklet every time the patient sees the GP, has a hospital appointment or visits the pharmacist.
- Report suspected pregnancy of patient/partner

Secondary care review:
Once disease controlled: 6-12 monthly review by Consultant

Availability:

Back up advice and support: Name, designation and contact telephone number)	Lynn Gray, IBD Nurse Consultant, IBD Helpline 0151 678 5111, Extension 2944

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