BNSSG Shared Care Guidance
Please complete all sections

Section 1: Heading

Drug	Methotrexate
Amber *one month*	
Indication	Induction and maintenance of remission in Crohn's Disease and Ulcerative Colitis (rarely) For steroid refractory or steroid-dependent disease.
Speciality / Department	Gastroenterology
Trust(s)	North Bristol NHS Trust
	Weston
	Click here to enter details

Section 2: Treatment Schedule

Usual dose and frequency of administration	Dosage schedule 1. Initially 25mg once a week orally 2. Decrease to 15mg once a week orally after 3 months as tolerated according to response. Some patients may be switched to subcutaneous methotrexate if oral absorption is low or if gastric side effects are intolerable. Some patients may be initiated on subcutaneous methotrexate is oral absorption is likely to be problematic e.g. past history of bowel surgery. Normal dose is between 15mg and 25mg weekly (syringes/pre-filled pens available in 2.5mg dose increments). All prescriptions for subcutaneous methotrexate in both primary and secondary care should state the generic and brand name. A lower staring dose may be required for the elderly or frail or for those patients with renal impairment (see SPC for methotrexate). Folic acid 5mg orally once a week, not on the same day as methotrexate, should be co-prescribed as it reduces the toxicity and side effects associated with methotrexate.

	As it can take up to 3 months for methotrexate to fully work, oral steroids are often started to bridge symptoms and tapered over 8-12 weeks.
Route and formulation	Oral or Subcutaneous 2.5mg tablets (10mg tablets are available but should not be used as per NPSA advice) Sub-cutaneous injection via prefilled pen or syringe. All prescriptions for subcutaneous methotrexate in both primary and secondary care should state the generic and brand name.
Duration of treatment	Ongoing

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist.

Baseline tests - where appropriate
1. FBC 2. U&Es 3. LFTs 4. Infection screening will preferably occur at diagnosis of IBD - check the 'Prevention of Opportunistic Infection in IBD patients' record before initiating methotrexate. Varicella status, history of MMR/DTaP vaccination, Hep B status, history of HPV vaccination (women only), CMV status, HIV status (high risk patients).
Subsequent tests - where appropriate
1. FBC, LFTs and U&Es - once a fortnight until dose is stable (if initiated on increasing dose) or for 1 month (if initiated on target dose), then monthly for 3 months, then every 3 months once the patient has been on a stable dose for 3 months. 2. Chest x-ray and lung function tests if symptoms occur. Withdraw treatment if there are pulmonary symptoms and review whether they may be due to infection or underlying pulmonary disease. 3. Consider fibroscan or liver biopsy if LFTs are persistently abnormal.

Section 4: Side Effects

Please list the most common side effects and management. Please provide guidance on when the GP should refer back to the specialist.

Side effects and management	The incidence and severity of adverse effects is thought to be dose-related. Common: -Anorexia, nausea, vomiting, diarrhoea, ulcerative stomatitis rarely gastrointestinal ulceration. - Alopecia (usually minor). - CNS disturbances (headache, drowsiness, blurred vision). - Symptoms of a cold or flu. Less Common: - Hypersensitivity reactions (fever, rigors, rash).

	- Bone marrow suppression (leucopaenia, thrombocytopaenia, anaemia), higher risk in elderly patients or those on other drugs which can also suppress bone marrow. Rare: - Hepatotoxicity (liver cirrhosis reported). Hepatotoxicity may be minimised by avoiding administration in patients with significant alcohol consumption, type II diabetes, obesity and concurrent liver diseases which may cause steatohepatitis. - Pulmonary toxicity (interstitial pneumonitis often associated with eosinophilia, rarely pulmonary fibrosis) (see BNF for more information) The patient should be advised to report any signs of bone marrow suppression (i.e. infection, fever, unexplained bruising or bleeding). Methotrexate may possibly increase the risk of lymphoproliferative disorders. Chicken pox/shingles infection - stop and commence aciclovir. Methotrexate increases the risk of opportunistic infections. Side effects & actions to take: Lymphocytes <0.5 x 10 x 9/L - Stop and discuss with hospital specialist clinician. Neutrophils <1.5 x 10 x 9/L OR Total WBC < 3.0 x 10 x 9/L OR Platelets < 150 x 10 x 9/L Stop and discuss with hospital clinician. Recheck FBC in 1 week. >2-fold rise in AST, ALT or falling albumin - Stop and discuss with hospital specialist clinician. Consider fibroscan or liver biopsy if persistent. Oral ulceration/stomatitis - Stop and contact hospital specialist clinician. New or increasing dyspnoea or persistent cough (with no other obvious cause – suspected pneumonitis) - Stop, take CXR and consider pulmonary function tests, contact hospital specialist clinician. Abnormal bruising or bleeding - Stop until clinical recovery and then check FBC. If FBC abnormal contact hospital specialist clinician. Persistent or severe sore throat - Take FBC and contact hospital specialist clinician. Severe or persistent infection - Stop, take FBC and contact hospital specialist clinician. Nausea, abdominal discomfort - Add folic acid 5mg as above if not already taking it. Consider change of timing of dose to before bed or consider an anti-emetic at time of dose. If not effective reduce dose or stop methotrexate and contact hospital specialist clinician. Overdose:

	Leucovorin (calcium folinate) is a specific antidote which should be administered within one hour of overdose at the same or greater dose than methotrexate. Haematological and gastrointestinal symptoms are common in accidental overdoses where a patient takes the weekly dose every day. Renal function and FBC must be monitored closely.
Referral back to specialist	As above

Section 5: Drug Interactions

Please list clinically significant drug interactions (eMC link please click here)

Significant Drug Interactions	Excretion of methotrexate reduced by NSAIDs, with possible increased toxicity – avoid. Excretion also reduced by high-dose PPIs- use with caution, avoid if possible. Concomitant administration of a folate antagonist including septrin (co-trimoxazole), trimethoprim, sulfamethoxazole, pyrimethamine and nitrous oxide may cause acute megaloblastic pancytopenia - avoid. Tetracyclines, penicillins, ciprofloxacin, phenytoin, ciclosporin, cisplatin, leflunomide, acitretin or probenicid may increase the toxicity of methotrexate – monitor closely for adverse effects. (See BNF Appendix 1 for further details of interactions)
Reminder to ask patient about specific problems	See section 7

Section 6: Contra-indications, Cautions and Special Recommendations

Please list

1. Contraindications: Hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption, severe renal impairment (CrCl <20mL/min), pregnancy and breast-feeding, active infection and immunodeficiency syndromes, suspected pneumonitis, stomatitis, severe haematological impairment or profound deterioration in FBC, liver disease (fibrosis, ascites, cirrhosis, recent or active hepatitis or any abnormality of LFT's before therapy or during therapy, if LFT's do not normalise after 2 weeks).

2. Cautions: Moderate renal impairment (use lower dose), peptic ulceration, acute porphyria.

3. Alcohol consumption in moderation is not contra-indicated.

4. Patients should avoid live vaccines such as oral polio, oral typhoid, MMR, BCG and yellow fever whilst on methotrexate. Pneumococcal and flu vaccines are safe.

5. Atypical and potentially harmful responses could occur to live vaccines such as polio, oral typhoid, MMR, BCG and yellow fever. Live vaccines are contraindicated during methotrexate therapy, within 3 weeks of initiation and for 3 months after stopping. A diminished response to killed live vaccines is likely, e.g. Hepatitis B vaccine.

6. Patients should avoid unpasteurised milk or cheese, uncooked meat and raw vegetables to prevent Listeria Monocytogenes infection.

7. Patients should avoid contact with people who have active chickenpox or shingles and report any contact to their GP and hospital specialist. If immunosuppressed patients are exposed to chickenpox or shingles, they will need to be assessed for susceptibility and the need for aciclovir post exposure

prophylaxis, see: UKHSA guidance: Guidelines on post-exposure prophylaxis (PEP) for varicella/shingles and the Green Book Chapter 34.

8. Methotrexate may reduce spermatogenesis - male patients should consider avoiding methotrexate 3-6 months before conception.

9. The teratogenic risk for women persists for at least 6 weeks after cessation - women of child bearing age should use dual contraception during therapy and avoid conception ideally for 3-6 months after stopping methotrexate.

Section 7: Advice to the patient

Advice for prescribing clinician to inform patient

Inform patient that this is a weekly dose and how many tablets (2.5mg strength) to take.

Inform patient of the side effects, particularly infection/leucopenia and the need for regular blood tests. If the patient does not comply with the monitoring programme methotrexate should be ceased as it is unsafe.

Take the methotrexate book to all outpatient appointments, GP visits & when having methotrexate dispensed in a pharmacy. Ask the surgery to record blood results in this book or to provide the results for the patient to record themselves.

Avoid people with infections. Report all signs of infection to the GP.

Report any signs of bone marrow suppression (i.e. infection, fever, unexplained bruising or bleeding), liver toxicity (nausea, vomiting, abdominal discomfort or dark urine) and respiratory effects (shortness of breath) to the GP.

Do not drive or use heavy machinery if feeling fatigued or unable to concentrate.

Drink alcohol only in moderation.

Avoid over the counter aspirin or nonsteroidal anti-inflammatory drugs.

Section 8: Responsibilities for Secondary Care

Core responsibilities

1. Initiating treatment and prescribing for the first month
2. Undertaking the clinical assessment and monitoring for the first month.
3. Communicate details of the above in 1 and 2 to GP within the first month of treatment. This information should be transferred in a timely manner.
4. Refer patients to GP and provide information of further action where appropriate e.g. blood test is due.
5. To provide advice to primary care when appropriate.
6. Review concurrent medications for potential interaction prior to initiation of Methotrexate.
7. Stopping treatment where appropriate or providing advice on when to stop.
8. Reporting adverse events to the MHRA.
9. Reminder to ask patients about particular problems see section 5.

Other specific to drug

1. All communication (letters, patient held record books etc.), discharge prescriptions and FP10's should show the weekly dose, day of the week dose taken and usual strength of tablets the patient takes (NPSA).

2. Ensure the patient understands the risks and benefits, monitoring required and dose schedule and consents to treatment (NPSA).

3. Provide a patient held methotrexate book - either the standard NPSA purple book or a book produced locally to NPSA standards. Ask patients to bring their book to all hospital and GP visits and when having methotrexate dispensed in a pharmacy (NPSA).

4. Record initial dose in patient held methotrexate book.

5. Enter initial blood results into patient held methotrexate book or provide the means for the patient to do so themselves (NPSA).

6. Record current dose in patient held methotrexate book and update it if the dose changes (NPSA).

Section 9: Responsibilities for Primary Care

Core responsibilities

1. Responsible for taking over prescribing after the first month
2. Responsible for the clinical assessment and monitoring after the first month
3. Review of any new concurrent medications for potential interactions.
4. Reporting adverse events to the MHRA.
5. Refer for advice to specialist where appropriate.
6. Reminder to ask patients about particular problems see section 5.

Other specific to drug

1. All communication (letters, patient held record books etc.), discharge prescriptions and FP10's should show the weekly dose, day of the week dose taken and usual strength of tablets the patient takes (NPSA).

2. Enter blood results into patient held methotrexate book or provide the means for the patient to do so themselves (NPSA).

3. Record current dose in patient held methotrexate book and update it if the dose changes (NPSA).

4. Administer all appropriate vaccines as recommended by secondary care.

5. Never issue a prescription without first checking blood results are in acceptable parameters.

Section 10: Contact Details

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Section 11: Document Details

Date prepared	August 2013 approved JFG December 2013 Updated July 2018
Prepared by	Amy Phipps (Specialist pharmacist - gastroenterology) Updated Louise Chung/Cara Leung Specialist Pharmacists – Gastroenterology and Hepatology Change to information about PEP for varicella/shingles February 2023 added by BNSSG Formulary Team.
Date approved by JFG	September 2018
Date of review	July 2020
Document Identification: Version	Methotrexate IBD SCP NBT v2.2

Section 12: Collaboration

Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

1. Click here to enter details

Section 13: References

Please list references

1. Improving compliance with oral methotrexate guideline, NPSA 2006, accessed at http://www.nrls.npsa.nhs.uk/resources/?entryid45=59800 on 25/9/2015
2. BNF online http://www.evidence.nhs.uk/formulary/bnf/current section 10.1.13, accessed on 3/7/18
3. http://www.uptodate.com/contents/immunomodulator-therapy-in-crohn-disease?source=machineLearning&search=methotrexate+crohns&selectedTitle=2%7E150&sectionRank=1&anchor=H13#H13 accessed 25/9/2015
4. SPC methotrexate (Hospira) 2.5mg tablets https://www.medicines.org.uk/emc/ accessed 3/7/2018.
5. SPC methotrexate (Medac) Metoject pen solution for injection in pre-filled pen https://www.medicines.org.uk/emc/ accessed 3/7/2018.
6. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations, 2010, accessed at https://www.ecco-ibd.eu/images/6_Publication/6_3_ECCO%20Guidelines/2010_CD_guidelines_special_situations.pdf accessed 25/9/2015

7. Guidelines for the management of inflammatory bowel disease in adults, BSG (2010) http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/ibd/ibd_2011.pdf accessed 25/9/2015

8. Methotrexate Fact Sheet Crohn's and Colitis UK http://www.crohnsandcolitis.org.uk/Resources/CrohnsAndColitisUK/Documents/Publications/Drug-Info/Methotrexate.pdf accessed 25/9/2015