SHARED CARE GUIDELINE

Drug: Methotrexate in Adult patients
Specialities: Rheumatology, Dermatology, Gastroenterology

Introduction	**Indication:** Licensed: Rheumatoid arthritis, severe psoriasis, severe active juvenile idiopathic arthritis, severe psoriatic arthritis, mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines Off-license: Severe Eczema, Lichen Planus, Felty's syndrome, steroid-sparing use in Rheumatology, other inflammatory rheumatological conditions. N.B. Not all brands/formulations are licensed for all indications – please refer to individual Summary of Product Characteristic documents (available at the electronic Medicine Compendium https://www.medicines.org.uk/emc/) **Background:** Methotrexate is a folic acid antagonist and its major site of action is the enzyme dihydrofolate reductase. Its main effect is inhibition of DNA synthesis but it also impairs RNA and protein synthesis. Response to treatment cannot be expected before two or three months and may not occur until after six months of treatment. In Rheumatology and Dermatology, patients are usually commenced on oral methotrexate, but also may use injectable methotrexate. The GP may be advised by secondary care to initiate oral treatment, or the hospital may initiate, but any injectable treatment will be commenced by the hospital, and then the GP may be asked to continue treatment. In Gastroenterology, subcutaneous treatment is used, as it is licensed and efficacious, and will be commenced by the hospital before the GP is asked to continue treatment. **Definitions:** Stable dose – the dose will be titrated to achieve efficacy at the lowest dose. Once efficacy achieved and provided the patient can tolerate the dose and they have been on this dose and monitored for 6 weeks, this will be termed "stable dose". Stable bloods – results of blood tests remain outside the "alert" thresholds as set by national guidelines and have stayed at similar levels for at least two consecutive tests. N.B. The patient can continue to have active disease despite being on a stable dose or having stable bloods, so the "patient" is not referred to as "stable".
Forms	Oral Tablets: 2.5mg, (only 2.5mg should be used to avoid confusion; **do not use 10mg**) Methotrexate solution for injection:(pre-filled syringe, ranging from 7.5mg to 25mg) Methotrexate solution for injection:(pre-filled pen for subcut injection, ranging from 7.5mg to 30mg)
Dose & Administration	**RHEUMATOLOGY and DERMATOLOGY:** Starting dose is between 2.5-15mg oral ONCE WEEKLY, usually 10mg-15mg. The starting dose may vary depending on the indication and severity of the condition and patient characteristics such as age, renal function and other comorbid conditions. The dose of methotrexate may be increased incrementally by 2.5-5mg every 1-6 weeks until disease is stabilised. The maximum licensed dose is 25mg/week. Exceptionally the dose may be advised by secondary care to increase to 30mg weekly. Patients may be switched to methotrexate injection by the hospital if their response is suboptimal or they suffer from gastrointestinal side effects on oral methotrexate. **GASTROENTEROLOGY:** Starting dose is 15mg subcutaneous, ONCE WEEKLY for one week, then the dose of methotrexate is then increased, until response, to a maximum of 25mg subcutaneous ONCE WEEKLY. Treatment will be initiated by the hospital, as this is a local initiation regime. Dose reductions may be required if side effects are a problem. It is possible to step down to 15mg subcut weekly for maintenance, if appropriate, and a switch to oral treatment is possible if patients prefer, though it may be less effective, and is not currently licensed.

	FOLIC ACID (ALL PATIENTS): Folic acid 5mg should be given alongside methotrexate as per local use, typically this is 5mg daily except on the day of methotrexate.
Secondary Care Responsibilities	• Confirm the diagnosis • Exclude active infections. Check for absence of pregnancy in women of child-bearing age and ensure the patient understands the importance of contraception. Reliable contraception should be used by both men and women whilst on methotrexate and for at least 6 months after stopping methotrexate. • Discuss the benefits and side effects of treatment with the patient. Ensure that the patient understands the importance of ongoing monitoring, that dosing of methotrexate is ONCE WEEKLY, which warning symptoms to report, and how to manage treatment at home. • Ensure that the patient will begin folic acid treatment also. • Perform pre-treatment screening: FBC, LFTs, U&Es, creatinine/eGFR and chest x-ray (unless done within 6 months). Pulmonary function tests should be considered in patients with abnormal shadowing on x-ray. Dermatology must also test for P3NP before treatment. • Provide the patient with a monitoring and dosage record booklet and ensure that the patient knows when and where to attend for monitoring. Encourage the patient to take responsibility for ensuring that results of tests are entered in the monitoring booklet. • Gastroenterology patients are provided with the CCUK Information booklet https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/methotrexate • If initiating medication, specify the day of the week on the prescription as methotrexate is given ONCE WEEKLY; don't use the dose term 'as directed'. • For patients undergoing initiation and stabilisation: Provide the patient with prescriptions for methotrexate until on stable dose and undergoing 3 monthly monitoring. • Communicate clearly with the GP about the treatment plan, including whether the patient has been initiated on treatment already, and the details of ongoing shared care, including being specific about when the GP is expected to initiate or take over treatment supply. • If the GP is expected to initiate oral treatment from the first dose, this should be made clear in the correspondence. Confirmation that benefits/side-effects, dose, folic acid, contraception have been discussed and that pre-treatment screening has been undertaken must be provided. • Review the patient regularly to monitor the patient's response to therapy. • Advise the GP on management of any dose adjustments and when to stop treatment. • Ensure that clear backup arrangements exist for GPs to obtain advice (see Help and Advice) • Dermatologists should include P3NP screening for patients with psoriasis. • If an unlicensed dose/form/route is used, this must be discussed with the patient, and documented consent given. This information must be shared with the GP. **Methotrexate Injection:** • If a patient is initiated on / switched to methotrexate injection, provide one month's supply and a purple lidded cytotoxic sharps bin. The Sharp Safe and Sharps Guard cyto com-plus bins are examples of bins which will hold the pen device. • The first injection should be performed under direct medical or nursing supervision in secondary care. • Provide training on self-administration of methotrexate injection using the chosen brand. • Inform the GP that the patient has been initiated on / switched to methotrexate injection and of the dose and brand and form.

Primary Care Responsibilities	• Ensure that the patient understands that dosing is ONCE WEEKLY and which warning symptoms to report. • Specify the day of the week on the prescription; don't use the dose term 'as directed'. • Reinforce advice about using reliable contraception for both men and women whilst on methotrexate and for at least 6 months after stopping methotrexate. For women, prescribe or refer to contraceptive services to receive highly effective contraception or effective contraception with advice to use barrier methods. • Monitor at the recommended frequencies (see MONITORING below) and ensure that test results are recorded in the monitoring booklet. • Report any adverse events to the consultant or specialist nurse and stop treatment on their advice or immediately if an urgent need arises (see MONITORING below). • Report any worsening of control of the condition to the consultant or the specialist nurse. • Follow recommended immunisation programme. **Additionally, for Methotrexate tablets:** • Provide patient with prescriptions for methotrexate 2.5mg tablets and folic acid 5mg tablets. • Do not prescribe the 10mg tablets of methotrexate. **Additionally, for Methotrexate Injection:** • Provide patient with prescriptions for methotrexate injections and folic acid 5mg tablets. • Provide the patient with purple lidded cytotoxic sharps bins as required. The SharpSafe Cyto and SHARPSGUARD® cyto com-plus bins are examples of bins which will hold the pen device. • Ensure systems are in place for the patient to receive their weekly injection if they are not self-administering. • If the practice wishes to use a different brand or form, they should provide any additional training required, and ensure the patient continues to have appropriate waste disposal.
Help and Advice	**RHEUMATOLOGY:** Helpline 01228 814732 **GASTROENTEROLOGY:** Helpline 01228 814261 **DERMATOLOGY:** Helpline 01228 814156 If in doubt, it can be safer to pause treatment while waiting for a response to a query.
Immunisations	• Annual flu vaccine is recommended. • Pneumococcal vaccination recommended. • In patients exposed to chicken pox or shingles, if required, passive immunisation should be considered for varicella. Refer to Green book: Varicella: the green book, chapter 34 - Publications - GOV.UK • Live vaccinations to be avoided. Shingles vaccine can be given as a precaution if dose of methotrexate is <0.4mg/Kg/week.
Adverse Effects	N.B. Please see MONITORING below for adverse effects which require an intervention. This list is not exhaustive, please refer to SPCs and BNF. Headache, tiredness, drowsiness, erythema, pruritus, exanthema, dyspepsia, anorexia, leucopenia, anaemia, thrombocytopenia, pneumonia, elevated transaminases, nausea and vomiting, diarrhoea. Decreased resistance to infections.
Common Drug Interactions	**Trimethoprim and co-trimoxazole must be avoided** Antifolate effect of methotrexate also increased by phenytoin. Caution with drugs with potential hepatotoxic or nephrotoxic effects. Tolbutamide – increases serum concentration of methotrexate. NSAIDs, aspirin and penicillins are known to reduce the excretion of methotrexate causing an increase in serum level (increased risk of toxicity) but are not contraindicated.
Cautions	Alcohol – caution is required, advise to stay well within national recommendations. Ulcers of the oral cavity and known gastrointestinal ulcer disease. Current illness that may cause renal impairment.
Contra-indications	Pregnancy – both men and women are advised to take contraceptive precautions while on methotrexate and for 6 months after stopping methotrexate. Breastfeeding. Serious active infection (suspected local or systemic). Severe renal or hepatic impairment. High alcohol intake/ alcohol abuse. Pre-existing blood dyscrasias, such as bone marrow failure or significant anaemia. Hypersensitivity to methotrexate. Some live vaccines – see under immunisation.
This guidance does not replace the SPCs, which should be read in conjunction with this guidance.	

Monitoring and Adverse Events

Bloods required:

Treatment status	FBC	LFT	U+E, eGFR	(Calcium and) Albumin	ESR or CRP	P3NP
Initial monitoring or after dose increase	Every 2 weeks				Every 12 weeks (for RA and GE only)	N/A
Once dose/bloods are stable (see definition)	Monthly for 3 months then every 12 weeks				Every 12 weeks (for RA and GE only)	Annual for dermatology only (if elevated monitor every 3 months)

Monitoring frequency may be reduced to 12 weekly on consultant advice once dose/bloods are stable (see definitions above):

- At dose increase changes advised by the specialist team, the monitoring will need to be 2 weekly until dose and bloods stable for 6 weeks. Thereafter revert back to standard monitoring as above.
- The patient should be asked about the presence of rash, oral ulceration, severe sore throat, abnormal bruising, diarrhoea, nausea and vomiting and whether they have new or increasing dyspnoea or cough, at each visit.
- If MCV > 105 fL check thyroid function, B12 and folate. Treat any underlying abnormality but if these results are normal, discuss with specialist team for further advice.

In the event of the following adverse laboratory results or patient reported symptoms, withhold methotrexate until discussed with specialist team:

- WCC < 3.5×10^9/L or less than the lower limit of reference range as per lab
- Platelets < 140×10^9/L or less than the lower limit of reference range as per lab
- Neutrophils < 1.6×10^9/L or less than the lower limit of reference range as per lab
- AST/ALT > 2 times the upper limit of reference range
- Albumin unexplained fall (in absence of active disease)
- Significant deterioration in renal function.
- Abnormal bruising or severe sore throat (do FBC)
- Rash, nausea and vomiting, diarrhoea or oral ulceration. Diarrhoea and severe ulcerative stomatitis are frequent toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.
- Cough or dyspnoea: methotrexate can cause pneumonitis. If a patient has an unexplained dry cough or dyspnoea methotrexate should be withheld and discussion with specialist team should take place urgently.
- Patient being systemically unwell with significant infection
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References

1. NICE - Rheumatoid arthritis in adults: management https://www.nice.org.uk/guidance/ng100
2. NICE - Crohn's disease: management https://www.nice.org.uk/guidance/ng129
3. NICE - Psoriasis: assessment and management https://www.nice.org.uk/guidance/cg153
4. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs https://academic.oup.com/rheumatology/article/56/6/865/3053478
5. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults https://gut.bmj.com/content/gutjnl/68/Suppl_3/s1.full.pdf
6. Methotrexate tablets SPC example https://www.medicines.org.uk/emc/product/1376
7. Methotrexate pen SPC example https://www.medicines.org.uk/emc/product/5443
8. Folic acid supplementation https://www.sps.nhs.uk/articles/what-is-the-dose-of-folic-acid-to-use-with-methotrexate-therapy-for-rheumatoid-arthritis/
9. MHRA contraceptive methods and pregnancy testing https://www.gov.uk/drug-safety-update/medicines-with-teratogenic-potential-what-is-effective-contraception-and-how-often-is-pregnancy-testing-needed#download-print-and-use-new-table
10. North of Tyne immune modifying drugs guidance http://www.northoftyneapc.nhs.uk/wp-content/uploads/sites/6/2018/10/Immune-Modifying-Drugs-Monitoring-guidance-July-2018-v0.1.pdf

Sample Template for letter to Primary Care (adapted from East Lancashire Health Economy Management Board with thanks):

Shared Care Agreement - Methotrexate

Request by Specialist Clinician for the patient's GP to enter into a shared care agreement

Reference: **Date:**

Patient name: **Date of Birth:** **NHS number:**

Patient address:

Diagnosis:_____

In accordance with the shared care guidelines I kindly request that you prescribe:

1. _____ **Dose** ___ **Frequency**_____
2. _____ **Dose**___ **Frequency**_____
3. _____ **Dose**___ **Frequency**_____

for the above named patient.

Shared care guidelines available @ https://medicines.necsu.nhs.uk/cumbria-shared-care-protocols/

Last Prescription issued:_____ **Next prescription due:**_____

Date of last blood test:_____ **Date of next blood test:** _____

Frequency of Blood test:_____

For patients initiated and stabilised: Tick box if applies: ☐

I can confirm that the patient has been stabilised and reviewed on the above regime in accordance with the Shared Care guideline.

If this is a Shared Care Agreement for a drug indication which is unlicensed or off label, I confirm that informed consent has been received.

I have provided the patient with a monitoring and dosage record booklet and confirm that the patient knows when and where to attend for monitoring.

OR

For patients GP is expected to initiate oral treatment from the first dose: Tick box if applies: ☐

I can confirm that benefits/side effects, dose, folic acid, contraception have been discussed and that pre-treatment screening has been undertaken.

If this is a Shared Care Agreement for a drug indication which is unlicensed or off label, I confirm that informed consent has been received.

I have provided the patient with a monitoring and dosage record booklet and confirm that the patient knows when and where to attend for monitoring.

I will accept referral for reassessment at your request.

Details of Specialist Clinician

Name:_____**Date:**_____

Consultant/ Associate Specialist/ Specialist Registrar /Specialist Nurse (circle or underline as appropriate)

When the request for Shared Care is made by a specialist nurse, it is the supervising consultant who takes medicolegal responsibility for the agreement.

Consultant:_____