SHARED CARE GUIDELINE

Drug: Methotrexate

Introduction	**Indication:** Licensed: Rheumatoid arthritis, severe psoriasis, severe active juvenile idiopathic arthritis, severe psoriatic arthritis, mild to moderate Crohn's disease Unlicensed: Severe Eczema, Lichen Planus, Felty's syndrome, severe Crohn's disease **N.B. Not all brands/formulations are licensed for all indications – please refer to individual SPCs** **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. This may not account however for its action in rheumatoid arthritis or psoriasis which is not fully understood. Response to treatment cannot be expected before two or three months and may not occur until after six months of treatment. In patients with psoriasis response to treatment is also variable and it may take up to a month or more before any significant effect. Patients commenced on methotrexate are usually commenced on oral methotrexate. They may be switched to methotrexate injection if their response is suboptimal or they suffer from gastrointestinal side effects on oral methotrexate. **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, this will be termed "stable dose" Stable bloods – results of blood tests remain below 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"
Form	Tablets: 2.5mg, (only 2.5mg should be used to avoid confusion; **do not use 10mg**) Various brands of solution for SC injection (ranging from 7.5mg to 30mg in pre-filled pen)
Dose & Administration	Starting dose is between 2.5-15mg once weekly. 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 for moderate to severe active RA is 20mg/week orally or for severe active RA, 25mg / week by IV, IM or SC injection. Exceptionally the dose may be increased to 30mg weekly. Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. If the patient misses a methotrexate dose on their normal dosing day, the dose may be taken one or two days later. Patients should not take a dose three or more days late as a flare up of the disease is unlikely in this time. Patient should take the next dose on their usual dosing day. Folic acid 5 mg should be given as per local policy
Secondary Care Responsibilities	• Confirm the diagnosis. • Exclude TB, HIV and Hepatitis. 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 3 months after stopping methotrexate

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	• Discuss the benefits and side effects of treatment with the patient. Ensure that the patient understands that dosing is ONCE WEEKLY and which warning symptoms to report. • Perform pre-treatment screening [1]: height, weight, BP, FBC, LFTs, albumin, calculated GFR and chest x-ray (unless done within 6 months). Pulmonary function tests should be considered in patients with abnormal shadowing on x-ray. • Patients should be assessed for co-morbidities, including evaluation for respiratory disease and screening for occult viral infection. • Dermatologists should include P3NP screening for patients with psoriasis. • Provide the patient with prescriptions for methotrexate until on stable dose and undergoing 3 monthly monitoring. 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. • If initiating medication specify the DAY OF THE WEEK on the prescription; don't use the dose term 'as directed'. • Make arrangements for shared care with the patient's GP. • Review the patient regularly to monitor the patient's response to therapy. • Advise the GP on frequency of monitoring, management of any dose adjustments and when to stop treatment. • Ensure that clear backup arrangements exist for GPs to obtain advice. **Methotrexate Injection pen:-** • If the decision is made to switch to methotrexate injection pen provide one month's supply and a purple lidded cytotoxic sharps bin. The Sharp Safe and Sharps Guard cyto com bins are examples of bins which will hold the pen device. • The first injection from a prefilled PEN should be performed under direct medical or nursing supervision in secondary care. • Provide training on self-administration of methotrexate injection with the pen. • Inform the GP that the patient has been switched to methotrexate pen and of the dose.
Primary Care Responsibilities	**Methotrexate tablets:-** • Provide the patient with prescriptions for methotrexate 2.5 mg tablets and folic acid 5 mg tablets once on stable dose and undergoing 3 monthly monitoring. **Do not prescribe the 10mg tablets of methotrexate.** **Methotrexate injection pen:-** • Provide the patient with prescriptions for methotrexate pen as advised by the specialist and a 1L purple lidded cytotoxic sharps bin as required. The Sharp Safe and Sharps Guard cyto com 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. **For both:-** • 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 3 months after stopping methotrexate • 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.
Immunisations	• Annual flu vaccine is recommended • Pneumococcal vaccination recommended • COVID-19 vaccination is 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 <25mg/week
Adverse Side 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, thrombopenia, 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. • Not an exhaustive list, for further drug interactions please refer to current BNF and SPC
Cautions	• Alcohol – cautions 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
Contraindications	• Pregnancy –Women are advised to take contraceptive precautions while on methotrexate and for 3 months after stopping methotrexate. Limited evidence suggests low-dose methotrexate may be compatible with paternal exposure. If pregnancy occurs whilst on low dose methotrexate or within 3 months of stopping, folate supplementation (5 mg/day) should be continued throughout pregnancy. If methotrexate taken during pregnancy a careful evaluation of foetal risk should be carried out by local experts. • 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
Patient and carer advice	**The patient should be advised to report the following side effects to either their doctor or hospital nurse specialist:** Patients and their carers should be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort and dark urine), and respiratory effects (e.g. shortness of breath). Patients and their carers should be advised to avoid exposure to UV light (including intense sunlight, sunlamps, and sunbeds)—see Important safety information. Patients should be advised to avoid self-medication with over-the-counter aspirin or ibuprofen. Patients should be counselled on the dose, treatment booklet, and the use of NSAIDs. A patient alert card should be provided to patients on once-weekly dosing. See BNF methotrexate monograph for further information.

This guidance does not replace the SPC's, which should be read in conjunction with this guidance.

MONITORING AND ADVERSE EFFECTS

Treatment Status	FBC	LFT	Albumin	Creatinine/ calculated GFR	ESR or CRP	P3NP
Initial monitoring until on stable dose for 6 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 3 months (for RA only)	Annual for dermatology only (if elevated monitor every 3 months)
For next 3 months	Every month	Every month	Every month	Every month		
Thereafter	Every 3 months	Every 3 months	Every 3 months	Every 3 months		

***Please note:** If the patient is also being treated with **leflunomide**, increased monitoring is required, as specified in the leflunomide shared care guidance. (Where other biologic/DMARDs are used in combination with methotrexate, the standard monitoring requirements, as outlined above, continue to apply).

Following dose increases FBC, creatinine/ calculated GFR, albumin should be monitored every 2 weeks until on a stable dose for 6 weeks. Thereafter monitoring should then revert to the previous schedule used for initiation of methotrexate.

As per secondary care responsibilities, for clarity the frequency of monitoring should be specified in the initial shared care request.

- 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 > 105fL check thyroid function, B12 and folate. Treat any underlying abnormality but if these results are normal, discuss with specialist team for further advice.

The team responsible for prescribing the medication should also hold responsibility for monitoring
i.e. prescribing to be carried out in Primary care only once patient on stable dose and undergoing 3 monthly monitoring

In the event of the following adverse laboratory results or patient reported symptoms, withhold methotrexate until urgently discussed with specialist team and consider interruption in treatment:

- WCC < 3.5 x 10^9/L or less than the lower limit of reference range as per lab
- Neutrophils < 1.6 x 10^9/L or less than the lower limit of reference range as per lab
- Platelets < 140 x 10^9/L or less than the lower limit of reference range as per lab
- Mean cell volume > 105 fL
- Creatinine increase > 30% over 12 months and/or calculated GFR < 60 mL/min
- Unexplained eosinophilia > 0.5 x 10^9/L
- ALT and/or AST > 100 U/L
- Unexplained reduction in albumin < 30 g/L

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decreases in white blood cells or albumin, or increasing liver enzymes). If urgent clinical abnormalities arise emergency access to specialist advice should be sought.

Other adverse reactions:

- 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

References

1. Summary of product characteristics. Methotrexate 2.5mg tablets. Sandoz Limited. Last updated on the EMC 14th June 2022. Accessed via: https://www.medicines.org.uk/emc/medicine/4608 [accessed online: 21st June 2022].
2. Summary of product characteristics. Metoject PEN 7.5mg solution for injection in prefilled pen. Sanofi. Last updated on the EMC 28th April 2022. Accessed via: https://www.medicines.org.uk/emc/medicine/5443 [accessed online: 21st June 2022].
3. Ledingham et al. BSR/BHPR Non-Biologic DMARD Guidelines, June 2017. Accessed via: https://academic.oup.com/rheumatology/article/56/6/865/3053478
4. Flint et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding, January 2016. Accessed via: https://academic.oup.com/rheumatology/article/55/9/1693/1744535
5. UK Health Security Agency. Immunisation Against Infectious Disease 'The Green Book', 2021. Department of Health and Social Care. London, UK.

RELEVANT CONTACT LIST

Speciality	
Name and Title	Tel. No.

The Shared Care agreement form is available here: https://www.lancashireandsouthcumbriaformulary.nhs.uk/docs/files/dmards-shared-care-agreement-v1.1.docx