NHS Cumbria Clinical Commissioning Group | NHS Lancashire North Clinical Commissioning Group | North Cumbria University Hospitals NHS Trust | University Hospitals of Morecambe Bay NHS Foundation Trust

SHARED CARE GUIDELINE

Drug: Methotrexate

Introduction	**Indication:** Licensed: Rheumatoid arthritis, severe psoriasis, severe active juvenile idiopathic arthritis, severe psoriatic arthritis. Off-license: Severe Eczema, Lichen Planus, Felty's syndrome, 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**)[2] Methotrexate PEN (solution for SC injection ranging from 7.5mg to 30mg in pre-filled pen)[3]. Methotrexate solution for injection (pre-filled syringe, ranging from 7.5mg to 25mg) Methotrexate oral solution 2mg per 1ml
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 in RA is 25mg/week. Exceptionally the dose may be increased to 30mg weekly. Folic acid 5mg should be given as per local policy.
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 that dosing is ONCE WEEKLY and which warning symptoms to report. • 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. • Dermatologists should include P3NP screening for patients with psoriasis. • 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 specifying 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 management of any dose adjustments and when to stop treatment. • Ensure that clear backup arrangements exist for GPs to obtain advice. **Methotrexate Injection:** • If the decision is made to switch to methotrexate injection 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 should be performed under direct medical or nursing supervision in secondary care. • Provide training on self-administration of methotrexate injection. • Inform the GP that the patient has been switched to methotrexate injection and of the dose.
Primary Care Responsibilities	**Methotrexate tablets:** • Provide the patient with prescriptions for methotrexate 2.5mg tablets and folic acid 5mg tablets. **Do not prescribe the 10mg tablets of methotrexate.** **Methotrexate injection:** • Provide the patient with prescriptions for methotrexate injection 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 device. • Ensure systems are in place for the patient to receive their weekly injection if they are not self-administering. **For both:** • 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 • 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 • 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, 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.
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
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 SPC's, which should be read in conjunction with this guidance.

Monitoring and Adverse Effects

Treatment status	FBC	LFT	U+E	Creatinine/ eGFR	ESR or CRP	P3NP
Initial monitoring	Every 2 Weeks	Every 2 Weeks	Every 2 Weeks	Every 2 Weeks	Every 3 months (for RA only)	N/A
Once dose is stable (see definition)	Every 2 months	Every 2 months	Every 2 months	Every 2 months	Every 3 months (for RA only)	Annual for dermatology only (if elevated monitor every 3 months)

- **Once dose is stable monitoring frequency may be reduced to 3 monthly on consultant advice**
- At dose increase changes advised by the specialist team, the monitoring will need to be 2 weekly until dose and bloods stable. 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 > 105fL 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 x 10^9/L or less than the lower limit of reference range as per lab
- Neutrophils < 2.0 x 10^9/L or less than the lower limit of reference range as per lab
- Platelets < 150 x 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

References

1. http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmard_therapy.pdf
2. http://www.medicines.org.uk/emc/medicine/24573/SPC/Methotrexate+2.5mg+Tablets+BP/
3. https://www.medicines.org.uk/emc/medicine/28982
4. BNF 66 September 2013-March2014
5. http://cks.nice.org.uk/dmards#!scenariorecommendation:9