City and Hackney Clinical Commissioning Group
Homerton University Hospital Foundation Trust

SHARED CARE GUIDELINE

METHOTREXATE

Treatment of Inflammatory Conditions in Adult Dermatology, Gastroenterology and Rheumatology Patients

DOCUMENT TO BE SCANNED INTO ELECTRONIC RECORDS AND FILED IN NOTES

INTRODUCTION – Indication and Licensing

Methotrexate is an antimetabolite cytotoxic drug, but its use is becoming increasingly common in the treatment of autoimmune inflammatory conditions. Methotrexate exerts anti-inflammatory effect *via* mechanisms that are different to its anti-proliferative effect in malignant conditions. It may take between 6 to 12 weeks for the therapeutic effect to be noticed by the patient.

Licensed indications: psoriasis, psoriatic arthritis and rheumatoid arthritis.

Unlicensed indications: Crohn's disease (CD), ulcerative colitis (UC), systemic lupus erythematosus (SLE), adult onset still's disease (AOSD), Sjogren's syndrome, vasculitis and other inflammatory conditions considered appropriate by the hospital specialist.

This Shared Care Guideline (SCG) does not cover the prescribing of Methotrexate in malignant conditions

PATIENT PATHWAY

Clinical Speciality / Indication	Prescribing Initiated by	Prescribing Continued by	Monitored by	Duration of treatment
Dermatology Gastroenterology Rheumatology	Dermatologist Gastroenterologist Rheumatologist	Hospital to transfer the prescribing to GP once patient is on a stable dose and blood results are stable.	Hospital or GP as per shared care agreement letter.	Ongoing if efficacious.

Reviews & dose adjustments

The patient will be reviewed periodically by the hospital specialist team in clinic. Dosing adjustments are to be done by the hospital and this information communicated to the GP in writing within 14 days.

Patients outside of City and Hackney area

It may be more appropriate for blood test monitoring to be done locally if this is more convenient for the patient. The patient should be given a copy of their latest blood results to bring to their clinic appointment (if the hospital specialist team is not able to access this information electronically).

ORAL DOSE AND ADMINISTRATION

	Dosing	Maximum dose
Usual regimen	5 – 15mg ONCE a week and increased gradually according to response and tolerability. CD & UC: 15 – 25mg ONCE a week.	25mg ONCE a week.
Elderly/frail patients and those with renal impairments	Start at a lower dose and titrate gradually according to response and side effects.	Dependent on tolerability and renal function (if applicable) and must not exceed 25mg ONCE a week.
Folic acid supplementation	5mg ONCE a week, increased if needed	5mg ONCE a day for up to 6 days a week

Prescription for oral Methotrexate

Methotrexate is usually taken in tablet form ONCE a week, on the same day of each week. It should be swallowed whole, not crushed or chewed. Methotrexate is available as 2.5mg and 10mg tablets. To avoid confusion and reduce the risk inadvertent overdose, Methotrexate should be prescribed and dispensed in multiples of 2.5mg tablets ONLY. In exceptional cases, clinicians may decide that for compliance reasons it would be in the patient's best interest to prescribe the dose in 10mg tablets. Patients already receiving 10mg tablets may be continued on this to ensure continuity and prevent confusion for the patient. This information should be documented in the patient's care record.

Prescriptions must be complete, legible and include in full the form, strength, dose and directions. "As directed" should NOT be used. See below for an example of how to write the prescription.

Methotrexate 15mg (6 x 2.5mg) once a week on Mondays, supply 24 x 2.5mg tablets.

Due to the cytotoxic nature and once weekly dosing requirement of Methotrexate, it is recommended that prescriptions for patients are not part of the repeat prescription scheme and care is taken to ensure that repeat prescription requests are referred to GPs and that repeat prescriptions are not generated by admin staff.

Parenteral Methotrexate

Parenteral Methotrexate will be prescribed by the hospital. The subcutaneous route can be considered if oral dose is limited by side effects. The intramuscular route is also used for inflammatory bowel disease but this is an unlicensed preparation. A reduction of the dose may be required due to the variable bioavailability of Methotrexate after oral administration (70% for oral versus 100% for subcutaneous injection). In a few exceptional cases a higher dose of Methotrexate might be clinically justified, but should not exceed a maximum weekly dose of 30mg as toxicity will markedly increase.

Folic acid supplementation

Folic acid supplementation must be given to all patients initiated on Methotrexate to reduce potential side effects (gastrointestinal, mucositis) and to reduce the risk of hepatotoxicity. Folic acid should NOT be taken on the same day as Methotrexate.

Vaccinations

- Annual vaccination against influenza is recommended.
- Pneumococcal vaccination should preferably be given prior to the initiation of Methotrexate, however if this is not possible it should still be administered and repeated every 5 years.
- Concomitant use of live vaccines could cause severe antigenic reaction and therefore should be avoided, these include: oral polio, oral typhoid, MMR, BCG and yellow fever vaccines.
- Treatment with Methotrexate at doses ≤25mg/week is not a contraindication for the shingles vaccine (Zostavax®) for most patients (see JCVI Green Book). Discuss with the specialist team if the shingles vaccine is required.
- Patients who have not been immunised against or who have not previously had chicken pox should report to their GP or specialist if they come in to contact with the virus. Passive immunisation should be carried out using varicella zoster immunoglobulin.

Alcohol intake

Patients should be advised to keep alcohol intake well within the government guidelines (maximum 2 units a day or 14 units per week). Note some specialists may suggest stricter limits which should be followed by the patient.

CAUTIONS

- Extreme caution in blood disorders (avoid if severe).
- Peptic ulceration, ulcerative colitis, diarrhoea and ulcerative stomatitis (withdraw if stomatitis develops—may be first sign of gastrointestinal toxicity).
- Risk of accumulation in pleural effusion or ascites—drain before treatment.
- Acute porphyria.

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CONTRAINDICATIONS

- Mothers who are breastfeeding.
- Pregnancy (including female patients who are trying to conceive or planning to do so in the next 3 months).
- Severe anaemia, leucopenia or thrombocytopenia.
- Severe/significant renal or significant hepatic impairment (including fibrosis, cirrhosis, recent or active hepatitis).
- Active infectious disease.
- Overt or laboratory evidence of immunodeficiency syndrome(s).

INTERACTIONS

- **AVOID concomitant use with the following drugs:** trimethoprim, co-trimoxazole, acitretin and clozapine.
- **CAUTION with the following drugs (reduced excretion of Methotrexate):** penicillins, ciprofloxacin, doxycycline, tetracycline, aspirin, NSAIDs and proton pump inhibitors. If aspirin or other NSAIDs are given concurrently the dose of Methotrexate should be carefully monitored. Patients should be advised to avoid self-medication with over-the-counter aspirin or ibuprofen.
- **CAUTION with hepatotoxic, nephrotoxic and anti-folate drugs** (e.g. phenytoin) due to the risk of toxicities with Methotrexate.
- **AVOID herbal remedies** if possible due to unknown interaction potential.

MONITORING STANDARDS FOR MEDICATION AT THE ACUTE NHS TRUST

Pre-treatment monitoring to be done by the specialist team
FBC, LFTs, U&Es, eGFR, CRP[#], ESR[#], folate and B12 levels. Chest X-ray, respiratory examination and check history of respiratory symptoms. *Additional tests to be determined on an individual patient basis:* Pulmonary function tests, Varicella zoster, Hepatitis B & C serology.
Ongoing monitoring to be done by specialist team until patient is stable then GP to take over monitoring as per shared care agreement.
FBC, LFTs, U&Es (including eGFR) every 2 weeks until on stable dose for 6 weeks, then monthly for 3 months (or longer if deemed necessary by the specialist team), then every 8-12 weeks thereafter. *Dose increases:* monitor every 2 weeks until on stable dose for 6 weeks then revert back to previous schedule.

[#]Monitoring of CRP and ESR may not be applicable in some conditions.

The patient should be given a patient held monitoring booklet containing details of their current dose and latest blood results. The booklet will need to be updated each time the patient gets their blood tests done or when the dose of Methotrexate is changed. The patient should be encouraged to bring the booklet to their GP and hospital appointments and to the pharmacy when they pick up their Methotrexate tablets.

KEY ADVERSE EFFECTS & ACTIONS

- Gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhoea, dyspepsia, stomatitis, gastrointestinal ulceration and bleeding).
- Blood disorders (leucopenia, anaemia, thrombocytopenia).
- Hepatotoxicity (raised liver enzymes, necrosis, cirrhosis).
- Pulmonary toxicity (interstitial pneumonitis, rarely pulmonary fibrosis but note this is also a complication of rheumatoid arthritis).
- CNS disturbances (headache, drowsiness, insomnia, mood changes).
- Hypersensitivity reactions (anaphylaxis, skin rashes).
- Alopecia.

Laboratory events	**Values**	**Actions (*what action should the GP take if identified in primary care)***
↓ WBC	$<3.5 \times 10^9$/l	Reduction in WBC alone is not usually considered clinically significant. If this is accompanied by a reduction in neutrophil count then **stop drug and seek advice** from the specialist team.

↓ Neutrophil count	<1.6 x 10^9/l	**Stop drug and seek advice** from the specialist team.
↓ Platelet count	<100 x 10^9/l	
↑ MCV	>105fl	Check alcohol intake, B12, folate and TSH and treat any underlying abnormality. If normal, **seek advice** from the specialist team.
↑ ALT	2 – 3 times upper limit of normal	**Seek advice** from the specialist team as dose reduction or interruption of treatment may be required.
	>3 times upper limit of normal	**Stop drug and seek advice** from the specialist team.
↓ Renal function	Creatinine increase >30% over 12 months and/or eGFR between 30-60ml/min/1.73	**Seek advice** from the specialist team.
	eGFR <30ml/min/1.73	**Stop drug and seek advice** from the specialist team.

Please note: a rapidly increasing or decreasing trend in any values should prompt caution and extra vigilance. Some patients may have abnormal baseline values, specialist team will advise.

Symptoms	**Actions (*what action should the GP take if identified in primary care)***
Rash	**Stop drug and seek advice** from the specialist team.
Oral ulceration (stomatitis)	Increase the dose of folic acid, **seek advice** from the specialist team if reaction is severe or not helped with increased dose of folic acid.
New or increasing dyspnoea, dry cough, or fever	**Stop drug and seek advice** from the specialist team.
Severe sore throat, abnormal bruising or bleeding	**Stop drug** and repeat FBC immediately. **Seek urgent advice** from the specialist team.
Infection	Treat infection. Cautious vigilance is necessary to detect early evidence of infection. **Methotrexate may be stopped** during this period. **Seek advice** from the specialist team if in doubt.
Dyspepsia, nausea and vomiting	Increase the dose of folic acid and/or advise patient to take tablets with a meal or before bed. Some patients may benefit from a dose of antiemetic taken 30 – 60 minutes prior to Methotrexate. Encourage patient to increase fluid intake to avoid dehydration. **Seek advice** from the specialist team if reaction is severe or persistent.
Diarrhoea	Check history and rule out infective diarrhoea. Increase the dose of folic acid and encourage patient to increase fluid intake to avoid dehydration. **Seek advice** from the specialist team if reaction is severe or not helped with increased dose of folic acid.

Patients should be advised to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), fever or any other signs of infection, liver toxicity (e.g. nausea, vomiting, abdominal discomfort, yellowing of the skin or eyes or dark urine), and respiratory effects (e.g. shortness of breath).

The SCG lists only the key information. Please refer to the current British National Formulary and Summary of Product Characteristics for comprehensive information on cautions, contraindications, interactions and adverse effects.

PREGNANCY AND BREAST FEEDING

- Methotrexate is present in milk and is contraindicated in breastfeeding.
- Methotrexate is teratogenic and is contraindicated in pregnancy. Female patients should wait 3 months after discontinuation of Methotrexate before trying to conceive; effective contraception should be used during this time period. Male patients wishing to start a family may be able to continue methotrexate but should discuss in advance of conception with their treating specialist.
- In women treated with Methotrexate within 3 months prior to conception, folic acid supplementation (5mg/day) should be continued prior to and throughout pregnancy.

- In the case of accidental pregnancy, Methotrexate should be stopped immediately, folic acid supplementation (5mg/day) continued and a careful evaluation of foetal risk carried out by local experts.

Please refer to the current British National Formulary and Summary of Product Characteristics for comprehensive information.

SHARED CARE

Shared care guideline*:* is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The intention to shared care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use**.**

Consultant

1. Ensure that the patient/carer is an informed recipient in therapy.
2. Ensure that patients understand their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate). Issue any local patient information leaflets where appropriate.
3. Ensure baseline investigations are normal before commencing treatment.
4. Initiate treatment and prescribe until the GP formally agrees to share care (as a minimum, supply the first month of treatment or until patient is stabilised).
5. Send a letter to the GP requesting shared care for this patient.
6. Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis.
7. Send a letter/results notification to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated (unless otherwise covered by letter e.g. from Rheumatology Clinical Nurse Specialist).
8. Where the GP is out of area and is not performing the phlebotomy, the blood test form/EPR request MUST specify that blood results are also copied to the GP. Specialist team to check with pathology IT if unsure on how to do this.
9. Evaluation of any reported adverse effects by GP or patient.
10. Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent action is required following tests the hospital team will telephone the patient and inform GP.
11. Inform GP of patients who do not attend clinic appointments.
12. Counsel the patient on contraception and what to do if pregnancy occurs. Document in the notes.
13. Ensure that backup advice is available at all times.
14. Advise that the patient receives appropriate vaccination in primary care either prior to commencing treatment and/or during a treatment that is likely to cause immunosuppression.

General Practitioner

1. Ensure that the patient understands the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate.
2. Monitor patient's overall health and well-being.
3. Report any adverse events to the consultant, where appropriate.
4. Report any adverse events to the MHRA / CHM, where appropriate.
5. Help in monitoring the progression of disease.
6. Provide contraception advice and prescription as appropriate.
7. Provide appropriate vaccinations to patients receiving treatments likely to cause immunosuppression.

City and Hackney Medicines Management Team

1. To provide feedback to acute trusts via Joint Prescribing and Medicines Management Group.
2. To support GPs to make the decision whether to accept clinical responsibility for prescribing.
3. To support acute trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist.
2. Ensure they have a clear understanding of their treatment.
3. Report any changes in disease symptoms to GP and/or specialist.
4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy.
5. Take/ administer the medication as prescribed.
6. Undertake any monitoring as requested by the GP and/or specialist.

Costs

Drug product	Cost in primary care
Methotrexate 2.5mg tablets	24-tab pack = £2.40, 28-tab pack = £2.92
Metoject solution for injection in pre-filled pen (50mg/mL)	1-pen pack: 0.15 mL (7.5 mg) = £14.85, 0.2 mL (10 mg) = £15.29, 0.25 mL (12.5 mg) = £16.50, 0.3 mL (15 mg) = £16.57, 0.35 mL (17.5 mg) = £17.50), 0.4 mL (20 mg) = £17.84, 0.45 mL (22.5 mg) = £18.45, 0.5 mL (25 mg) = £18.48, 0.55 mL (27.5 mg) = £18.89, 0.6 mL (30 mg) = £18.95

Based on BNF edition 73 (March – September 2017)

RESOURCES AVAILABLE

- Arthritis Research UK website, accessible *via* http://www.arthritisresearchuk.org
- Crohn's & Colitis UK website, accessible *via* https://www.crohnsandcolitis.org.uk
- Psoriasis Association website, accessible *via* https://www.psoriasis-association.org.uk
- British Association of Dermatologists website, accessible *via* http://www.bad.org.uk
- Drinkaware website, accessible *via* https://www.drinkaware.co.uk
- Methotrexate patient held booklet can be downloaded from the NPSA website, accessible *via* http://www.nrls.npsa.nhs.uk/resources/?EntryId45=59800
- The Joint Committee on Vaccination and Immunisation (JCVI) Green Book, accessible *via* https://www.gov.uk

Relevant contact details	
Consultant or Registrar on-call *via* switchboard	020 8510 5555
Clinical Nurse Specialist or departmental (helpline)	**Dermatology** 0208 510 7690 **Gastroenterology** 07920 546 260 **Rheumatology** 07917 521 117
Generic email	**Gastroenterology** huh-tr.gastro@nhs.net **Rheumatology** huh-tr.rheumliaison@nhs.net (clinical queries) huh-tr.rheumatologyadmin@nhs.net (admin queries)
Homerton University Hospital NHS Foundation Medicines Information	020 8510 7000
City & Hackney Medicines Management Team	0203 816 3224

References

- SCG template adapted from NELMMN and Barts Health NHS Trust.
- BNF edition 73, accessible *via* https://ebnf.homerton.nhs.uk (last accessed 26 April 2017).
- Summary of product characteristics. Accessible *via* www.medicines.org.uk (last accessed 26 April 2017).
    1. Maxtrex tablets 2.5mg.
    2. Metoject pen solution for injection in pre-filled pen.
- British Association of Dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease (2016). Accessible *via* www.bad.org.uk (last accessed 4 May 2017).
- The British Society for Rheumatology, accessible *via*: http://www.rheumatology.org.uk (last accessed 25 April 2017).
    1. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease modifying anti-rheumatic drugs (2017).
    2. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists (2008).

3. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding – Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids (2016).

Date SCG approved by Joint Prescribing Group (JPG): 07/2017 Review date: 07/2020