SHARED CARE PROTOCOL	NHS Lothian
Subcutaneous Methotrexate	
Clinical indication: For the treatment of rheumatological inflammatory diseases	
Version 1.0: February 2010	**Due for review: February 2012**

Introduction

With the exception of sulfasalazine, DMARDs are usually started after assessment by a rheumatologist. 'Rheumatological Management and Shared Care Guidelines' available on website: *www.refhelp.scot.nhs.uk*

Shared Care

A shared care protocol is used to **facilitate the sharing of care and transfer of prescribing.** This would usually take place once the patient's condition is stable; the patient is demonstrably benefiting from the treatment and is free from any significant side effects. GPs should only take on the prescribing when they are confident in the use of the drug, in the context of the protocol. Contingency plans must be in place to enable the patient to receive the recommended treatment, should the GP decline to prescribe.

Indication for Therapy

Indications – active joint inflammation usually supported by indices of inflammation. Parenteral methotrexate is indicated when oral methotrexate has failed or the patient experiences side effects. Patients will initially be assessed to ensure that they are competent and confident in self-administration of this formulation.
Duration – most drugs require up to 3 months trial to assess efficacy. Therapy is continued providing the drug is working and there are no side effects. Relapse is common after withdrawal of therapy.

Preparations Available

Subcutaneous methotrexate is available as the licensed preparation Metoject® from Medac® as a 50mg/ml pre-filled syringe. The dose range is:
1 pre-filled syringe of 0.15 ml contains 7.5 mg methotrexate
1 pre-filled syringe of 0.20 ml contains 10 mg methotrexate
1 pre-filled syringe of 0.30 ml contains 15 mg methotrexate
1 pre-filled syringe of 0.40 ml contains 20 mg methotrexate
1 pre-filled syringe of 0.50 ml contains 25 mg methotrexate.

Recommended Dosage and Administration

Patients are generally commenced on the dose equivalent to maximum tolerated oral dose and the target dose is 25mg once weekly. The dose is administered **subcutaneously once weekly** and dose increments are 5mg every 4 weeks. Folic acid 5mg (orally) is to be taken the day after methotrexate.

Cost

7.5mg = £14.85; 10mg = £15.29; 15mg = £16.57
20mg = £17.84; 25mg = £18.48.
Therefore, the cost per patient year is dependant upon the maintenance dose. For most patients this will be 20mg or 25mg once weekly, resulting in an average annual cost of £894 per patient.

Shared Care Responsibilities

Aspects of care for which the consultant is responsible:

- Assessing the need for parenteral methotrexate and arranging the first 3 month's supply until the patient is stabilised.
- Arranging for the patient to receive counselling in verbal and written form.
- Providing relevant baseline investigations.
- Following the patient's response to treatment at the out- patient clinic.
- Communicating advice to the patient's GP re monitoring requirements.
- At any stage of treatment, advising GP of concerns re monitoring or potential adverse effects of treatment.

Aspects of care for which the general practitioner is responsible:

- Prescribing parenteral methotrexate under the guidance of the consultant.
- Reporting any suspected adverse reactions to the patient's consultant and complete a Yellow Card where appropriate. Discuss any significant abnormalities or complications of treatment with consultant.
- Monitoring the general health of the patient.
- Monitoring for specific side effects as detailed in "Monitoring" section.
- Provision of pneumococcal and annual influenza vaccination.
- Prescribing a 1 litre sharps bin (purple lid) for safe disposal of cytotoxic waste (to be returned by patient to community pharmacy).

Monitoring

Test	Frequency	Abnormal result	Action if abnormal result
FBC	Fortnightly from initiation of therapy until the dose and tests have been stable for 6 weeks. Then monthly until the dose and disease has been stable for one year. Thereafter, the frequency of monitoring must be maintained as monthly where risk factors exist e.g. age, co-morbidity, chronic kidney disease, hypoalbuminaemia etc. In the absence of such risk factors and after one year, the frequency of monitoring may be reduced to 3 monthly.	WBC <3.5 x 10^9/l neutrophils <2.0 x 10^9/l platelets <150 x 10^9/l	Withhold methotrexate and discuss with specialist.
		MCV >105 fl	Check B12, folate and TSH. If abnormal, treat underlying abnormality; if normal, discuss with specialist.
LFTs and albumin		AST > twice upper limit of normal reference range. ALT > twice upper limit of normal reference range. Unexplained fall in albumin (in absence of active disease).	Withhold methotrexate and discuss with specialist.
U&Es and creatinine		Creatinine clearance 20-50ml/min. Creatinine clearance <20ml/min.	Reduce dose by 50% and discuss with specialist. Withhold methotrexate and discuss with specialist.

- Abnormal trends should prompt extra vigilance.
- Withhold and discuss urgently with specialist team if new or increasing dyspnoea or dry cough develops.
- Temporarily withdraw if the patient reports sore throat, unexplained bleeding or bruising, mouth ulcers or other signs of blood dyscrasia or evidence of infection. Perform repeat blood monitoring.
- In the event of an unexplained acute widespread rash, withhold methotrexate and inform rheumatologist.
- Trends in ESR are useful in decision-making.

Adverse Effects and Drug Interactions

The incidence and severity of side effects are considered to be dose related.
Common: nausea, diarrhoea, mouth ulcers, rash, haematological abnormalities (bone marrow suppression and pancytopenia) and raised LFTs (> 2-3 times upper limit of normal). Uraemia (though usually only at higher doses), headaches, drowsiness, blurred vision. Local damage at injection site is very rare, however, patients are taught to rotate site weekly.

Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate *unless clearly necessary* and the consumption of alcohol should be avoided or greatly reduced. Liver cirrhosis has been reported and is associated with cumulative dosing of methotrexate.

Pneumonitis is a rare, but potentially fatal side effect of methotrexate use. This may present initially as a dry, non-productive cough and/or dyspnoea. If pneumonitis is suspected, methotrexate should be discontinued and the patient admitted to hospital urgently for review and treatment.

New prescription of NSAIDs and aspirin can reduce the excretion of methotrexate, increasing the risk of toxicity. NSAIDs are commonly used in conjunction with methotrexate in inflammatory diseases, therefore, monitoring is essential. Co-trimoxazole and trimethoprim should not be co-administered with methotrexate (rare reports of acute megaloblastic pancytopenia). Folic acid or its derivatives may alter the response to methotrexate (folic acid must not be administered on the same day as methotrexate).

This is not a complete list of all potential drug interactions. For more information please refer to the relevant section of the British National Formulary and/or the Summary of Product Characteristics for Metoject®.

Precautions and Contra-Indications

As per oral methotrexate, cautioned in the elderly; contra-indicated in suspected/actual local or systemic infection and bone marrow failure. Cautioned in chronic kidney disease – reduce dose by 50% if creatinine clearance 20-50ml/min and do not use if creatinine clearance is <20ml/min.
Contraindicated in pregnancy. Breast-feeding should be discontinued prior to and throughout administration. Reliable contraception should be used by males or females during treatment and for at least 3 months after treatment discontinued.
Methotrexate is a cytotoxic agent and should be prescribed, supplied and administered in accordance with local guidelines. All patients who are to commence on subcutaneous methotrexate are counselled by a rheumatology nurse or pharmacist on both the agent itself and its safe administration. Patients are counselled both verbally and are provided with patient information, which provides details on safe handling and disposal.

Contact Points

Rheumatology SpR (via switchboard):	0131 537 1000
Rheumatology Clinical Pharmacist:	0131 537 1000 (bleep 8461)
Rheumatic Diseases Unit (WGH):	0131 537 1798
Rheumatology Clinical Nurse Practitioners:	0131 537 3677
Rheumatology Secretary (St John's Hospital):	01506 52 3824

For urgent enquiries, contact the on-call rheumatologist. For other enquiries please contact the nurse practitioners.

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This information was prepared by the Rheumatic Diseases Unit and Pharmacy Department, Western General Hospital, through liaison with the General Practice Prescribing Committee and the Lothian University Hospitals Division Drug and Therapeutics Committee.