SHARED CARE GUIDELINE

Methotrexate for use in Neurology

Implementation Date: June 2018 **Review Date: June 2022**

This guidance has been prepared and approved for use within Sunderland and South Tyneside in consultation within the CCGs, and Secondary Care Trust.
The guideline sets out the details of the transfer of prescribing and respective responsibilities of GPs and specialist services within shared care prescribing arrangements. It is intended to provide sufficient information to allow GPs to prescribe this treatment within a shared care setting

Approved by:

Committee	Date
SCCG Medicines optimisation and guideline group	20.6.18
STS APC – review date extended to December 2020	August 2020
STS APC – review date extended to June 2021	February 2021
STS APC – review date extended to June 2022	October 2021

- ☐ Consultant to counsel patient on medication and ensure patient has been provided with information leaflet
- ☐ Consultant to ensure all clinical details completed on this document
- ☐ Consultant to ensure patient understands proposed monitoring and prescribing arrangements if a shared care agreement is entered into
- ☐ GP to complete final section of form and return to specialist prescriber within 28 days
- ☐ GP to retain copy of document on patient record within surgery

Clinical details:

SHARED CARE GUIDELINE					
Non-proprietary name	Methotrexate	Brand name	Maxtrex	Licensed Yes/No	*No (see below)*
Dosage form and strength	Tablets. To avoid fatal accidents please prescribe 2.5mg tablets only			BNF class	8.1.3
Indication	Unlicensed indications: Myasthenia gravis, myositis, chronic inflammatory demyelinating polyradiculoneuropathy, neuromyelitis optica, autoimmune encephalitis, neurosarcoidosis.				
Dosage and Administration	Methotrexate 5- 10mg (oral) **weekly**, on the same day each week, up to a weekly maximum of 25mg. The prescription should clearly state the dose and frequency of administration Folic acid 5mg AS A SINGLE DOSE should be also given 4 days after methotrexate.				
Eligibility criteria for shared care	Patients must be under the care of a CHS consultant neurologist Must have a diagnosis consistent with one of the indications outlined above Patients who have been stable on their maintenance dose of methotrexate for three months				
Excluded patients	Any patient in whom methotrexate is contraindicated or not tolerated. Not for patients under the age of 16 years.				
Initiation	Shared care to be initiated once patient has been stable on maintenance dose for three months				
Monitoring	**Baseline assessment** The following should be performed prior to starting MTX: • Routine bloods including FBC, (ESR optional),U&E, LFTS, HIV, Hepatitis B & C				

- BMI
- Chest X-ray if any concern regarding latent TB
- Lung function tests plus further investigations if concern of chronic lung disease
- Pregnancy test should be performed in women of reproductive age

Assessment for acute infection, including urine analysis

Monitoring

Ongoing blood test monitoring of high risk or low risk patients according to monitoring schedules below and review of laboratory abnormalities prior to transfer.

Monitoring of high risk patients

The patient is 'high risk' if any of the following apply:

- Extremes of weight: BMI <18 or >30kg/m2
- Renal impairment: CKD stage III or above
- Pre-existing liver disease (including NAFLD)
- Significant other co-morbidity (e.g. malignancy)
- Age >80 years
- Previous DMARD toxicity.

Routine Bloods: FBC, U&E, ALT, Albumin, eGFR
Frequency: Every week until stable on a dose for 6 weeks.

- Once on a stable dose: monthly blood tests.
- Following a dose increase bloods should be checked weekly for 6 weeks, then revert back to previous schedule

For patients who are NOT high risk:

Routine Bloods: FBC, U&E, LFTs
Frequency: Every 2 weeks until stable on a dose for 6 weeks

- Once on a stable dose: monthly blood tests for 3 months
- Then: at least every 12 weeks for the duration of treatment
- Following a dose increase bloods should be checked 2 weekly for 6 weeks, then revert back to previous schedule

Laboratory abnormalities requiring action

The abnormalities in table below should trigger action/review. **If any abnormal blood test results are obtained, withhold the medication and discuss with the patient's consultant neurologist.** Do not forget to consider the possibility that the abnormal blood result may be unrelated to the immunosuppressant medication.

Test	Result
White cell count	<3.5 * 10^9/l (or downward trend over 2 consecutive tests)
Neutrophils	<1.6 * 10^9/l
Unexplained eosinophilia	>0.5 * 10^9/l
Platelet count	<140 * 10^9/l
MCV	> 105 f/l
Creatinine/ eGFR	Creatinine increase >30% over 12 months and/or GFR <60ml/min/1.73m2
ALT (and or AST)	>100 U/L
Albumin	Unexplained reduction in albumin to <30g/l

	If the patient develops oral ulceration, abnormal bruising, sore throat or an unexplained rash then reduce dose or withhold methotrexate if severe until FBC available and discuss with neurology team
Infection	During serious infections, the immunosuppressant agent (IA) should be temporarily discontinued until the patient has recovered from the infection. If infection develops requiring antibiotics, **stop methotrexate for duration of antibiotics**. Patient should be seen by GP/Clinician within 12 hours of onset of infective symptoms. It is usually appropriate to continue IAs in minor infections (e.g. a treated, uncomplicated UTI). The IA would usually be restarted after antimicrobial treatment is complete and the patient has started to make a significant clinical improvement. When the IA is restarted, the same monitoring schedule should be followed. Patients treated with immunosuppressants are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). If Herpes Zoster occurs stop methotrexate and prescribe aciclovir. If patient is in contact with chicken pox, contact neurology team (may need Zoster Immunoglobulin).
Respiratory symptoms	Methotrexate can very rarely cause pneumonitis. This usually occurs in the first year of treatment. If the patient develops acute or subacute dyspnoea (with or without a dry cough) and there is an absence of other signs and symptoms to point to an alternative cause, then stop the methotrexate and contact the neurology team.
Vaccination	Vaccination against influenza and pneumococcus should be offered. Live vaccines should not be given.
Pregnancy and breastfeeding	If the patient becomes pregnant, contact the neurology team. All patients, both men and women, should be advised against conception and pregnancy whilst taking methotrexate and for 3 months after stopping it, Methotrexate is teratogenic and is contraindicated in pregnancy and breastfeeding. Methotrexate should be stopped in both men and women 3 months before trying to conceive. Men and women should be advise to use effective contraception throughout treatment
Perioperative use	Steroid exposure should be minimised prior to surgical procedures and increases in steroid doses to prevent adrenal insufficiency are not routinely required
Nausea and vomiting	IAs may cause nausea, vomiting or diarrhoea on their introduction or on an escalation of the dose. In this situation, contact the neurology team. Once the patient has been established on a stable dose of an IA it would be unusual for this to cause significant GI symptoms.
Cancer risk	Patients receiving long-term IAs are at increased risk of developing a malignancy. The most frequently occurring types are lymphoma and skin malignancy. The avoidance of excessive exposure to the sun, and the use of high factor sunscreen and protective clothing are advised.

Specialist Responsibilities	• The decision to initiate immunosuppressive therapy must be made in conjunction with the patient/carer and be supervised by an expert in the condition in question • Patients must be provided with education about their treatment • Patient will be provided with an methotrexate patient information leaflet • Patients must be assessed for contra-indications and co-morbidities • Where appropriate, patients should be advised about the impact of the immunosuppressive agent (IA) on fertility, pregnancy and breastfeeding • Vaccinations against pneumococcus and influenza are recommended • Interactions between the proposed IA and current medication should be identified and actioned
Specialist Responsibilities	• Direct the patient to report any sign of infection or side effect to their GP or hospital clinic • Conduct baseline monitoring • Prescribe medication until responsibility agreed to be transferred to patients GP • Complete checklist contained in this guidance prior to transfer • Supply general immunosuppressant background information to GP as per this guidance • Request GP participate in shared care in writing no sooner than patient has been <u>stable on same dose for 3 months</u> • Pre-agreed quantity of medication supplied at point of transfer, info regarding initial quantities to be supplied by GP • The secondary care specialist will communicate with the patient and GP when treatment is changed and/or needs to be changed by GP on future prescriptions, and/or when any changes to the monitoring are required, usually within 24 hrs • Conduct routine monitoring as per schedule while prescribing responsibility with specialist – this could be during initiation or at any point in time where the responsibility has been transferred back to the specialist • Observe advice relating to vaccination, perioperative use, infections etc contained in this document • Specialist responsible for ongoing disease monitoring– clinical response to therapy will be assessed by the hospital physician in all cases and communicated to the GP
GP Responsibilities	• The GP should reply to the request for shared care as soon as possible, but always within 14 days, either accepting shared care or informing the specialist why shared care is not felt appropriate in this case. • If GP declines shared care responsibilities it is still the GPs responsibility to record on the primary care record that the drug is being prescribed by secondary care • Shared care to be initiated once patient has been stable on maintenance dose for three months. • Prescribe medication as per document • Conduct routine monitoring as per schedule while responsible for prescribing • Observe advice relating to vaccination, perioperative use, infections etc contained in this document
Contraindications,	**Contra-indications** Known hypersensitivity to the product

<table>
<tr>
<td>Precautions and Adverse Effects</td>
<td>
Suspected local or systemic infection
Pregnancy and breast feeding (see below)
Bone marrow failure, with unexplained anaemia and cytopenia
Alcohol abuse
Significant liver impairment/disease

Precautions
Chronic kidney disease (CKD)
In renal disease, IAs that are renally excreted accumulate, and some IAs are nephrotoxic. Patients with CKD should be graded as per NICE definition of CKD (table 1) and have IA dose reductions as per recommendations by the British Society of Rheumatology (BSR) (table 2).
Table 1: NICE Definitions of CKD
<table>
<tr><th>Degree of Impairment</th><th>Calculated GFR ml/min/1.73m2</th></tr>
<tr><td>Normal, Stage I</td><td>>90 (other evidence of kidney damage)</td></tr>
<tr><td>Mild, Stage II</td><td>60-89 (other evidence of kidney damage)</td></tr>
<tr><td>Moderate, Stage III</td><td>30-59</td></tr>
<tr><td>Severe, Stage IV</td><td>15-29</td></tr>
<tr><td>Established renal failure, Stage V</td><td><15</td></tr>
</table>
Table 2: Recommended dose adjustment in CKD by the BSR
<table>
<tr><td colspan="3"></td><td colspan="3">Recommended adjustment (% of standard dose)</td></tr>
<tr><td>Drug</td><td>Accumulates in renal failure</td><td>Nephrotoxic</td><td>CKD III</td><td>CKD IV</td><td>CKD V</td></tr>
<tr><td>Azathioprine</td><td>No</td><td>No</td><td>Normal dose</td><td>75-100</td><td>50-100</td></tr>
<tr><td>Methotrexate</td><td>Yes</td><td>Yes</td><td>50%</td><td colspan="2">Contraindicated</td></tr>
<tr><td>Mycophenolate</td><td>Yes</td><td>No</td><td>Normal dose</td><td colspan="2">1g BD maximum</td></tr>
</table>
Adverse Effects
Nausea, diarrhoea, stomatitis, oral ulcers, leucopenia, thombocytopenia, pulmonary fibrosis, GI ulceration, alopecia, erythematous skin reactions, and suppression of ovarian and testicular function. Megaloblastic anaemia has been reported. Hepatic impairment may occur through prolonged use (elevated transaminases is a common adverse effect).
For a full list of contraindications/precautions/side effects please consult either the current BNF or SPC
</td>
</tr>
<tr>
<td>Common Drug Interactions</td>
<td>
Interactions:

Never prescribe co-trimoxazole and trimethoprim.
Live vaccines should not be given.
Caution with penicillins.
Ciprofloxacin — potentially increases the risk of toxicity when given with methotrexate.
Alcohol may be consumed in moderation, on average one unit per day but avoid binge drinking
Aspirin and NSAIDs – reduced methotrexate excretion. Clinically significant interaction with NSAIDs is rare, continue standard doses advised by specialist, but patients should be advised to avoid self-medication with over the counter aspirin or ibuprofen. Low dose aspirin can be continued.

For a full list of interactions please consult either the current BNF or SPC.
</td>
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</table>

<table>
<tr><td>Communication/ Contact Details</td><td>Contact the patient's Consultant Neurologist at Sunderland Royal Hospital. In their absence please contact the Consultant Neurologist on-call through the hospital switch board on 0191 565 6256.</td></tr>
<tr><td>Caveat</td><td>This document should be ready in conjunction with the general guidance on immunosuppression attached</td></tr>
<tr><td>Checklist and References</td><td>Weight: _____ BP:_____
Starting dose:_____ twice daily
<table>
<tr><th></th><th>YES</th><th>NO</th></tr>
<tr><td>Received education and written information about their treatment?</td><td></td><td></td></tr>
<tr><td>Advised of potential adverse effects of drug including allergy</td><td></td><td></td></tr>
<tr><td>Advised about reproductive issues as above</td><td></td><td></td></tr>
<tr><td>Assessed for contraindication to drug</td><td></td><td></td></tr>
<tr><td>Evaluated for chronic lung disease? If chronic lung disease present: had lung function tests, CXR +/- high resolution CT chest and respiratory referral</td><td></td><td></td></tr>
<tr><td>Assessed if any risk of latent TB, if so, CXR performed</td><td></td><td></td></tr>
<tr><td>Smoking status checked and cessation advice given if necessary</td><td></td><td></td></tr>
<tr><td>Evaluated for liver disease and any causes addressed and managed if necessary.</td><td></td><td></td></tr>
<tr><td>Evaluated for renal disease and any dose reduction made if necessary (dose of 1g BD maximum in CKD stages IV and V)</td><td></td><td></td></tr>
<tr><td>Discussed possible risk of increased malignancy</td><td></td><td></td></tr>
<tr><td>Made aware of the national screening programmes for cervical, breast, bowel and prostate cancer</td><td></td><td></td></tr>
<tr><td>Given skin cancer advise and assessed whether had previous/current skin cancer, and, if so, consideration made as to whether to refer to dermatologist</td><td></td><td></td></tr>
<tr><td>Screening blood tests performed: FBC, U&Es, LFTs, HIV, hepatitis B and C</td><td></td><td></td></tr>
<tr><td>Pregnancy test</td><td></td><td></td></tr>
</table>
<table>
<tr><th></th><th>YES</th><th>NO</th></tr>
<tr><td>Assessed if any symptoms of acute infection</td><td></td><td></td></tr>
<tr><td>Urinalysis</td><td></td><td></td></tr>
<tr><td>Recommended yearly flu and pneumococcal vaccination</td><td></td><td></td></tr>
<tr><td>Asked whether had previous history of chickenpox. If not, consider testing VZV IgG and vaccination if necessary</td><td></td><td></td></tr>
<tr><td>Counselled that live vaccines not recommended. There is no guidance as to whether it is safe to administer the shingles) vaccine. Therefore, if possible, eligible patients should be vaccinated at least 4 weeks prior to commencing therapy. (Patients at 70 years of age as part of the national vaccination programme.)</td><td></td><td></td></tr>
<tr><td>Counselled that if develops persistent cough or breathlessness, fever, sore throat, abnormal bleeding/bruising, rashes or jaundice to stop medication and seek immediate medical advice</td><td></td><td></td></tr>
<tr><td>Counselled that if has recurrent infections, seek medical advice (immunoglobulins should be checked)</td><td></td><td></td></tr>
<tr><td>Discussed need for monitoring</td><td></td><td></td></tr>
</table>
References
1. British Society for Rheumatology guideline for the prescription and monitoring of non-biologic disease modifying anti-rheumatic drugs. Ledingham J, Gullick N, Irving K et al 2017, Oxford University Press.
2. Myasthenia gravis: Association of British Neurologists' management guidelines. Sussman J, Farrugia ME, Hill M et al. Pract neurol 2015;15:199-206.
3. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Palace J, Newsom-Davis J, Lecky B. Neurology 1998;50(6):1778-83.
4. EFNS guidelines on diagnosis and management of neuromyelitis optica. Sellner J, Boggild M, Clanet M et al. Eur J Neurol 2010;17:1019-32.
5. Use of azathioprine for non-thymoma myasthenia and risk of cancer: a nationwide case-control study in Denmark. Pederse EG, Pottegard A, Hallas J et al. Eur J Neurol 2013;20:942-948.</td></tr>
</table>

6. Risk of non-melanoma skin cancer in myasthenia patients treated with azathioprine. Pederse EG, Pottegard A, Hallas J et al. Eur J Neurol 2014;21:454-458.
7. BSR and BHPR guideline on prescribing drugs in pregnancy and breast-feeding- Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Flint J, Panchal S, Hurrell A et al. Rheumatol 2016;55:1693-97.
8. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> Accessed: 11/1/18
9. Maxtrex 2.5 mg tablets SPC (Date of last update: 2/10/14). electronic Medicines Compendium (eMC). http://www.medicines.org.uk/emc/. Accessed on 11/1/18

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to full prescribing data in the SPC or the BNF.

Shared Care Request/Confirmation

Private and Confidential

Patient information:

To be completed by specialist prescriber:

		Patient details (use hospital label if preferred)	
Consultant	……	**Name**	……
Department	……	**Address**	……
Hospital	……		……
		Postcode	**Sex** ……...
		NHS or Hosp. Reg. No. ……	**DoB** ……...

Treatment Requested for Prescribing in Accordance with Shared Care Arrangement:

To be completed by specialist prescriber:

Drug name	
Dose	
Frequency	
Indication	
Other information	

Name (print)…… Signature (of specialist prescriber)…….…….. Date……..

Acceptance/rejection of treatment under Shared Care Agreement:

To be completed by GP:

Please tick one box

I ACCEPT the proposed shared care arrangement for this patient ❑

or

I ACCEPT the proposed shared care arrangement with the caveats below ❑

or

I DO NOT ACCEPT the proposed shared care arrangement for this patient ❑

My caveats / reason(s) for not accepting include:
……
……

Name (print)…… Signature (of GP)…….……... Date…

N.B. Participation in this shared care arrangement implies that prescribing responsibility is shared between the specialist prescriber and the patient's GP