SHARED CARE GUIDELINE
Azathioprine 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 guidelines 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	Azathioprine	Brand name	Imuran	Licensed Yes/No	*Some neurological indications are licensed and some are not (see below)*
Dosage form and strength	25mg tablets 50mg tablets			BNF class	10.1.3
Indication	Licensed: dermatomyositis and polymyositis Unlicensed: Myasthenia gravis, Lambert-Eaton myasthenic syndrome; chronic inflammatory demyelinating polyradiculoneuropathy (CIDP); multifocal motor neuropathy; neuromyelitis optica; autoimmune encephalitis, neurosarcoidosis.				
Dosage and Administration	Initially 25-50mg daily with or after food and then gradually increased to a maximum of 200mg daily. Usual dose range 2-3mg/kg/day. Max dose 3mg/kg/day.				
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 azathioprine for three months				
Excluded patients	Any patient in whom azathioprine is contraindicated or not tolerated See below for further information. 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 azathioprine: • Routine bloods including FBC, (ESR optional),U&E, LFTS, HIV, Hepatitis B & C • BMI<18 or>30kg/m^2 • 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 • Thiopurinemethyltransferase (TPMT) This enzyme metabolises azathioprine – deficiency therefore increases risk of marrow toxicity **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. <u>Monitoring of high risk patients</u> The patient may be at higher risk of toxicity 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, LFTs **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 <u>For patients who are NOT high risk:</u> **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**.** **<u>If any abnormal blood test results are obtained, withhold the medication and discuss with the patient's consultant neurologist.</u>** Do not forget to consider the possibility that the abnormal blood result may be unrelated to the immunosuppressant medication.

<table>
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<tr><th>Test</th><th>Result</th></tr>
<tr><td>White cell count</td><td><3.5 * 10^9/l (or downward trend over 2 consecutive tests)</td></tr>
<tr><td>Neutrophils</td><td><1.6 * 10^9/l</td></tr>
<tr><td>Unexplained eosinophilia</td><td>>0.5 * 10^9/l</td></tr>
<tr><td>Platelet count</td><td><140 * 10^9/l</td></tr>
<tr><td>MCV</td><td>> 105 f/l</td></tr>
<tr><td>Creatinine/ eGFR</td><td>Creatinine increase >30% over 12 months and/or GFR <60ml/min/1.73m2</td></tr>
<tr><td>ALT (and or AST)</td><td>>100 U/L</td></tr>
<tr><td>Albumin</td><td>Unexplained reduction in albumin to <30g/l</td></tr>
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If the patient develops oral ulceration, abnormal bruising, sore throat or an unexplained rash then reduce dose or withhold azathioprine if severe until FBC available and discuss with neurology team.
(Stomatitis protocol available on www.gatesheadhealth.nhs.uk/rheumatology for Gateshead patients only).</td></tr>
<tr><td>Infection</td><td>During serious infections, the immunosuppressant agent (IA) should be temporarily discontinued until the patient has recovered from the infection. It is usually appropriate to continue them in minor infections (e.g. a treated, uncomplicated UTI).
Patients treated with immunosuppressants are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). During serious infections, the IA should be temporarily discontinued, until the patient has recovered from the infection. The patient should be clinically assessed and the assessing clinician should be informed that the patient has been on azathioprine
If infection develops requiring antibiotics, stop azathioprine for duration of antibiotics. Patient should be seen by GP/clinician within 12 hours of onset of infective symptoms. Azathioprine can be restarted after antibiotics have been completed and the patient is clinically improving with monitoring as per dose change.
If Herpes Zoster occurs stop azathioprine and prescribe aciclovir. <u>If patient is in contact with chicken pox, contact neurology team (may need Zoster Immunoglobulin).</u></td></tr>
<tr><td>Vaccination</td><td>Vaccination against influenza and pneumococcus should be offered. Live vaccines should not be given.</td></tr>
<tr><td>Pregnancy and breastfeeding</td><td>All patients, both men and women, should seek the advice of the consultant neurologist when considering pregnancy whilst taking Azathioprine. It is safe in pregnancy at usual doses (max 2mg/kg/day). If continued in pregnancy, dose should be reduced at 32wks gestation to prevent neonatal leucopoenia. Present in the breast milk of lactating women, although current guidelines suggest breast feeding is safe.</td></tr>
<tr><td>Perioperative use</td><td>Steroid exposure should be minimised prior to surgical procedures and increases in steroid doses to prevent adrenal insufficiency are not routinely required</td></tr>
<tr><td>Nausea and vomiting</td><td>a) add anti-emetic e.g. prochlorperazine 5mg three times a day
b) reduce azathioprine dose
c) stop and refer if severe or if no improvement with above</td></tr>
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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 azathioprine 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 • 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 stable on same dose for 3 months • 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.

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- Observe advice relating to vaccination, perioperative use, infections etc contained in this document

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<tr><td>Contraindications,Precautions and Adverse Effects</td><td>

Contra-indications
Known hypersensitivity to the product
Suspected local or systemic infection
Pregnancy and breast feeding (see below)
Bone marrow failure, with unexplained anaemia and cytopenia
Absent or low TPMT levels
Previous allergy to mercaptopurine

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

Degree of Impairment	**Calculated GFR ml/min/1.73m2**
Normal, Stage I	>90 (other evidence of kidney damage)
Mild, Stage II	60-89 (other evidence of kidney damage)
Moderate, Stage III	30-59
Severe, Stage IV	15-29
Established renal failure, Stage V	<15

Table 2: Recommended dose adjustment in CKD by the BSR

			Recommended adjustment (% of standard dose)		
Drug	Accumulates in renal failure	Nephrotoxic	CKD III	CKD IV	CKD V
Azathioprine	No	No	Normal dose	75-100	50-100
Methotrexate	Yes	Yes	50%	Contraindicated	
Mycophenolate	Yes	No	Normal dose	1g BD maximum	

Adverse Effects
The most common side effects (affecting approximately 20% of patients) are flu-like symptoms (myalgia, headache, diarrhoea) which characteristically occur 2-3 weeks after initiating treatment and usually subside if treatment is continued.

- Gastro-intestinal disturbances - Nausea, vomiting, diarrhoea, anorexia and abdominal discomfort
- Hepatotoxicity (hepatic necrosis, biliary stasis)
- Bone marrow suppression (leucopoenia, thrombocytopenia) and therefore increased risk of infection. Most likely to occur in the first few weeks of treatment.
- Oral ulceration, rarely gastrointestinal ulceration

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- Hypersensitivity reactions (fever, rigors, rash, myalgia, arthralgia, hypotension, dizziness)
- Rarely pancreatitis, interstitial nephritis
- Alopecia

For a full list of contraindications/precautions/side effects please consult either the current BNF or SPC
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<tr><td>Common Drug Interactions</td><td>

Interactions:

- **Never prescribe co-trimoxazole and trimethoprim.**
- Live vaccines should not be given.
- Caution with penicillins.
- Alcohol may be consumed in moderation, on average one unit per day but avoid binge drinking
- Avoid allopurinol if possible. If it is initiated the dose of azathioprine must be reduced to 25% and increase monitoring frequency to weekly.
- Other significant interactions occur between azathioprine, rifampicin and warfarin.
- Reduced absorption of phenytoin, valproate and carbamazepine.
- Aminosalicylates (e.g. sulfasalazine) contribute to bone marrow toxicity and increased monitoring may be required.
- ACE inhibitors - potential to increase the risk of anaemia and/or leucopenia and/or renal impairment when given with azathioprine.
- Febuxostat – potential to increase azathioprine levels

For a full list of interactions please consult either the current BNF or SPC.
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<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 via Sunderland switchboard (0191) 5656256.</td></tr>
<tr><td>Caveat</td><td>This document should be read in conjunction with the general guidance on immunosuppression attached</td></tr>
<tr><td>Checklist and References</td><td>

Weight: _____ BP:_____

Starting dose:_____ twice daily

	YES	NO
Received education and written information about their treatment?		
Advised of potential adverse effects of drug including allergy		
Advised about reproductive issues as above		
Assessed for contraindication to drug		
Evaluated for chronic lung disease? If chronic lung disease present: had lung function tests, CXR +/- high resolution CT chest and respiratory referral		
Assessed if any risk of latent TB, if so, CXR performed		
Smoking status checked and cessation advice given if necessary		
Evaluated for liver disease and any causes addressed and managed if necessary.		
Evaluated for renal disease and any dose reduction made if necessary (dose of 1g BD maximum in CKD stages IV and V)		
Discussed possible risk of increased malignancy		
Made aware of the national screening programmes for cervical, breast, bowel and prostate cancer		
Given skin cancer advise and assessed whether had previous/current skin cancer, and, if so, consideration made as to whether to refer to dermatologist		

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	Screening blood tests performed: FBC, U&Es, LFTs, HIV, hepatitis B and C		
	Pregnancy test		
	Assessed if any symptoms of acute infection		
	Urinalysis		
	Recommended yearly flu and pneumococcal vaccination		
	Asked whether had previous history of chickenpox. If not, consider testing VZV IgG and vaccination if necessary		
	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.)		
	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		
	Counselled that if has recurrent infections, seek medical advice (immunoglobulins should be checked)		
	Discussed need for monitoring		

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.
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