GMMMG Interface Prescribing Subgroup

Shared Care Guideline

Shared Care Guideline **AZATHIOPRINE for autoimmune renal conditions**		**Reference Number**
Version: 2	**Replaces:** Version 1	**Issue date:** *20/02/2017*
Author(s)/Originator(s): (please state author name and department) *Elizabeth Lamerton/ Dr Smeeta Sinha* *Pharmacy Department/ Department of renal medicine* *Salford Royal NHS Foundation Trust*		**To be read in conjunction with the following documents:** Current Summary of Product characteristics (http://www.medicines.org.uk) BNF
Date approved by Interface Prescribing Group: *N/A*	**Date approved by SRFT Medicines Management Group:** *20/02/2017*	
Date approved by Commissioners: *N/A*	**Review Date:** 20/02/2019	

Please complete all sections

1. Name of Drug, Brand Name, Form and Strength	*Azathioprine tablets 25mg/50mg*
2. Licensed Indications	Azathioprine is indicated in severe cases of the following diseases in patients who are intolerant to steroids or who are dependent on steroids and in whom the therapeutic response is inadequate despite treatment with high doses of steroids: - Systemic lupus erythematosus;
3. Criteria for shared care	Prescribing responsibility will only be transferred when ▪ Treatment is for a specified indication and duration. ▪ Treatment has been initiated and established by the secondary care specialist. ▪ The patient's initial reaction to and progress on the drug is satisfactory. ▪ The GP has agreed in writing in each individual case that shared care is appropriate. ▪ The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements

<table>
<tr><td>4. Patients excluded from shared care</td><td colspan="3">• Unstable disease state
• Patient does not consent to shared care
• Patient does not meet criteria for shared care</td></tr>
<tr><td>5. Therapeutic use & background</td><td colspan="3">Off label use as a steroid sparing agent in glomerulonephritis therapy during both the induction and maintenance phase of treatment.</td></tr>
<tr><td>6. Contraindications (please note this does not replace the SPC or BNF and should be read in conjunction with it).</td><td colspan="3">a) Hypersensitivity to azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any of the excipients.
b) Severe infections.
c) Severely impaired hepatic or bone-marrow function.
d) Pancreatitis.
e) Any live vaccine especially BCG, smallpox, yellow fever.

TPMT (thiopurine methyl transferase) deficiency (homozygous state) - avoid can be fatal.

<u>Cautions</u>
TPMT deficiency (heterozygous state), may be associated with delayed haemato-toxicity, including bone marrow toxicity. Localised or systemic infection (including hepatitis B or C or history of tuberculosis).
.</td></tr>
<tr><td>7. Prescribing in pregnancy and lactation</td><td colspan="3">This drug can be prescribed in the pregnancy/ breast feeding patient. Under these circumstances prescribing should be the responsibility of GP and specialist renal obstetric clinic.</td></tr>
<tr><td rowspan="5">8. Dosage regimen for continuing care</td><td>Route of administration</td><td colspan="2">oral</td></tr>
<tr><td colspan="3">Preparations available (include in this section any necessary information relating to availability of special preparations for children or those with swallowing difficulties)
Special product suspension available</td></tr>
<tr><td colspan="3">Please prescribe:
As per clinic letter -</td></tr>
<tr><td>Is titration required</td><td>Yes (complete the following section)</td><td>No</td></tr>
<tr><td colspan="3">.usual dose 1-2.5mg/kg/day
Maintenance dosage up to a maximum 250mg day</td></tr>
<tr><td colspan="4">Adjunctive treatment regime:
Annual flu vaccinations are safe and recommended.

Pneumococcal vaccination is safe and recommended.

In non-immune patients exposed to chickenpox or shingles, passive immunisation should be carried out using Varicella zoster immunoglobulin (VZIG). It is the specialist’s responsibility to make the recommendation for vaccination at the appropriate time</td></tr>
</table>

	Conditions requiring dose reduction: *Low white cell count* *Raised liver enzymes*
	Usual response time : *Two to four weeks*
	Duration of treatment: *months to lifelong*
	Treatment to be terminated by: *secondary care*
	NB. All dose adjustments will be the responsibility of the initiating specialist care unless directions have been specified in the medical letter to the GP.
9.Drug Interactions ***For a comprehensive list consult the BNF or Summary of Product Characteristics***	The following drugs must <u>not</u> be prescribed without consultation with the specialist: The following drugs must not be prescribed without consultation with the specialist: • Immunisation using a live organism vaccine (e.g.: oral polio, oral typhoid, MMR, BCG, yellow fever) has the potential to cause infection in immunocompromised Patients. • Allopurinol has the potential to cause azathioprine toxicity; please see Section 6 under "conditions requiring dose reduction". • Coumarins – Azathioprine possibly reduced anticoagulant effect. • Febuxostat – avoid in combination with Azathioprine. • Sulfamethoxazole (e.g. Trimethoprim or Co-trimoxazole) and Trimethoprim – increased risk of haematological toxicity when Azathioprine given concurrently. • Avoid use with clozapine, increased risk of agranulocytosis. • Ribavirin - severe myelosuppression has been reported following concomitant administration of azathioprine and ribavirin; therefore co-administration is not advised

The following drugs may be prescribed with caution:
The following drugs may be prescribed with caution:

- ACE inhibitors - co-prescription may cause anaemia.
- Phenytoin, Sodium Valproate, Carbamazepine - there is reduced absorption of these drugs.
- Aminosalicylates may contribute to bone marrow toxicity.
- Alcohol intake maximum 6 units weekly.

10. Adverse drug reactions

For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult Summary of Product Characteristics or BNF

Specialist to detail below the action to be taken upon occurrence of a particular adverse event as appropriate. Most serious toxicity is seen with long-term use and may therefore present first to GPs.

Adverse event System – symptom/sign	**Action to be taken** **Include whether drug should be stopped prior to contacting secondary care specialist**	**By whom**
<u>*Haematological*</u> e.g. Leukopenia, anaemia, neutropenia, thrombocytopenia, macrocytosis, erythroid hypoplasia.	See monitoring below	GP
<u>*Hepatic:*</u> *e.g.* Liver dysfunction (tends to be dose-related).	See monitoring below	GP
<u>*Gastrointestinal:*</u> e.g. Nausea, loss of appetite and diarrhoea.	Review for reversible causes / see dose advice Discuss with renal teamy if persistent or severe	GP
<u>*Mucocutaneous*</u>**:** e.g. Urticaria, drug rash, pruritus, oral ulceration, alopecia	Review for reversible causes Urgent FBC	GP
<u>*Other:*</u> *e.g.* Myalgia, arthralgia, fevers, pancreatitis, opportunistic infections and idiosyncratic hypersensitivity reactions.	Review for reversible causes Urgent Blood tests Withhold and discuss with renal team	GP

The patient should be advised to report any of the following signs or symptoms to their GP without delay:

- Signs or symptoms indicating blood dyscrasias e.g. sore throat, infection, unexplained or abnormal bruising or bleeding. These may suggest bone

	marrow suppression. Stop the drug and obtain an urgent FBC. • Any signs of bone marrow suppression (e.g. infection, fever, unexplained bruising or bleeding) Stop the drug and obtain an urgent FBC. • Jaundice. • Abdominal pain – may suggest pancreatitis. **Please note that, in addition to absolute values for haematological indices, a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.**
	Other important co morbidities (e.g. Chickenpox exposure): • History of TB – treatment with these drugs should be avoided and infectious diseases specialist advice sought if treatment with Azathioprine deemed necessary. • History of active hepatitis B or C – treatment with these drugs should be avoided (consider vaccination where appropriate). • Live vaccines should not be given concurrently with these treatments. • Annual flu vaccinations are safe and recommended (due to suppressed immune system with these drugs). • Pneumococcal vaccination is safe and recommended (due to suppressed immune system with these drugs). • Human-Papilloma Virus (HPV) vaccination should be considered. • In non-immune patients exposed to chickenpox or shingles, passive immunization should be carried out using varicella zoster immunoglobulin (VZIG). • Patients should try to avoid contact with people who have active chickenpox or shingles and should report any such contact urgently to their GP or specialist. • Sunscreens should be encouraged to reduce excessive sunlight exposure (to reduce skin cancer risk).
	Any adverse reaction to a black triangle drug or serious reaction to an established drug should be reported to the MHRA via the "Yellow Card" scheme.
11.Baseline investigations	*List of investigations / monitoring undertaken by secondary care* • Pre-screening for TPMT. • TPMT – patients who are deficient or lacking in the enzyme thiopurine methyltransferase (TPMT) are at higher risk of myelosuppression* • Full Blood Count (FBC) and Liver function tests (LFTs). U&Es, • Hepatitis B & C and HIV screen; TB screen (at risk groups); • Varicella zoster immunity screen (if no clear Hx of chicken pox). • Weight (kg) – for initial dosing of drugs. *Patients with reduced TPMT activity can still have treatment but at a reduced dose and should be monitored monthly. Treatment should remain under the care of the Specialist, unless the GP is willing and able to take on this responsibility. • The specialist team will undertake initial monitoring of patients including FBC, U+Es and LFTs until therapeutic dose is established, typically every 2 weeks

<table>
<tr><td></td><td colspan="5">until on stable dose for 6 weeks then monthly for 3 months. Thereaafter at least every 12 weeks and more frequently if patients are at higher risk of toxicity.
• If dose changes during course of treatment, the specialist service will be responsible for monitoring until patient is stabilised on new regimen. Monitoring should be carried out every 2 weeks for 6 weeks.
• Once patient stabilised on medication, shared care will be initiated with the GP.</td></tr>
<tr><td rowspan="6">12. Ongoing monitoring requirements to be undertaken by GP</td><td colspan="2">Is monitoring required?</td><td colspan="3">Yes or No (if yes complete following section) [insert]</td></tr>
<tr><td>Monitoring</td><td>Frequency</td><td>Results</td><td>Action</td><td>By whom</td></tr>
<tr><td>FBC</td><td>Minimum of every 3 months when stable</td><td>WBC < 3.5 x 10^9 / L

Neutrophils <2.0 x 10^9 / L

Platelets <150 x 10^9 / L</td><td>Withhold until discussed with renal team</td><td>GP</td></tr>
<tr><td>LFT</td><td>Every three months for duration of treatment unless a further dose increase</td><td>>2-fold rise in AST, ALT or Alk Phos (from upper limit of reference range)</td><td>Withhold until discussed with renal team</td><td>GP</td></tr>
<tr><td>U&E</td><td>Every three months for duration of treatment unless a further dose increase</td><td>>30% increase in creatinine from baseline

Potassium >5.5</td><td>Withhold until discussed with renal team</td><td>GP</td></tr>
<tr><td>MCV</td><td>Every three months for duration of treatment unless a further dose increase</td><td>MCV>105fl</td><td>Investigate.
If B12 or folate low, start appropriate supplementation.</td><td>GP</td></tr>
<tr><td>13. Pharmaceutical aspects</td><td colspan="5">e.g. special storage requirements, washout periods Or where there are “no special considerations”
Azathioprine – providing the film coating of the tablets remains intact, there is no risk or additional precautions required when handling them. These tablets should not be divided / split / crushed.

Named patient suspension available as a special product</td></tr>
</table>

14. Responsibilities of initiating specialist	• Initiate treatment and prescribe until dose is stable.
	• Undertake baseline monitoring.
	• Dose adjustments.
	• Monitor patient's initial reaction to and progress on the drug.
	• Ensure that the patient has an adequate supply of medication until GP supply can be arranged.
	• Patients will be considered suitable for transfer to GP prescribing ONLY when they meet the criteria listed in section 3 above.
	• The consultant team will write formally to the GP to request shared care using the Shared Care Agreement Form (Appendix 2) which must be fully completed. Failure to supply all the required information will result in the refusal of the request until all information has been supplied.
	• Patients will only be transferred to the GP once the GP has agreed via signing copies of the Shared Care Agreement Form (Appendix 2).
	• Continue to monitor and supervise the patient according to this protocol, while the patient remains on this drug, and agree to review the patient promptly if contacted by the GP
	• Provide GP with diagnosis, relevant clinical information and baseline results, treatment to date and treatment plan, duration of treatment before consultant review.
	• Provide GP with details of outpatient consultations, ideally within 14 days of seeing the patient or inform GP if the patient does not attend appointment.
	• Provide GP with advice on when to stop this drug.
	• Act upon communication from the GP in a timely manner.
	• Provide patient with relevant drug information to enable Informed consent to therapy.
	• Provide patient with relevant drug information to enable understanding of potential side effects and appropriate action.
	• Patients should be advised to seek medical attention for the following:
	  ○ Patients should report all symptoms and signs suggestive of blood disorders (e.g. sore throat, bruising and mouth ulcers);
	  ○ Patients should report all symptoms and signs suggestive of liver toxicity (e.g. nausea, vomiting, abdominal discomfort, dark urine and jaundice);
	  ○ Patient should report any upper abdominal pain as this is an indicator of development of pancreatitis.
	• Provide patient with relevant drug information to enable understanding of the role of monitoring.
	• Provide patient with monitoring booklet where appropriate.
	• Be available to provide patient specific advice and support to GPs as necessary

15. Responsibilities of the GP	• Continue treatment as directed by the specialist. • Ensure no drug interactions with concomitant medicines. • To monitor and prescribe in collaboration with the specialist according to this protocol. • To ensure that the monitoring and dosage record is kept up to date. • To undertake vaccination as directed by the initiating consultant, the BNF or Green Book. • Symptoms or results are appropriately actioned, recorded and communicated to secondary care when necessary. • Formally reply to the consultant's request to shared care within 14 days of receipt, using the shared care agreement forms (Appendix 2). NB. The GP should only agree to the transfer of prescribing if all details of the form have been completed.

	• If the GP does not feel it is appropriate to take on the prescribing then the prescribing responsibilities will remain with the specialist. The GP should indicate the reason for declining. • Enter a READ code on to the patient record to highlight the existence of shared care for the patient. • Undertake more frequent tests if there is evidence of clinical deterioration, abnormal results, or symptoms suggesting abnormal hepatic function or other risk factors. Contact consultant team for advice on monitoring in these circumstances if required. • Check all monitoring results prior to issuing a repeat prescription to ensure it is safe to do so. • If a patient fails to attend for monitoring: o Only issue a 28 day prescription and send them the next available appointment for a blood test; o If they fail to attend a second blood test then contact the consultant team for advice and to discuss suitability for continued shared care before supplying further prescriptions. • Monitor the patient's general wellbeing. • Seek urgent advice from secondary care if: o Signs or symptoms indicating blood dyscrasias, e.g. sore throat, infection, unexplained or abnormal bruising or bleeding. o Any signs of bone marrow suppression (e.g. infection, fever, unexplained bruising or bleeding). o Jaundice. o The patient becomes pregnant. o Non-compliance is suspected. o The GP feels a dose change is required. o There is marked deterioration renal function. o The GP feels the patient is not benefiting from the treatment. • The shared care agreement will cease to exist, and prescribing responsibility will return to secondary care, where: o The clinical situation deteriorates such that the shared care criterion of stability is not achieved. o The clinical situation requires a major change in therapy. o GP feels it to be in the best stated clinical interest of the patient for prescribing responsibility to transfer back to the consultant team. The consultant team will accept such a transfer within a timeframe appropriate to the clinical circumstances. There must be discussion between the consultant team and GP on this matter and agreement from the consultant team to take back full prescribing responsibility for the treatment of the patient. The consultant team should be given 14 days' notice in which to take back prescribing responsibilities from primary care
16. Responsibilities of the patient	• To take medication as directed by the prescriber, or to contact the GP if not taking medication • To attend hospital and GP clinic appointments, bring monitoring booklet (if issued) • Failure to attend will result in medication being stopped (on specialist advice). • To report adverse effects to their Specialist or GP.

17.Additional Responsibilities e.g. Failure of patient to attend for monitoring, Intolerance of drugs,	**List any special considerations**	**Action required**	**By whom**	**Date**

Monitoring parameters outside acceptable range, Treatment failure, Communication failure				
	[insert]	***[insert]***	***[insert]***	***[insert]***
	[insert]	***[insert]***	***[insert]***	***[insert]***
18. Supporting documentation	The SCG must be accompanied by a patient information leaflet. (Available from http://www.medicines.org.uk/emc OR http://www.mhra.gov.uk/spc-pil/) http://www.medicines.org.uk/emc/PIL.29120.latest.pdf			
19. Patient monitoring booklet (may not be applicable for all drugs)	**n/a**			
20. Shared care agreement form	Attached below			
21. Contact details	See Appendix 1			

Appendix 1 – Local Contact Details

Lead author contact information	**Name:** *Elizabeth Lamerton*
	Email: *Elizabeth.lamerton@srft.nhs.uk*
	Contact number: *0161 2065220*
	Organisation: *Salford Royal NHS Foundation Trust*

Commissioner contact information	**Name:** *[insert text here]*
	Email: *[insert text here]*
	Contact number: *[insert text here]*
	Organisation: *[insert text here]*

Secondary care contact information	**If stopping medication or needing urgent advice please contact:**
	Renal baton bleep via switch
	Contact number: *0161 7897373*
	Fax:*n/a*
	Hospital: *Salford Royal NHS Foundation Trust*

Shared Care Agreement Form

Specialist request

***IMPORTANT: ACTION NEEDED**

Dear Dr *[insert Doctors name here]*

Patient name: *[insert Patients name here]*
Date of birth: *[insert date of birth]*
NHS Number: [insert NHS Number]
Diagnosis: *[insert diagnosis here]*

This patient is suitable for treatment with *azathioprine* for the treatment of
Autoimmune renal disease

This drug has been accepted for Shared Care in Greater Manchester. I am therefore requesting your agreement to share the care of this patient.

The patient has received drug education on the medication.

Treatment was initiated *[insert date started]* *[insert dose].*

If you are in agreement, please undertake monitoring and treatment from *[insert date]*

NB: date must be at least 1 month from initiation of treatment.

Baseline tests: *[insert information]*

Next review with this department: *[insert date]*

You will be sent a written summary within 14 days. The clinical staff of the department are available for advice and the consultants secretary should be contacted first . Out of hours the renal baton bleep holder may be contacted through switchboard.

The patient will not be discharged from out-patient follow-up while taking *[insert text here]*.

Please use the reply slip overleaf and return it as soon as possible.

Thank you.

Yours

[insert Specialist name]

Shared Care Agreement Form

GP Response

Dear Dr *[insert Doctors name]*

Patient *[insert Patients name]*

NHS Number *[insert NHS Number]*

Identifier *[insert patient date of birth/address]*

I have received your request for shared care of this patient who has been advised to start *[insert text here]*

A I am willing to undertake shared care for this patient as set out in the protocol

B I wish to discuss this request with you

C I am unable to undertake shared care of this patient.

My reasons for not accepting are: *(Please complete this section)*

GP signature Date

GP address/practice stamp

Shared Care Guideline Summary:
Azathioprine* for the treatment of *autoimmune renal disease

Drug	Azathioprine
Indication	Autoimmune renal disease (glomerulonephropathies) as a steroid sparing agent
Overview	Azathioprine is converted to mercaptopurine, an anti-metabolite interfering with nucleic acid synthesis, and so acts as an immunosuppressant. It is commonly used is various severe inflammatory skin diseases unresponsive to standard therapy.
Specialist's Responsibilities	**Initial investigations:** FBC, U&Es, creatinine, LFTs and TPMT assay. Hepatitis B & C serology; HIV. Consider VZV serology (if no Hx of varicella), TB screen (at risk groups) and CXR. **Initial regimen:** Azathioprine 1mg/kg/day; increase to 2-2.5mg/kg/day if necessary. **Clinical monitoring:** Clinical response assessment – condition dependent. Review of side effects and skin examination. **Frequency:** As required; Minimum 6 monthly review. **Safety monitoring:** Monthly FBC U&E / LFT every 3 months **Prescribing duration:** Variable – depends on condition and response **Prescribing details:** As per shared care agreement **Documentation:** Shared care agreement Clinic letters
GP's Responsibilities	**Maintenance prescription:** Azathioprine 1-2.5mg/kg/day **Clinical monitoring:** *Review of side effects* **Safety monitoring:** Monthly FBC U&E / LFT every 3 months **Duration of treatment:** Variable – dependant on condition and response. **Documentation:** Shared care agreement

Adverse Events	Adverse events | Action | | | | | |
Contra-indications Cautions Drug Interactions	Please refer to the BNF and/or SPC for information
Other Information	
Contact Details	**Name:** **Address:** **Telephone:**