South Tyneside and Sunderland
Area Prescribing Committee

SHARED CARE GUIDELINE

Azathioprine and Mercaptopurine for use in Gastroenterology

Implementation Date: May 2021 **Review Date: May 2024**

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
STS Area Prescribing Committee and relevant groups / committees within stakeholder organisations	**May 2021 (STS APC December 2020)**

Instructions for completion:

- ☐ 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	Azathioprine Imuran Azapress	Licensed No	*As per BNF "Unlicensed use - Azathioprine … for suppression of transplant rejection and autoimmune conditions"*
	Mercaptopurine	Brand name	Mercaptopurine Hanixol Xaluprine	Licensed No	*As per BNF "Unlicensed use - Azathioprine … for suppression of transplant rejection and autoimmune conditions"*
Dosage form and strength	Azathioprine 25mg, 50mg tablets, 50mg/5ml Suspension			BNF class	*eBNF 8.1.3*
	Mercaptopurine 10mg, 50mg tablets, 20mg/ml Suspension			BNF class	*eBNF 8.1.3*
Indication	Inflammatory Bowel Disease Severe acute Crohn's disease, Maintenance of remission of Crohn's disease, Maintenance of remission of acute ulcerative colitis Autoimmune conditions (e.g. Auto Immune Hepatitis)				

Dosage and Administration	**Azathioprine** Normal daily dose of 2-2.5mg/kg or less if TPMT (thiopurine methyltransaminase) is low. **Mercaptopurine** Normal daily dose of 1-1.5mg/kg or less if TPMT (thiopurine methyltransaminase) is low
Eligibility criteria for shared care	Patients must be under the care of a consultant Gastroenterologist. Must have a diagnosis of Inflammatory Bowel Disease (e.g. Crohn's disease, ulcerative colitis) or an Autoimmune condition (e.g. Auto Immune Hepatitis). Patients who have been stabilised and have been treated by specialist for at least three months. Patients who are not stable should not be transferred to primary care for monitoring.
Excluded patients	Any patient in whom azathioprine or Mercaptopurine 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 will be completed by specialist prior to initiation** **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 and/or AST, Albumin, creatinine/eGFR **Frequency:** Every two weeks until stable on a dose for 6 weeks. • Once on a stable dose: monthly blood tests. • Following a dose increase bloods should be checked every two weeks for 6 weeks, then revert back to previous schedule **For patients who are NOT high risk:** **Routine Bloods**: FBC, U&E, ALT and/or AST, Albumin, creatinine/eGFR **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 Gastroenterologist**. 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 * 109 /l (or sequential falls in WBC on 3 occasions)
Neutrophils	<1.6 * 109 /l (or sequential falls neutrophils >10% on 3 occasions)
Unexplained eosinophilia	>0.5 * 109 /l
Platelet count	<140 * 109 /l or sequential falls
MCV	> 105 fL
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 azathioprine / mercaptopurine if severe until FBC available and discuss with specialist.

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 azathioprine / Mercaptopurine 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 azathioprine / Mercaptopurine in minor infections (e.g. a treated, uncomplicated UTI). The azathioprine / Mercaptopurine would usually be restarted after antimicrobial treatment is complete and the patient has started to make a significant
clinical improvement. When the azathioprine / Mercaptopurine 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 azathioprine / Mercaptopurine and prescribe aciclovir. If patient is in contact with chicken pox, contact specialist (may need Zoster Immunoglobulin). Discuss the clinical situation with the Specialist.

Vaccination	Vaccination against influenza and pneumococcus should be offered. Live vaccines should not be given. Shingles vaccination (Zostavax®) contains live, attenuated virus. The Green Book advises that shingles vaccine can be administered provided the dose of azathioprine is ≤3.0mg/kg/day and no other contraindications exist. Please refer to the latest Green Book for current advice: https://www.gov.uk/government/collections/immunisation-against-infectiousdisease-the-green-book
Pregnancy and breastfeeding	Seek specialist advice if patient is considering pregnancy from Consultant Gastroenterologist. Azathioprine / Mercaptopurine should not be used in pregnancy without careful assessment of risks and benefit. Adequate contraceptive precautions should be advised in both men and women taking Azathioprine / Mercaptopurine Women taking Azathioprine / Mercaptopurine should avoid breastfeeding unless the benefits outweigh the potential risks.
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	Azathioprine / Mercaptopurine may cause nausea, vomiting or diarrhoea on their introduction or on an escalation of the dose. In this situation, contact the specialist. Once the patient has been established on a stable dose of an IA it would be unusual for this to cause significant GI symptoms.
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 3 months after initiation and patient is stable • At least 4 weeks of medication supplied at point of transfer • 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 • Specialist responsible for assessing if a patient is defined as ‘high risk’ and communicating this to the GP

<table>
<tr><td>GP Responsibilities</td><td>

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 is stable and at least 3 months after initiation
Prescribe medication as per document
Conduct routine monitoring as per schedule while responsible for prescribing
Observe advice relating to vaccination, perioperative use, infections etc

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<tr><td>Adverse Effects, Precautions and Contraindications</td><td>
Contra-indications
Known hypersensitivity to the product
Suspected local or systemic infection
Pregnancy and breast feeding
Bone marrow failure, with unexplained anaemia and cytopenia
Absent or low TPMT levels
Previous allergy to mercaptopurine / Azathioprine

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. The Gastroenterology team recommend using the guidance outlined by the British Society of Rheumatology (BSR) (table 2) as a pragmatic approach to this patient group.

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></td><td></td><td></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 / Mercaptopurine</td><td>No</td><td>No</td><td>Normal Dose</td><td>75-100%</td><td>50-100%</td></tr>
</table>
Adverse Effects
• Nausea
• Bone marrow suppression (leucopoenia, thrombocytopenia) and therefore increased risk of infection. Most likely to occur in the first few weeks of treatment.
• Hypersensitivity reactions (malaise, vomiting, diarrhoea, fever, rigors, rash, myalgia, arthralgia, hypotension, dizziness, renal dysfunction) – contact specialist
• Pancreatitis
• Alopecia
For a full list of adverse effects please consult either the current BNF or SPC:
https://bnf.nice.org.uk/
https://www.medicines.org.uk/emc
</td></tr>
<tr><td>Common Drug Interactions</td><td>
Interactions:
• Ribavirin – co-administration with azathioprine is not advised
• Alcohol may be consumed in moderation, on average one unit per day Azathioprine / Mercaptopurine but avoid binge drinking
• Avoid allopurinol if possible. If it is initiated the dose of Azathioprine / Mercaptopurine must be reduced to 25% and increase monitoring frequency to weekly.
</td></tr>
</table>

<table>
<tr><td></td><td colspan="3">• Warfarin – Azathioprine / Mercaptopurine decreases the anticoagulant effect
• ACE inhibitors - potential to increase the risk of anaemia and/or leucopenia and/or renal impairment when given with Azathioprine / Mercaptopurine.
• Febuxostat – potential to increase Azathioprine / Mercaptopurine levels
• Trimethoprim
For a full list of interactions please consult either the current BNF or SPC:
https://bnf.nice.org.uk/
https://www.medicines.org.uk/emc</td></tr>
<tr><td rowspan="2">Communication/ Contact Details</td><td>IBD Nurses
Emily Hopkins or Claire Maclennan
South Tyneside and Sunderland
Foundation NHS Trust
South Tyneside District Hopsital
Harton Lane
South Shields
NE34 0PL
Tel: 0191 404 1000 ext 2274 or bleep 791</td><td>IBD Nurses
Nichola Pringle or Wenna Torres
Sunderland Royal Hospital
Kayll Rd
Sunderland
SR4 7TP
0191 5410054 Ext: 47446/47420
Bleep: 52017/53087
E-Mail: stsft.ibdchs@nhs.net</td><td>For Liver Patients – contact Named Consultant
(If not possible then Hepatology Nurse Julie Walker)
South Tyneside and Sunderland
Foundation NHS Trust
Sunderland Royal Hospital
Kayll Rd
Sunderland
SR4 7TP
0191 5656256
Ext 41270</td></tr>
<tr><td colspan="3">If out of Hours advice is required: The On Call Gastroenterologist can be contacted via the switchboards of the Hospital</td></tr>
</table>

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.

NHS

South Tyneside and Sunderland
Area Prescribing Committee

Shared Care Request/Confirmation

Private and Confidential

Patient information:

To be completed by specialist prescriber:

Consultant ……	**Patient details (use hospital label if preferred)**
Department ……	**Name** ……
Hospital ……	**Address** ……
	……
	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