One + all | we care

Royal Cornwall Hospitals NHS Trust

Azathioprine and Mercaptopurine in Inflammatory Bowel Disease and Autoimmune Liver Disease Shared Care Guideline

V3.1

April 2023

1. Aim/Purpose of this Guideline

1.1. This guideline applies to medical, nursing and pharmacy staff in the safe and appropriate prescription and administration of azathioprine or mercaptopurine when used in inflammatory bowel disease and autoimmune liver disease.

1.2. This shared care guideline sets out details for the sharing of care of patients with inflammatory bowel disease (IBD) and autoimmune liver disease (AIH) prescribed azathioprine or Mercaptopurine. These guidelines provide additional limited information necessary to aid in the treatment these patients. As with all shared care guidelines they highlight relevant prescribing issues but should be used in conjunction with relevant NICE guidance, the BNF, ABPI summary of product characteristics and do not replace them.

1.3. This version supersedes any previous versions of this document.

Data Protection Act 2018 (General Data Protection Regulation – GDPR) Legislation

The Trust has a duty under the Data Protection Act 2018 and General Data Protection Regulations 2016/679 to ensure that there is a valid legal basis to process personal and sensitive data. The legal basis for processing must be identified and documented before the processing begins. In many cases we may need consent; this must be explicit, informed, and documented. We cannot rely on opt out, it must be opt in.

Data Protection Act 2018 and General Data Protection Regulations 2016/679 is applicable to all staff; this includes those working as contractors and providers of services.

For more information about your obligations under the Data Protection Act 2018 and General Data Protection Regulations 2016/679 please see the Information Use Framework Policy or contact the Information Governance Team

Royal Cornwall Hospital Trust rch-tr.infogov@nhs.net

2. The Guidance

2.1. Azathioprine and Mercaptopurine are antimetabolite drugs that interfere with nucleic acid synthesis.

Azathioprine is extensively metabolised to Mercaptopurine in vivo. Mercaptopurine is an option where azathioprine has been beneficial but side effects are affecting tolerability. Mercaptopurine in Inflammatory Bowel Disease and azathioprine in Autoimmune Liver Disease are common but unlicensed uses of these drugs.

2.2. **Preparations and Dosage**

2.2.1. Azathioprine: The usual dose range is 2-2.5mg/kg daily for IBD. The usual dose for autoimmune liver disease is 1-2mg/kg daily, usually with a starting dose of 50mg.

2.2.2. Mercaptopurine: The usual dose range is 1-1.5mg/kg daily.

The target dose will be clearly specified in the clinic letter.

2.2.3. Special patient groups: Use doses at the lower end of the range for the elderly and patients with hepatic or renal impairment.

2.2.4. Products are Azathioprine 25mg, 50mg tablets and Mercaptopurine 50mg tablets.

2.3. Contraindications and Precautions

2.3.1. Contraindications:

- Avoid azathioprine in patient with very low TPMT activity – can be fatal.
- Hypersensitivity to azathioprine.
- Hypersensitivity to Mercaptopurine.
- Live vaccines.

2.3.2. Azathioprine / Mercaptopurine should be used with caution:

2.3.2.1. Pregnancy: In most cases azathioprine should not be prescribed if there is a risk of pregnancy although there may be some circumstances where continuing treatment for the safety of the individual outweighs the possible risks related to the unborn child. When planning a pregnancy it is important that both men and women on this drug discuss medication with the Gastroenterology team (at least six months before conception) since all drugs can potentially affect the unborn child.

2.3.2.2. Lactation: Only use if potential benefit outweighs risk and mother has been counselled.

2.3.2.3. Renal or hepatic impairment – more frequent monitoring of FBC and LFTs if severe renal or hepatic disorder or high doses (Azathioprine) used. Both azathioprine and MP can cause abnormal LFTs and hepatotoxicity so consider increased monitoring also required if receiving other potentially hepatotoxic drugs. Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor to minimise the risk of skin cancer and photosensitivity.

2.3.2.4. Varicella zoster – check if patient has history of chicken pox before starting treatment. If any doubt check serology. If no history of exposure, patient should avoid contact with individuals with chickenpox or herpes zoster. If exposed, passive immunisation with varicella zoster immunoglobulin may be considered.

2.3.2.5. Increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (predominantly non-melanoma), sarcomas and uterine cervical cancer in situ.

2.4. **Monitoring**

2.4.1. Prior To Starting Therapy – Gastroenterology

2.4.1.1. Patient weight.

2.4.1.2. Blood pressure.

2.4.1.3. Measure baseline full blood count, LFTs, U and E.

2.4.1.4. Pre-screening for TPMT level will be conducted by the Gastroenterology team and if required, an alternative dosing and monitoring strategy will be recommended. This test is sent to an external laboratory and the result is available in 2-4 weeks. This pre-screening is not routinely required in autoimmune liver disease.

2.4.1.5. Hepatitis B and C serology, VZV serology if no history of exposure (as above).

2.4.1.6. Testing Epstein-Barr virus (EBV) is recommended.

2.4.1.7. HIV testing can be done at the clinicians' discretion.

2.4.2 Ongoing Monitoring - General Practice:

2.4.2.1. FBC, LFT, and UandEs 14 days after starting; then at 4, 8, and 12 weeks; then 3 monthly. Frequency of monitoring may be changed at discretion of specialist.

2.4.2.2. Repeat FBC and LFTs 2 weeks after dose change and then 3-monthly (as above).

2.4.2.3. UandE should be checked 3 monthly.

2.4.3 Stop Treatment And Refer To The Gastroenterology Team If:

- WBC $<3.5 \times 10^9$/l.
- Neutrophils $<1.6 \times 10^9$/l.
- Platelets $<140 \times 10^9$/l.
- ALT or AST >100 units/L, or any sudden increases (e.g. double of baseline).
- Rash (significant new) or oral ulceration - discuss with Gastroenterology team as soon as possible (ideally within 24 hours).
- Abnormal bruising or bleeding – refer to specialist to discuss FBC results as soon as possible (ideally within 24 hours).

- MCV>105fl – check serum folate and B12 and TSH and refer to specialist to discuss results.

- Severe or persistent infections, fever, chills and/or persistent sore throat – clinically assess the patient, request urgent FBC and stop treatment.

2.5. **Side Effects**

Common and uncommon side effects listed for the licensed indications for azathioprine and Mercaptopurine:

- Anorexia, nausea, vomiting, pancreatitis. Nausea with azathioprine can be relieved by administering tablets after meals.

- Bone marrow depression, leucopenia, thrombocytopenia and anaemia.

- Azathioprine: hypersensitivity reactions.

- Azathioprine: cholestasis, abnormal liver function tests. Hepatotoxicity is common with Mercaptopurine, especially at high doses.

- Increased susceptibility to infections - During a serious infection STOP azathioprine. During minor infections (e.g. uncomplicated UTI treated with a short antibiotic course) treatment can be continued.

2.6. **Significant Drug Interactions**

- ACE inhibitors – increased risk of anaemia when azathioprine given with captopril or Enalapril especially in renal impairment and of leucopenia with co-prescribing of captopril.

- Allopurinol – Allopurinol has the potential to cause azathioprine and mercaptopurine toxicity and should be avoided where possible. Allopurinol should only be prescribed in combination under Consultant supervision.

- Amino salicylates (e.g. Mesalazine, Olsalazine, sulfasalazine) – possible increased risk of leucopenia with concurrent use of azathioprine or Mercaptopurine.

- Antibacterials - Co-trimoxazole and trimethoprim – increased risk of haematological toxicity with concurrent use of azathioprine or Mercaptopurine.

- Anticoagulants – possible reduction in anticoagulant effect of coumarins.

- Antipsychotics – avoid concomitant use of Mercaptopurine with clozapine (increased risk of agranulocytosis.

- Antivirals – myelosuppressive effects of azathioprine possibly enhanced by ribavirin.

- Febuxostat – concomitant use not recommended as may result in increased levels of azathioprine or Mercaptopurine.

- Live vaccines are contraindicated. These include measles, mumps and rubella; BCG; herpes zoster, poliomyelitis – oral Sabin vaccine; yellow fever; typhoid – oral.

- Passive immunisation should be carried out using Varicella Zoster Immunoglobulin (VZIG) in non-immune patients if exposed to chickenpox or shingles.

2.7. Areas of Responsibility for the Sharing of Care

2.7.1. These are suggested ways in which the responsibilities for the management of adult patients with who are prescribed **Azathioprine or Mercaptopurine** can be shared between the specialist and the general practitioners. The expectation is that these guidelines should provide sufficient information to enable GPs to be confident to take clinical and legal responsibility for prescribing these drugs. If a specialist asks the GP to prescribe this drug the GP should reply to this request as soon as practical. Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and be accepted by them.

2.7.2. **In the NHS E guidelines on responsibility for prescribing (January 2018) between hospitals and GPs, it is advised that legal responsibility for prescribing lies with the doctor who signs the prescription.**

2.7.3. **Specialist:**

2.7.3.1. Decision to prescribe azathioprine or mercaptopurine.

2.7.3.2. Prescribe azathioprine or mercaptopurine for three months or until the drug monitoring is stable and then ask the GP whether they are willing to participate in shared care using the suggested wording template (Appendix 3).

2.7.3.3. Discuss benefits and side effects of treatment with patient or patient's carers including where appropriate the risks associated with pregnancy and need for reliable method of contraception.

2.7.3.4. Undertake screening tests. Ascertain immune status by enquiring about history of chickenpox. Measurement of antibodies to varicella-zoster virus is optional and not routinely recommended.

2.7.3.5. Conduct baseline tests including full blood count, liver function tests, UandE. Prompt communication with GP of any changes in treatment and assessment of adverse events.

2.7.3.6. Test for TPMT deficiency and if required, advice on alternative dosing and monitoring strategy.

2.7.3.7. In some circumstances, the Specialist may choose to check Thiopurine metabolite levels.

2.7.3.8. Specify review dates.

2.7.3.9. Prompt verbal communication followed up in writing to GP of changes in treatment or monitoring requirements, assessment of adverse events or when to stop treatment. Urgent changes to treatment should be communicated by telephone to GP.

2.7.3.10. Ensure clear arrangements for back-up advice and support.

2.7.3.11. Reporting adverse events to the MHRA and GP.

2.7.4. **General Practitioner:**

2.7.4.1. To respond to the shared care request from the consultant in writing without undue delay.

2.7.4.2. Prescribing of azathioprine or mercaptopurine after communication with specialists regarding the need for treatment.

2.7.4.3. Be aware of criteria for referral to Gastroenterology team.

2.7.4.4. Ensure compatibility with other concomitant medication.

2.7.4.5. Prescribe at the dose recommended.

2.7.4.6. Monitor FBC, LFTs and U+E at recommended frequencies (see 2.4.2) and refer if abnormal.

2.7.4.7. Adjust the dose as advised by the specialist.

2.7.4.8. Stop treatment on the advice of the specialist or immediately if any urgent need to stop treatment arises.

2.7.4.9. Report adverse events to the specialist and MHRA.

2.7.4.10. Ensure the patient is offered an annual flu vaccination and a baseline pneumococcal vaccination with 3-yearly booster.

2.7.5. **Patient / parent / guardian / carer:**

2.7.5.1. Report to the specialist or GP if there is not a clear understanding of the treatment and share any concerns in relation to treatment.

2.7.5.2. Ensure they attend for monitoring requirements.

2.7.5.3. Inform specialist or GP of any other medication being taken including over the counter products.

2.7.5.4. Report any adverse effects or warning symptoms to the specialist or GP whilst taking the drug.

2.7.6. **Back-Up Advice And Support Is Available From The Relevant Clinical Team:**

Inflammatory Bowel Disease Nurse Specialist:

Email rch-tr.IBDnurse@nhs.net

Tel 01872 252178.

3. Monitoring compliance and effectiveness

Information Category	Detail of process and methodology for monitoring compliance
Element to be monitored	Compliance with prescribing and administration in accordance with this guideline (or other safe practice).
Lead	Head of Prescribing Support Unit.
Tool	Audit and review tool using patient documentation.
Frequency	As required according to clinical incident reports.
Reporting arrangements	Via Cornwall Area Prescribing Committee / Medication Practice Committee.
Acting on recommendations and Lead(s)	Relevant Clinical Staff.
Change in practice and lessons to be shared	Lessons and changes in practice will be communicated through various channels to relevant staff.

4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the Equality Diversity And Inclusion Policy or the Equality and Diversity website.

4.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Information Category	Detailed Information
Document Title:	Azathioprine and Mercaptopurine in Inflammatory Bowel Disease and autoimmune liver disease Shared Care Guideline V3.1
This document replaces (exact title of previous version):	Azathioprine and Mercaptopurine in Inflammatory Bowel Disease Shared Care Guideline V3.0
Date Issued/Approved:	April 2023
Date Valid From:	April 2023
Date Valid To:	07 June 2025
Directorate / Department responsible (author/owner):	Gastroenterology Team / Pharmacy - Head of Prescribing Support Unit
Contact details:	01872 253548
Brief summary of contents:	Some clinical issues and details of prescribing responsibilities for GP and specialists
Suggested Keywords:	Azathioprine, Mercaptopurine
Target Audience:	**RCHT:** Yes **CFT:** No **CIOS ICB:** Yes
Executive Director responsible for Policy:	Chief Medical Officer
Approval route for consultation and ratification:	Cornwall Area Prescribing Committee
General Manager confirming approval processes:	Richard Andrzejuk
Name of Governance Lead confirming approval by specialty and care group management meetings:	Kevin Wright
Links to key external standards:	None
Related Documents:	Summaries of Product Characteristics
Training Need Identified?	No

Information Category	Detailed Information
Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet and Intranet
Document Library Folder/Sub Folder:	Clinical / Pharmacy

Version Control Table

Date	Version Number	Summary of Changes	Changes Made by
May'13	V1.0	New document	M Wilcock, Pharmacy
May'16	V1.1	Renewal	M Wilcock, Pharmacy
March'19	V2.0	New format and minor additional text re screening 2.4.1	M Wilcock, Pharmacy
March 2020	V2.1	Appendix 3 added following FRG approval - CHA4215 Shared Care Agreement Letter Consultant Request	Demi Louise Kent, Corporate Records Manager
Sept 2021	V2.2	Substitution of Shared Care Agreement Letter with suggested wording template instead (Appendix 3)	M Wilcock, Pharmacy
May 2022	V3.0	Changes to monitoring requirements at baseline and ongoing to align more with SPS guidance. Changes to text re side effects and interactions	M Wilcock, Pharmacy
April 2023	V3.1	Change title page to include 'and autoimmune liver disease'. Page 9 to correctly read Gastroenterology Team and CIOSICB	M Wilcock, Pharmacy

All or part of this document can be released under the Freedom of Information Act 2000

All Policies, Strategies and Operating Procedures, including Business Plans, are to be kept for the lifetime of the organisation plus 6 years.

This document is only valid on the day of printing.

Controlled Document

This document has been created following the Royal Cornwall Hospitals NHS Trust The Policy on Policies (Development and Management of Knowledge Procedural and Web Documents Policy). It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Equality Impact Assessment

Section 1: Equality Impact Assessment (EIA) Form

The EIA process allows the Trust to identify where a policy or service may have a negative impact on an individual or particular group of people.

For guidance please refer to the Equality Impact Assessment Policy (available from the document library) or contact the Equality, Diversity and Inclusion Team rcht.inclusion@nhs.net

Information Category	Detailed Information
Name of the strategy / policy / proposal / service function to be assessed:	Azathioprine and Mercaptopurine in Inflammatory Bowel Disease and autoimmune liver disease Shared Care Guideline V3.1
Directorate and service area:	Pharmacy
Is this a new or existing Policy?	Existing
Name of individual completing EIA (Should be completed by an individual with a good understanding of the Service/Policy):	Dan Thomas, Pharmaceutical Services Contracting Team, NHS Kernow
Contact details:	01726 627953

Information Category	Detailed Information
1. Policy Aim - Who is the Policy aimed at? (The Policy is the Strategy, Policy, Proposal or Service Change to be assessed)	To provide information on prescribing Azathioprine and Mercaptopurine to enable General Practitioners to take over prescribing responsibility from secondary care.
2. Policy Objectives	To promote a consistent level of shared care between primary and secondary care (in relation to RCHT catchment area)
3. Policy Intended Outcomes	Confident and competent prescribers, enabling medicines to be access in a primary care setting.
4. How will you measure each outcome?	Six monthly review
5. Who is intended to benefit from the policy?	General practitioners, hospital specialists and community pharmacists – from understanding local guidance around use of these medicines. Patients/carers, from being able to access medicines from their GP.

Information Category	Detailed Information
6a. Who did you consult with? (Please select Yes or No for each category)	• Workforce: Yes • Patients/ visitors: No • Local groups/ system partners: No • External organisations: No • Other: No
6b. Please list the individuals/groups who have been consulted about this policy.	**Please record specific names of individuals/ groups:** Cornwall Area Prescribing Committee
6c. What was the outcome of the consultation?	Agreed
6d. Have you used any of the following to assist your assessment?	**National or local statistics, audits, activity reports, process maps, complaints, staff or patient surveys:** No

7. The Impact

Following consultation with key groups, has a negative impact been identified for any protected characteristic? Please note that a rationale is required for each one.

Where a negative impact is identified without rationale, the key groups will need to be consulted again.

Protected Characteristic	(Yes or No)	Rationale
Age	No	
Sex (male or female)	No	
Gender reassignment (Transgender, non-binary, gender fluid etc.)	No	
Race	No	
Disability (e.g. physical or cognitive impairment, mental health, long term conditions etc.)	No	
Religion or belief	No	

Protected Characteristic	(Yes or No)	Rationale
Marriage and civil partnership	No	
Pregnancy and maternity	No	
Sexual orientation (e.g. gay, straight, bisexual, lesbian etc.)	No	

A robust rationale must be in place for all protected characteristics. If a negative impact has been identified, please complete section 2. If no negative impact has been identified and if this is not a major service change, you can end the assessment here.

I am confident that section 2 of this EIA does not need completing as there are no highlighted risks of negative impact occurring because of this policy.

Name of person confirming result of initial impact assessment:
Dan Thomas, Pharmaceutical Services Contracting Team, NHS Kernow

If a negative impact has been identified above OR this is a major service change, you will need to complete section 2 of the EIA form available here:
Section 2. Full Equality Analysis

Appendix 3. Suggested wording for Specialist communication re commencement of shared care

This patient is suitable for treatment with (insert drug name) for the treatment of (insert indication) which has been accepted for Shared Care. I am therefore requesting your agreement to share the care of this patient, as they are now stable on the treatment. Where baseline investigations are set out in the shared care protocol, I have carried these out.

Treatment was started on (insert date started) (insert dose).

If you are in agreement, please undertake monitoring and treatment from (insert date). (please note: date must be at least 1 month from stabilisation of treatment.)

Baseline tests: (insert information)

Next review with this department: (insert date)

You will be sent a written summary within (XX) days. The medical staff of the department are available at all times to give you advice. The patient will not be discharged from out-patient follow-up while taking (insert drug name).

Please could you reply to this request for shared care and initiation of the suggested medication to either accept or decline within 14 days.