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Royal Cornwall Hospitals NHS Trust

Azathioprine and Mercaptopurine in Inflammatory Bowel Disease Shared Care Guideline

V2.0

April 2019

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.

1.4. **Data Protection Act 2018 (General Data Protection Regulation – GDPR) Legislation**

The Trust has a duty under the DPA18 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 can't rely on Opt out, it must be Opt in.

The DPA18 covers how the Trust obtains, hold, record, use and store all personal and special category (e.g. Health) information in a secure and confidential manner. This Act covers all data and information whether held electronically or on paper and extends to databases, videos and other automated media about living individuals including but not limited to Human Resources and payroll records, medical records, other manual files, microfilm/fiche, pathology results, images and other sensitive data.

DPA18 is applicable to all staff; this includes those working as contractors and providers of services.

For more information about your obligations under the DPA18 please see the 'information use framework policy', or contact the Information Governance Team 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

2.4.1.2. Measure baseline full blood count, LFTs, U&E.

2.4.1.3. 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.

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

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

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

2.4.2 Ongoing Monitoring - General Practice:

2.4.2.1. FBC and LFT weekly for first 8 weeks and if stable 3-MONTHLY thereafter. 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. U&E and should be checked 6 monthly.

2.4.3 Stop Treatment And Refer To The Gastroenterology Team If:

- WBC $<3.5 \times 10^9$/l
- Neutrophils $<2.0 \times 10^9$/l
- Platelets $<150 \times 10^9$/l
- AST, ALT >2 normal upper limit reference range
- Rash or oral ulceration
- Abnormal bruising or severe sore throat – discuss FBC results with Gastroenterology team.
- MCV>105fl – check serum folate and B12 and TSH and discuss results with Gastroenterology team.

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.
- Increased susceptibility to infections.

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 – increased toxicity of azathioprine or Mercaptopurine, reduce dose of azathioprine or Mercaptopurine to one quarter of usual dose. In some circumstances allopurinol can be given in low dose in conjunction with azathioprine to maximise efficacy of dosing when measuring Thiopurine metabolite levels - this should only be done under strict supervision of Consultant Gastroenterologist
- 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 shared care agreement letter.

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, U&E. 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 CHM and GP.

2.7.4. General Practitioner:

2.7.4.1. If the GP disagrees to undertake shared care he/she will notify the consultant in writing without undue delay by completing the shared care agreement letter.

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 CHM.

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. Sign the shared care agreement letter

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

2.7.5.3. Ensure they attend for monitoring requirements.

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

2.7.5.5. 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

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	No specific tool
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, Inclusion & Human Rights 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

Document Title	Azathioprine and Mercaptopurine in Inflammatory Bowel Disease Shared Care Guideline V2.0		
Date Issued/Approved:	March 2019		
Date Valid From:	April 2019		
Date Valid To:	April 2022		
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	CFT	KCCG
	✓		✓
Executive Director responsible for Policy:	Medical Director		
Date revised:	March 2019		
This document replaces (exact title of previous version):	Azathioprine and Mercaptopurine in Inflammatory Bowel Disease Shared Care Guideline		
Approval route (names of committees)/consultation:	Cornwall Area Prescribing Committee		
Care group general Manager confirming approval processes	Karen Jarvill		
Name and Post Title of additional signatories	Not required		
Name and Signature of Divisional/Directorate Governance Lead confirming approval by specialty and divisional management meetings	{Original Copy Signed}		
	Name: Kevin Wright		
Signature of Executive Director giving approval	{Original Copy Signed}		

Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet & Intranet	✓	Intranet Only	
Document Library Folder/Sub Folder	Pharmacy			
Links to key external standards	None			
Related Documents:	Summaries of Product Characteristics			
Training Need Identified?	No			

Version Control Table

Date	Version No	Summary of Changes	Changes Made by *(Name and Job Title)*
May'13	V1.0	New document	M Wilcock, Head of Prescribing Support Unit
May'16	V1.1	Renewal	M Wilcock, Head of Prescribing Support Unit
March'19	V2.0	New format and minor additional text re screening 2.4.1	M Wilcock, Head of Prescribing Support Unit

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

This document is to be retained for 10 years from the date of expiry.
This document is only valid on the day of printing

Controlled Document

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

Appendix 2. Initial Equality Impact Assessment Form

This assessment will need to be completed in stages to allow for adequate consultation with the relevant groups.

<table>
<tr><td colspan="6">Azathioprine and Mercaptopurine in Inflammatory Bowel Disease Shared Care Guideline V2.0</td></tr>
<tr><td colspan="3">Directorate and service area: Pharmacy</td><td colspan="3">Is this a new or existing Policy?
Existing</td></tr>
<tr><td colspan="3">Name of individual completing assessment:
Dan Thomas, Pharmaceutical Services Contracting Team, NHS Kernow</td><td colspan="3">Telephone:
01726 627953</td></tr>
<tr><td>1. Policy Aim*

Who is the strategy / policy / proposal / service function aimed at?</td><td colspan="5">To provide information on prescribing Azathioprine and Mercaptopurine to enable General Practitioners to take over prescribing responsibility from secondary care.</td></tr>
<tr><td>2. Policy Objectives*</td><td colspan="5">To promote a consistent level of shared care between primary and secondary care (in relation to RCHT catchment area)</td></tr>
<tr><td>3. Policy – intended Outcomes*</td><td colspan="5">Confident and competent prescribers, enabling medicines to be access in a primary care setting.</td></tr>
<tr><td>4. *How will you measure the outcome?</td><td colspan="5">Six monthly review</td></tr>
<tr><td>5. Who is intended to benefit from the policy?</td><td colspan="5">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.</td></tr>
<tr><td rowspan="3">6a Who did you consult with

b). Please identify the groups who have been consulted about this procedure.</td><td>Workforce</td><td>Patients</td><td>Local groups</td><td>External organisations</td><td>Other</td></tr>
<tr><td>X</td><td></td><td></td><td>X</td><td></td></tr>
<tr><td colspan="5">Please record specific names of groups
Cornwall Area Prescribing Committee</td></tr>
<tr><td>What was the outcome of the consultation?</td><td colspan="5">Agreed</td></tr>
</table>

7. The Impact
Please complete the following table. **If you are unsure/don't know if there is a negative impact you need to repeat the consultation step**.

Are there concerns that the policy **could** have differential impact on:

Equality Strands:	Yes	No	Unsure	Rationale for Assessment / Existing Evidence
Age		**X**		
Sex (male, female, trans-gender / gender reassignment)		**X**		
Race / Ethnic communities /groups		**X**		
Disability - Learning disability, physical impairment, sensory impairment, mental health conditions and some long term health conditions.		**X**		
Religion / other beliefs		**X**		
Marriage and Civil partnership		**X**		
Pregnancy and maternity		**X**		
Sexual Orientation, Bisexual, Gay, heterosexual, Lesbian		**X**		

You will need to continue to a full Equality Impact Assessment if the following have been highlighted:

- You have ticked "Yes" in any column above and
- No consultation or evidence of there being consultation- this excludes any *policies* which have been identified as not requiring consultation**. or**
- Major this relates to service redesign or development

8. Please indicate if a full equality analysis is recommended.	**Yes**		**No X**	

9. If you are **not** recommending a Full Impact assessment please explain why.

Not indicated.

Signature of policy developer / lead manager / director		Date of completion and submission
M Wilcock		March 2019
Names and signatures of members carrying out the Screening Assessment	1. M Wilcock 2. Policy review Group (PRG)	**PRG APPROVED**

This EIA will not be uploaded to the Trust website without the approval of the Policy Review Group.

A summary of the results will be published on the Trust's web site.

Signed __ M Wilcock

Date ____March 2019