INTRODUCTION

Mercaptopurine and its pro-drug azathioprine, are immunosuppressant agents used to induce and maintain remission in Ulcerative Colitis and Crohn’s Disease. Although neither drug is licensed for these indications, their use is widely established in treating Inflammatory Bowel Disease (see BNF Section 1.5). The predominant toxic effect is myelosuppression, although hepatotoxicity is also well recognised. Mercaptopurine and azathioprine are metabolised by the enzyme thiopurine methyltransferase (TPMT). Approximately 89% of the population have normal TPMT activity, 11% have intermediate TPMT activity and are at greater risk of adverse drug reactions on standard doses and 0.3% have no detectable TPMT activity and are at risk of suffering life-threatening complications even when treated with low doses of either drug. TPMT activity is usually measured before a patient is prescribed mercaptopurine or azathioprine.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Dose and administration</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercaptopurine</td>
<td><strong>TARGET dose</strong> is 1mg to 1.5 mg/kg daily by mouth. Drug should be started at half target dose for <strong>first week</strong> to minimise side effects. <strong>In patients with normal TPMT levels below normal, dose should be discussed with Gastroenterology Consultant.</strong></td>
<td>• Bone marrow suppression (leucopenia, thrombocytopenia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hepatotoxicity (hepatic necrosis, biliary stasis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anorexia, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oral ulceration, rarely gastrointestinal ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypersensitivity reactions (fever, rigors, rash)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rarely pancreatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CNS disturbances (headache, drowsiness, blurred vision)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Alopecia</td>
</tr>
<tr>
<td>Azathioprine</td>
<td><strong>TARGET dose</strong> is 2mg to 2.5 mg/kg daily by mouth. Drug should be started at half target dose for <strong>first week</strong> to minimise side effects. <strong>In patients with normal TPMT levels below normal, dose should be discussed with Gastroenterology Consultant.</strong></td>
<td>• Dose related bone marrow suppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liver impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cholestatic jaundice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypersensitivity reactions (malaise, dizziness, vomiting, diarrhoea, fever, rigors, rash, interstitial nephritis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rarely pancreatitis, pneumonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Alopecia</td>
</tr>
</tbody>
</table>

See BNF Section 8.1.3 for further information.
**Mercaptopurine/Azathioprine:**
- Thiopurine methyltransferase (TPMT) status
- Monitoring of FBC, LFT (see monitoring standards below)
- Reduce dose in elderly, hepatic impairment
- Increased risk of haematological toxicity with co-trimoxazole/trimethoprim
- Anticoagulant effect of warfarin possibly reduced by mercaptopurine
- Patients must avoid 'live' vaccines such as oral polio, MMR, BCG and yellow fever.
- Patients should avoid contact with people who have active chickenpox or shingles and should report any such contact urgently to their GP or specialist.
- Careful assessment of risk versus benefit should be carried out before use during pregnancy and breast-feeding.
- Any other interacting drugs (refer to the latest BNF Edition)

**Cautions**

- Avoid prescribing allopurinol in patients on mercaptopurine/azathioprine due to a clinically significant interaction that can lead to increased toxicity. If concomitant prescription of allopurinol is required, then 25% of the original dose of mercaptopurine or azathioprine must be given.

**Contra-indications**

**Mercaptopurine:**
- a) Hypersensitivity to mercaptopurine
- b) Severe infections
- c) Moderate/severe renal or liver impairment
- d) Haematological impairment
- e) Thiopurine methyltransferase (TPMT) deficiency
- f) Pregnancy. Treatment should not generally be initiated during pregnancy
- g) Lactation. Use if potential benefit outweighs risk
- h) Use of Live vaccines

**Azathioprine:**
- 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) Thiopurine methyltransferase (TPMT) deficiency
- e) Pancreatitis
- f) Use of any live vaccines especially BCG, smallpox, yellow fever
- g) Pregnancy. Treatment should not generally be initiated during pregnancy
- h) Lactation. Use if potential benefit outweighs risk.

**Initiating monitoring standards for Mercaptopurine & Azathioprine at BHRUT NHS Trust**

The following standards have been agreed for the monitoring of mercaptopurine and azathioprine in gastroenterology patients at BHRUT NHS Trust.

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>FBC, U&amp;Es, LFTs, TPMT phenotype Varicella Zoster,</th>
<th>Results to be known before drug is commenced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>FBC, LFT</td>
<td>At initiation and after any increase in dose - Every week for 4 weeks. Thereafter at least every 3 months</td>
</tr>
<tr>
<td></td>
<td>U&amp;E’s</td>
<td>Annual</td>
</tr>
</tbody>
</table>

Monitoring will need to be continued by the General Practitioner once the patient is deemed stable.
## Actions for GPs on monitoring patients blood results & symptoms

Please see recommendations table below for general medical management of a patient presenting with the following blood results & symptoms:

<table>
<thead>
<tr>
<th>BLOOD RESULT</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils &lt; 1.5 x 10⁹/L</td>
<td>STOP mercaptopurine/azathioprine</td>
</tr>
<tr>
<td>AST/ALT &gt; 4 fold rise (from upper normal limit)</td>
<td>Contact IBD nurse or specialist hospital clinician</td>
</tr>
<tr>
<td>Neutrophils &lt; 2.0 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes &lt; 0.5 x 10⁹/L</td>
<td>Discuss with IBD nurse or specialist hospital clinician</td>
</tr>
<tr>
<td>Platelets &lt; 150 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>AST/ALT &gt; 2 fold rise (from upper normal limit)</td>
<td></td>
</tr>
<tr>
<td>GFR 20-50ml (Mild) renal impairment</td>
<td>Mercaptopurine- Caution: Reduce dose in impairment.</td>
</tr>
<tr>
<td>GFR 10-20ml/min- (Moderate) renal impairment</td>
<td>Azathioprine- Reduce dose in moderate &amp; severe impairment</td>
</tr>
<tr>
<td>GFR &lt;10ml/min (Severe) renal impairment</td>
<td>Discuss with IBD nurse or specialist hospital clinician</td>
</tr>
<tr>
<td>MCV &gt; 105 fl</td>
<td>Check B12 and folate. Start supplementation if low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash, abnormal bruising or bleeding, Severe or persistent sore throat, infection, fever, rigors, oral ulceration</td>
<td>STOP mercaptopurine/azathioprine. CHECK FBC urgently. Discuss with IBD nurse or specialist hospital clinician</td>
</tr>
<tr>
<td>Jaundice</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain suggestive of pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td></td>
</tr>
</tbody>
</table>

If patient is non-immune and in contact with varicella or shingles, they will require Varicella Zoster immunoglobulin within the first 10 days of exposure. Please contact Consultant Microbiologist for advice. Supplies of this can be obtained from the Health Protection Agency (HPA) (contact details are available from the HPA website [http://www.hpa.org.uk](http://www.hpa.org.uk))
**MERCAPTOPURINE & AZATHIOPRINE** in Inflammatory Bowel Disease

### SHARED CARE
Sharing of care assumes communication between the specialist, GP and the patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy.

**The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.**

### SHARED CARE RESPONSIBILITIES

**Consultant**
1. Initiate treatment and prescribe until patient is stabilised (after 3 months) and the GP formally agrees to shared care
2. Send a letter to the GP requesting shared care for this patient.
3. Clinical and laboratory supervision of the patient at routine clinic follow-up on a regular basis.
4. Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated (unless otherwise covered by letter from Gastroenterology Drug Monitoring Clinic).
5. Evaluation of any reported adverse effects by GP or patient.
6. Advise GP on review, duration or discontinuation of treatment where necessary.
8. Inform GP, by letter, of clinic visits and action taken for management of patient.
9. Ensure that backup advice is available at all times.

**General Practitioner**
1. Monitor patient's overall health and well-being.
2. Prescribe the drug treatment as described after the first three months of stabilisation.
3. Monitor blood results (FBC, LFT U&E) in line with recommendations in this document after the first three months of stabilisation.
4. Report any adverse events to the consultant, where appropriate.
5. Report any adverse events to the CSM, where appropriate.
6. Help in monitoring the progression of disease.

**CCG**
1. To provide feedback to the Trust via Trust Drug & Therapeutics Committee.
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
3. To support trusts in resolving issues that may arise as a result of shared care.

**Patient**
1. Report promptly any adverse effects to their GP and/or specialist whilst taking mercaptopurine/azathioprine.
2. Ensure they have a clear understanding of their treatment.
3. Report any changes in disease symptoms to GP and/or specialist whilst taking mercaptopurine/azathioprine.
4. Discuss with GP and/or specialist of any change of circumstance that could affect management of disease e.g. plans for pregnancy whilst taking mercaptopurine/azathioprine.

### Costs

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>BNF 65 (exc. VAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercaptopurine 50mg tablets (25tabs)</td>
<td>£22.54</td>
</tr>
<tr>
<td>Azathioprine 50mg tablets (56 tabs)</td>
<td>£5.04</td>
</tr>
<tr>
<td>Azathioprine 25mg tablets (28 tabs)</td>
<td>£6.02</td>
</tr>
</tbody>
</table>
Contact Numbers for advice and support

Barking, Havering and Redbridge University Hospitals NHS Trust

<table>
<thead>
<tr>
<th>Contact</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant via switchboard</td>
<td>Queens Hospital: 01708 435000</td>
</tr>
<tr>
<td>Registrar on-call out of hours</td>
<td>Bleep via switchboard</td>
</tr>
<tr>
<td>Clinical IBD Nurse Specialist (where appropriate)</td>
<td>Bleep via switchboard</td>
</tr>
<tr>
<td>Pharmacy Medicines Information Department</td>
<td>01708 435418</td>
</tr>
<tr>
<td>NHS ONELPrescribing Team</td>
<td>To confirm new number</td>
</tr>
</tbody>
</table>

References

1. BNF 65. March-September 2013
2. [www.medicines.org.uk](http://www.medicines.org.uk) (last accessed 26/07/2013)

Refer to the relevant BHR CCG website to obtain the latest version of this guideline


Guideline written by: Uma Horton, Pharmacy Clinical Business Manager & Gastroenterology Liaison Pharmacist & Dr Pranab Gyawali, Consultant Gastroenterologist & General Physician. Checked by: Stephen Grainger, Consultant Gastroenterologist Date: September 2013
Approved by: BHRuT Drug & Therapeutics Committee Date: September 2013
Approved by: BHR CCGs Area Prescribing sub-Committees Date: November 2013
Review date: November 2015
APPENDIX 1

Shared Care information Form

You have been prescribed ……………………………………………….tablets
for…………………………………………………………

This treatment should be continued until stopped by your doctor

Your GP has been given all the necessary information regarding your condition and treatment.

The date for your next hospital appointment is ……………………………

The success and safety of your treatment also depends on you.

- You will have been given information from Crohn’s & Collitis UK, which tells you about your treatment and condition
- Avoid excessive alcohol consumption
- Do not take any over-the-counter medicines, herbal, complementary or alternative medicines and treatments without getting advice from your doctor
- Avoid contact with chicken pox or shingles
- Avoid driving and hazardous work until you have learned how azathioprine or mercaptopurine affects you, as these drugs can occasionally cause dizziness.
- Azathioprine and mercaptopurine increase the skin’s sensitivity to sunlight and the risk of developing some forms of skin cancer. Use sun block and wear a hat and light clothing when out in strong sunshine. Do not use sunlamps or sun beds.
- You will need to have blood tests at least every three months
- Your GP/Practice Nurse needs to see you every …………………

If you experience any of the following side-effects, urgently see your GP:

- Mouth ulcer, sore throat, sore mouth
- Feeling generally unwell
- Feeling sick, upset stomach, diarrhoea.
- Rashes – new rash or severe itching anywhere on the body.

Stop treatment and get immediate medical advice if you develop:

- An infection with fever and or chills or a severe sore throat
- Sudden shortness of breath (breathlessness)
- The whites of your eyes or skin become yellow
- Severe itching of the skin
- New unexplained bleeding or bruising
- Severe and continuing abdominal pain or diarrhea or vomiting

If you think you are pregnant contact the IBD nurse or specialist

If you have any concerns about your treatment contact your GP or the hospital.

The direct-dial telephone numbers for the department are……………………………………
APPENDIX 2

Barking, Havering and Redbridge University Hospitals NHS Trust

Mercaptopurine Shared Monitoring Agreement Letter

Name of GP .................................................. Address ..................................................
Drop code of GP.......................................... .............................................................. ............................................................

Dear GP

Re: Patient's name..................................................

Date of birth..................................................

Hospital number............................................. NHS number.............................................

Indication for treatment..................................................

Patient is on Mercaptopurine 50mg tablets
Take....................... tablets (............mg) ...................times per day

This patient is being treated with mercaptopurine for the above condition. This treatment will be long term. I hope that you will agree to share the care of this patient with the hospital.

Enclosed is a copy of the shared care monitoring guidelines for mercaptopurine to be retained in the patient’s notes. It is safer for monitoring and prescribing to be done by the same clinician. It is not possible for secondary care to do all the prescribing.

Should you agree to take over responsibility for monitoring, we will send a letter containing the details of the patient’s treatment plan, the dose to be prescribed and all relevant blood results.

The patient has been given drug information regarding Mercaptopurine Please tick □
The patient has been counselled about the need for regular blood test monitoring Please tick □
The patient has been advised to seek urgent medical attention in the event of a febrile illness. Please tick □

You must ensure access to blood results to enable you to prescribe further mercaptopurine.

Please sign below and return this letter by fax to the Hospital Specialist if you agree to take over shared monitoring for this patient.

Many thanks

Hospital Specialist

Signature................................................. Name ..............................................

Date.................................................... Date....................................................

If you are not taking on the monitoring responsibility for this patient please state the reason why and return this letter to the Hospital Specialist

You will retain the responsibility to check the blood results prior to prescribing. This should be available via electronic access, or please provide your drop code to enable the patients blood results to be sent to you.

Fax to..............................................................

Guideline written by: Uma Horton, Pharmacy Clinical Business Manager & Gastroenterology Liaison Pharmacist & Dr Pranab Gyawali, Consultant Gastroenterologist & General Physician. Checked by: Stephen Grainger, Consultant Gastroenterologist Date: September 2013
Approved by: BHRuT Drug & Therapeutics Committee Date: September 2013
Approved by: BHR CCGs Area Prescribing sub-Committees Date: November 2013 Review date: November 2015
APPENDIX 2

Barking, Havering and Redbridge University Hospitals NHS Trust

Azathioprine Shared Monitoring Agreement Letter

Name of GP ......................................... Address ........................................
Drop code of GP.................................. ......................................................

Dear GP

Re: Patient’s name............................................................... Date of birth.................................

Hospital number........................................ NHS number........................................

Indication for azathioprine treatment........................................

Patient is on Azathioprine ....mg tablets

Take................. tablets ( .........mg) ............... times per day

This patient is being treated with Azathioprine for the above condition. This treatment will be long term. I hope that you will agree to share the care of this patient with the hospital.

Enclosed is a copy of the shared care monitoring guidelines for Azathioprine to be retained in the patient’s notes. It is safer for monitoring and prescribing to be done by the same clinician. It is not possible for secondary care to do all the prescribing. Should you agree to take over responsibility for monitoring, we will send a letter containing the details of the patient’s treatment plan, the dose to be prescribed and all relevant blood results.

The patient has been given drug information regarding Azathioprine Please tick □
The patient has been counselled about the need for regular blood test monitoring Please tick □
The patient has been advised to seek urgent medical attention in the event of a febrile illness. Please tick □

You must ensure access to blood results to enable you to prescribe further azathioprine.

Please sign below and return this letter by fax to the Hospital Specialist if you agree to take over shared monitoring for this patient.

Many thanks

Hospital Specialist GP

Signature................................. Signature.................................
Name ................................. Name .................................

Date................................. Date.................................

If you are not taking on the monitoring responsibility for this patient please state the reason why and return this letter to the Hospital Specialist.

You will retain the responsibility to check the blood results prior to prescribing. This should be available via electronic access, or please provide your drop code to enable the patients blood results to be sent to you.

Fax to:.......................................................................................................................