Shared Care

Azathioprine & Mercaptopurine* for Inflammatory Bowel Disease (Adults)

It is vital for safe and appropriate patient care that there is a clear understanding of where clinical and prescribing responsibility rests between Consultants and General Practitioners (GPs).
This guideline reinforces the basic premise that:
When clinical and / or prescribing responsibility for a patient is transferred from hospital to GP, the GP should have full confidence to prescribe the necessary medicines. Therefore, it is essential that a transfer of care involving medicines that a GP would not normally be familiar with, should not take place without the "sharing of information with the individual GP and their mutual agreement to the transfer of care."
These are not rigid guidelines. On occasions, Consultants and GPs may agree to work outside of this guidance. As always, the doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Indications:
Azathioprine and mercaptopurine have immunosuppressive and steroid-sparing properties.

Unlicensed indication: treatment of resistant or frequently relapsing Crohn's disease and Ulcerative Colitis.

Treatment for patients must be initiated by Consultant Gastroenterologist.

*Mercaptopurine may be used in IBD when patients are unable to tolerate azathioprine.

Dosage and administration:
Azathioprine
The usual starting dose is 50mg daily for 4 weeks. If thiopurine s-methyltransferase (TPMT) is low, patients should be started on 25mg. This should be increased to 100mg daily and, depending on response and haematological tolerance, to a typical maintenance dose of 2-2.5mg/kg/day.
When the therapeutic response is evident, this dose can be maintained, although consideration can be given to reducing the maintenance dose to the lowest level that maintains the response.
Patients with renal or hepatic insufficiency should be given the lowest effective dose.
Azathioprine is taken as a single dose after food.
Mercaptopurine
The usual starting dose is 50mg daily for 4 weeks. If TPMT is low, patients should be started on 25mg .This should be increased to 75mg daily and, depending on response and haematological tolerance, to a typical maintenance dose of 1-1.5mg/kg/day.

Additional Information

- Mercaptopurine is the active metabolite of azathioprine.
- Pneumovac® II and annual influenza vaccine is recommended.
- Vaccination for varicella zoster prior to treatment with a 3 week window before commencing treatment in those with negative varicella zoster serology is advised if no contraindication.
- Passive immunisation should be carried out in non-immune patients exposed to chickenpox or shingles, using Varicella Zoster Immunoglobulin.

Monitoring requirements:
Before treatment:

- Full blood count (FBC) including platelets, urea and electrolytes (U&Es), creatinine and liver function tests (LFTs) (hospital)
- Test for thiopurine methyl transferase (TPMT), as a deficiency increases the risk of myelosuppression.

During treatment:

- FBC weekly for the first four weeks, then monthly for 3 months thereafter if stable. Once fully stabilised, monitoring can be every 3 months.
- LFTs and U&Es weekly for the first four weeks, then monthly thereafter if stable.
- If dose is increased, repeat FBC and LFTs after 2 weeks, and then return to monthly.

For patients with Crohn's disease and Ulcerative Colitis, responsibility for monitoring, once stable, rests with the GP.

Action to be taken if abnormal results/adverse effects:	
• **WBC< 3.5 x 10^9/l**	Check neutrophil count
• **Neutrophils <2.0 x 10^9/l**	Monitor weekly, If it falls below 1.5 x 10^9/l STOP DRUG and contact GI consultant.
• **Platelets <150 x 10^9/l**	Monitor weekly. If it falls below 100 x 10^9/l contact hospital
• **3 fold rise in ALT/AST**	Monitor weekly. If ALT continues to rise, contact hospital.
• **Rash**	Mild – drug can be continued at reduced dose if necessary. Severe – **STOP** azathioprine / mercaptopurine and contact the hospital
• **Oral ulceration**	Repeat FBC and act on results as above. **Mild** – salt water mouth wash. **Moderate** – Hydrocortisone mucoadhesive buccal tablets 2.5 mg (1 applied to affected area four times a day) and **STOP** azathioprine / mercaptopurine for at least one week and if resolved, restart but consider reduced dose. **Severe** – **STOP** azathioprine / mercaptopurine. Prescribe hydrocortisone mucoadhesive buccal tablets 2.5mg and contact hospital.
• **MCV> 105fl**	Check B12 and Folate and, if low, start appropriate supplements
• **Abnormal bruising**	Repeat FBC and act on results as above.
• **Sore throat**	Repeat FBC and act on results as above.
• **Drug related acute shortness of breath**	STOP DRUG, contact hospital and if severe, refer to Medical Assessment Unit, Arrowe Park Hospital.
• **Sudden cough**	If persistent, organise chest X-Ray and if abnormal, contact help-line.

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.

Contraindications:

- Azathioprine and mercaptopurine should not be given to women who are pregnant, or likely to become pregnant without a careful assessment of risk versus benefit.
- TPMT deficiency (TMPT absent or extremely low) - associated with delayed haematotoxicity
- Live vaccines are contra-indicated in patients receiving azathioprine and mercaptopurine on theoretical grounds.
- Hypersensitivity to azathioprine or mercaptopurine

Cautions:

- Renal or hepatic insufficiency may enhance the toxicity of azathioprine and mercaptopurine. The haematological response should be carefully monitored and doses at the lower end of the range should be used.
- Increased risk of skin cancers; avoid exposure to sunlight and UV light by using sunscreen and protective clothing
- For patients with low TPMT levels, use lower doses of azathioprine/ mercaptopurine
- Localised or systemic infection including hepatitis B, hepatitis C or history of tuberculosis.

Drug interactions:

- **Allopurinol** - azathioprine and mercaptopurine activity is inhibited by allopurinol, avoid co-prescription where possible. If essential, contact helpline for advice on azathioprine/ mercaptopurine dose reduction.
- **Warfarin -** anticoagulant effect inhibited by azathioprine and mercaptopurine.
- **Myelosuppressive drugs e.g. penicillamine, co-trimoxazole –** increased risk of myelosuppression. Avoid concomitant use
- **ACE inhibitors –** increased risk of anaemia and/or leucopenia.
- **Febuxostat –** avoid. Increased risk of toxicity
- **Aminosalicylate derivatives e.g. olsalazine, mesalazine or sulfasalazine** inhibit TPMT and should be used with caution with azathioprine/mercaptopurine.
- **Vaccines** - A diminished response to killed vaccines is likely. Live vaccines are predicted to increase the risk of generalised infection. Public Health England advises to avoid.
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Adverse Effects:

Depression of bone marrow function, leucopenia, thrombocytopenia, anaemia and other blood disorders.
Viral, fungal and bacterial infections.

Neoplasms, including non-Hodgkin's Lymphomas, skin cancers, sarcomas and uterine cervical cancer.
Nausea, pancreatitis, altered liver function, alopecia, hypersensitivity reactions, SJS, toxic epidermal necrolysis.

Specialist responsibilities:

1. Confirm the diagnosis of Inflammatory Bowel Disease (IBD) and discuss with the patient the benefits and side effects of treatment with azathioprine/ mercaptopurine. If the patient is a woman of child bearing potential ensure that they are aware of the importance of effective contraception and the need to discuss with their consultant if they wish to become pregnant.
2. Screen patients for Varicella Zoster, Hepatitis B and Hepatitis C before commencing treatment and refer patient to GP for vaccinations when appropriate.
3. Ensure baseline monitoring of full blood count, biochemical profile and TPMT, also subsequent monitoring until dose is stabilised.
4. Review the patient after one month (this can be in the gastroenterology specialist nurse clinic) and if the patient is tolerating and benefiting from azathioprine/ mercaptopurine at this first visit, a written request should be made to the GP to continue prescribing the medication and to continue the monitoring.
5. Prescribe the initial 2 months of azathioprine/ mercaptopurine during the trial period and discontinue if no response or significant adverse effect.
6. Provide the patient with a shared care booklet and enter the blood results into the booklet.
7. Ensure patient understands the dose to be administered and instructions are clear on the prescription for the medication to be labelled appropriately. For example, for a 25mg dose, the patient needs to cut 50mg tablet into half using a tablet cutter.
8. Regularly review the patient to monitor efficacy of the treatment and the ability to tolerate it, and consider whether continuation of treatment is appropriate.
9. Communicate promptly with the GP when treatment is changed and each time the patient is seen.
10. Undertake any necessary monitoring at review appointments.
11. Ensure clear backup arrangements exist for GPs for advice and support.
12. Report serious adverse events to the MHRA through the yellow card scheme.

GP responsibilities:

1. Initial referral to Consultant Gastroenterologist raising the possibility of IBD.
2. Provide the patient with monthly repeat prescriptions of medication once the specialist has recommended continuation therapy.
3. Ensure patient understands the dose to be administered and instructions are clear on the prescription for the medication to be labelled appropriately. For example, for a 25mg dose, the patient needs to cut 50mg tablet into half using a tablet cutter.
4. Ensure patient's shared care booklet and practice computer system are updated with any dose changes.
5. Continue monitoring as outlined on the first page and document the results in the shared care booklet.
6. Report any adverse effects to the consultant.
7. Refer back to the consultant if :
   - the patient's condition deteriorates or if there is a change in the patient's status.
   - signs and symptoms indicating blood dyscrasias e.g. sore throat, infection, unexplained or abnormal bruising or bleeding. Request urgent blood test and assess the patient. Discuss with secondary care urgently as per results. Referring patient back to secondary care may take a few weeks. In the interest of patient safety, the GP should therefore monitor patient in the interim.
   - the patient becomes pregnant
   - GP feels a dose change is required
   - there is a marked deterioration in renal/hepatic function
   - patient fails to attend monitoring appointment(s)
   - patient does not agree with the treatment recommendation, or if there is a perceived problem with compliance or concordance, or if they have any questions about the management plan.
8. Administer Pneumovac® II and annual influenza vaccines.
9. Administer Varicella vaccine to patients with negative varicella zoster serology 3 weeks before commencing treatment as recommended by specialist.
10. Administer Varicella Zoster Immunoglobulin in non-immune patients exposed to chickenpox or shingles.

Patient responsibilities:

1. Read the written information provided about the drug and have a clear understanding of the risks / benefits of oral azathioprine/ mercaptopurine treatment.
2. Attend for blood tests.
3. Allow at least 48 hours for the prescription from the GP to be generated once they have agreed to take on prescribing.
4. Report any adverse effects, concerns or lack of understanding of the treatment to the GP or specialist.
5. Limit alcohol to national safe limits.
6. Take monitoring booklet every time the patient sees their GP, has a hospital appointment or visits the pharmacist.

Secondary care review: Patients will be reviewed one month after starting azathioprine/ mercaptopurine and thereafter at a frequency determined by the clinical need by the consultant clinic, or if requested to review by the GP.

Availability: Azathioprine 25mg tablet: 28 = £1:46
50mg tablet: 56 = £2.16
Mercaptopurine 50mg tablet: 25 = £49.15

Prices from Drug Tariff January 2018

References:

1. BNF online
2. Current SPC from https://www.medicines.org.uk/
3. The Green book:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/456562/Green_Book_Chapter_34_v3_0.pdf

Back up advice and support: IBD Specialist Nurse	**Telephone:** 0151 604 7459 **Email:** wih-tr.IBDnurses1@nhs.net

Written By:	Helen Dingle, Prescribing Adviser, Medicines Management Team, Wirral (reviewed by Mariah Zavery, Medicines Optimisation Pharmacist, MLCSU, Medicines Management Team, Wirral)	Dr G Pritchard, Consultant Gastroenterologist and IBD Lead, Wirral University Teaching Hospital NHS Trust