SHARED CARE GUIDELINE

Drug: Azathioprine and Mercaptopurine

Introduction	**Azathioprine Indications**: Licensed: Rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel diseases including ulcerative colitis and Crohn's disease, dermatomyositis and polymyositis, autoimmune and chronic active hepatitis, pemphigus vulgaris, polyarteritis nodosa, ITP and auto-immune haemolytic anaemia. Unlicensed: Polyarteritis and giant cell arteritis, psoriasis and psoriatic arthritis, severe eczema and other autoimmune skin conditions. **Mercaptopurine Indications**: Unlicensed: Inflammatory bowel diseases. **N.B. Please see the respective SPCs for detailed information on licensed indications on the branded and generic products** **Background:** Azathioprine is used as an immunosuppressant either alone or in combination with corticosteroids when it produces a steroid-sparing effect. It is rapidly converted in vivo to mercaptopurine, a purine analogue that inhibits DNA synthesis and hence the proliferation of cells involved in the immune response. Clinical response may not be evident before 6 weeks and may take up to 3 months.[1] **Definitions:** Stable dose – the dose will be titrated to achieve efficacy at the lowest dose. Once efficacy achieved and provided the patient can tolerate the dose, this will be termed "stable dose" Stable bloods – results of blood tests remain below the "alert" thresholds as set by national guidelines and have stayed at similar levels for at least two consecutive tests. N.B. The patient can continue to have active disease despite being on a stable dose or having stable bloods, so the "patient" is not referred to as "stable"
Form	Azathioprine tablets: 25mg[2], 50mg[3] Mercaptopurine tablets: 50mg[4]
Dose & Administration	**Azathioprine** 1mg/kg/day increasing to 2-3mg/kg/day adjusted within these limits depending on clinical response and haematological tolerance. Doses are rounded to the nearest 25mg (may be started at 25mg daily increasing by 25mg daily at weekly intervals until the desired dose is reached to improve tolerance) **Mercaptopurine** 50mg daily increasing to 1-1.5mg/kg/day (may be started at 12.5mg daily increasing by 12.5mg daily at weekly intervals)
Secondary Care Responsibilities	• Confirm the diagnosis. • Exclude serious infections. Check for absence of pregnancy in women of child-bearing age and ensure the patient understands the importance of contraception. Azathioprine can be prescribed in pregnancy where continued treatment outweighs the risks. • Discuss the benefits and side effects of treatment with the patient. Ensure that the patient understands which warning signs and symptoms to report. • Perform pre-treatment screening: FBC, LFTs, U&Es, creatinine/ eGFR and TPMT assay. • Ensure that the patient understands not to expect improvement from the treatment straight away. • Provide the patient with a monitoring and dosage record booklet and ensure that the patient

	knows when and where to attend for monitoring. Encourage the patient to take responsibility for ensuring that results of tests are entered in the monitoring booklet. • Make arrangements for shared care with the patient's GP. • Review the patient regularly to monitor the patient's response to therapy. • Advise the GP on initial dose, management of any dose adjustments and when to stop treatment. • Ensure that clear backup arrangements exist for GPs to obtain advice.
Primary Care Responsibilities	• Provide the patient with prescriptions for azathioprine or mercaptopurine tablets. • Ensure that the patient understands their treatment and which warning symptoms to report (see under adverse reactions below). • Monitor at the recommended frequencies (see MONITORING below) and ensure that test results are recorded in the monitoring booklet. • Report any adverse events to the consultant or specialist nurse and stop treatment on their advice or immediately if an urgent need arises (see MONITORING below). • Report any worsening of control of the condition to the consultant or the specialist nurse. • Follow recommended immunisation programme.
Immunisation	• Annual flu vaccination is recommended. • Pneumococcal vaccination is recommended. • In patients exposed to chicken pox or shingles, if required, passive immunisation should be considered for varicella. Refer to Green book: Varicella: the green book, chapter 34 - Publications - GOV.UK • Live vaccines should be avoided, in particular BCG, smallpox and yellow fever. Note: Varicella- zoster vaccine (Zostavax®) can be given as a precaution in patients on low doses: (azathioprine <3.0 mg/kg/day, or mercaptopurine <1.5mg/kg/day; these are not considered sufficiently immunosuppressive and are not contraindications for administration of zoster vaccine.
Common Drug Interactions	• Allopurinol: azathioprine and mercaptopurine should be **reduced to 25% of the original dose or avoided completely** • Co-trimoxazole and trimethoprim: **AVOID** concomitant use - increased risk of serious haematological toxicity • Warfarin: azathioprine and mercaptopurine may reduce the anticoagulant effect of warfarin • ACE inhibitors: increased risk of anaemia and leucopenia • Febuxostat: AVOID concomitant use • Aminosalicylates: increased risk of leucopenia • Ribavirin This list is not exhaustive; please refer to SPCs and BNF.
Cautions	• There are individuals with an inherited deficiency of the enzyme thiopurine methyl transferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine or mercaptopurine and prone to developing rapid bone marrow depression following the initiation of treatment. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Azathioprine should be prescribed with caution and at a reduced dosage in these patients. • Renal and/or hepatic insufficiency and frail elderly: dosages used should be at the lower end of the range. • Patients prescribed azathioprine or mercaptopurine should be advised to limit exposure to sunlight by wearing protective clothing and using high factor sunscreens. • For further cautions please refer to the SPC and BNF
Contra-indications	• Pregnancy (except where continuing treatment outweighs the risks – if pregnancy occurs or is

planned discuss with the specialist team).

- Breastfeeding.
- Severe infection
- Severely impaired hepatic or bone marrow function
- Pancreatitis
- Lactose intolerance or hypersensitivity to active ingredients or excipients
- Some live vaccines while on treatment and for three months following treatment – see above in immunisation

This guidance does not replace the SPC's, which should be read in conjunction with this guidance.

Monitoring and Adverse Effects

Treatment status	FBC	LFT	U+E	Creatinine/ eGFR	ESR or CRP
Initial monitoring until bloods stable (see definition)	Weekly	Weekly	Weekly	Weekly	Every 3 months (for RA only)
Once dose is stable	Every 3 months	Every 3 months	Every 6 months	Every 6 months	Every 3 months (for RA only)
If patient has positive TMPT deficiency assay	Every month	Every month	Every month	Every month	Every 3 months (for RA only)

- At dose increase changes advised by the specialist team, the monitoring will need to be weekly until dose and bloods are stable. Thereafter revert back to standard monitoring as above.
- The patient should be asked about the presence of rash, oral ulceration, severe sore throat and abnormal bruising at each visit.
- Azathioprine or mercaptopurine should be stopped if patient is systemically unwell with significant infection. However in SLE patients, check FBC and where possible discuss with the rheumatologist before stopping as SLE flair can sometimes mimic infection, otherwise default to stopping drug.
- Dose-related increases in MCV commonly occur. When MCV >105fL, check thyroid function, B12 and folate. Treat any underlying abnormality but if results are normal discuss with specialist team for further advice.

In the event of the following adverse laboratory results or patient reported symptoms, withhold azathioprine or mercaptopurine until discussed with specialist team:

- WCC < 3.5 x 10^9/L or less than the lower limit of reference range as per lab
- Neutrophils < 2.0 x 10^9/L or less than the lower limit of reference range as per lab
- Platelets < 150 x 10^9/L or less than the lower limit of reference range as per lab
- AST/ALT >2 times the upper limit of reference range
- Rash or oral ulceration
- Abnormal bruising or severe sore throat (monitor FBC)
- Patient is systemically unwell with significant infection – see above

Other adverse reactions:

- Decreased resistance to infection
- Benign and malignant neoplasms
- Nausea, anorexia, leukopenia, pancreatitis, alopecia, hepatic dysfunction

This is not exhaustive. Please refer to SPCs and BNF.

References

1. http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmard_therapy.pdf
2. http://www.medicines.org.uk/emc/medicine/26877/SPC/Azathioprine+25+mg+film-coated+tablets/
3. http://www.medicines.org.uk/emc/medicine/26876/SPC/Azathioprine+50+mg+film-coated+tablets/
4. http://www.medicines.org.uk/emc/medicine/24688/SPC/Mercaptopurine+50+mg+tablets/
5. BNF 66 September 2013-March 2014
6. http://cks.nice.org.uk/dmards#!scenariorecommendation:1