East Lancashire Health Economy Medicines Management Board
www.elmmb.nhs.uk NHS

SHARED CARE GUIDELINE

Lancashire & South Cumbria Medicines Management Group NHS

Drug: Azathioprine and Mercaptopurine

Introduction	**Azathioprine Indications**: Licensed: Rheumatoid arthritis, systemic lupus erythematosus, 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, inflammatory bowel diseases including ulcerative colitis and Crohn's disease, **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, 50mg Mercaptopurine tablets: 50mg
Dose & Administration	**Azathioprine** 1mg/kg/day increasing to 2-3mg/kg/day after 4-6 weeks adjusted within these limits depending on clinical response and haematological tolerance. **Mercaptopurine** 1-1.5mg/kg/day. Mercaptopurine may be taken with food or on an empty stomach, but patients should standardise the method of administration. The dose should not be taken with milk or dairy products. Mercaptopurine should be taken at least 1 hour before or 2 hours after milk or dairy products**.**
Secondary Care Responsibilities	• Confirm the diagnosis. • Exclude serious infections. • 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[1]: weight, height, BP, albumin, FBC, LFTs, calculated GFR and TPMT assay. • Patients should be assessed for co-morbidities, including evaluation for respiratory disease and screening for occult viral infection • Ensure that the patient understands not to expect improvement from the treatment straight away. • Provide the patient with prescriptions for azathioprine or mercaptopurine until on stable dose and undergoing 3 monthly monitoring. • 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 frequency of monitoring, 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 once on stable dose and undergoing 3 monthly monitoring • 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 • Covid-19 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 unless specialist advice has been sought. Note: shingles can be given as a precaution in patients on low doses: (azathioprine <3.0 mg/kg/day, or mercaptopurine <1.5 mg/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	• Thiopurine methyl transferase (TPMT) deficiency - homozygous state: may be associated with delayed haematological toxicity including bone marrow toxicity. It is linked to serious adverse events, although symptoms may not be evident until 6 months after commencing treatment. Minor unrecognised infections or drug interaction, particularly when co-prescribed with aminosalicylates, such as sulfasalazine, mesalazine or olsalazine, may precipitate fatal toxicity. 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
Contraindications	• 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
Pregnancy and Breastfeeding	• According to the BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding, azathioprine is compatible throughout

	pregnancy at ≤2 mg/kg/day and is compatible with breastfeeding. It is also considered to be compatible with paternal exposure.

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	Albumin	Creatinine/ calculated GFR	ESR or CRP
Initial monitoring until on stable dose for 6 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 3 months (for RA only)
For next 3 months	Every month	Every month	Every month	Every month	
Thereafter (If the patients have normal baseline TMPT levels)	Every 3 months	Every 3 months	Every 3 months	Every 3 months	

***Please note:** If the patient is also being treated with **leflunomide**, increased monitoring is required, as specified in the leflunomide shared care guidance. (Where other biologic/DMARDs are used in combination with azathioprine or mercaptopurine, the standard monitoring requirements, as outlined above, continue to apply).

The team responsible for prescribing the medication should also hold responsibility for monitoring
i.e. prescribing to be carried out in Primary care only once patient on stable dose and undergoing 3 monthly monitoring. (In people heterozygous for thiopurine methyl transferase (TPMT), monitoring should continue at monthly intervals)

Following dose increases FBC, creatinine/ calculated GFR, albumin should be monitored every 2 weeks until on a stable dose for 6 weeks. Thereafter monitoring should then revert to the previous schedule used for initiation of azathioprine/mercaptopurine.

As per secondary care responsibilities, for clarity the frequency of monitoring should be specified in the initial shared care request.

- 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 urgently discussed with specialist team and consider interruption in treatment:

- WCC < 3.5 x 10^9/L or less than the lower limit of reference range as per lab
- Neutrophils < 1.6 x 10^9/L or less than the lower limit of reference range as per lab
- Platelets < 140 x 10^9/L or less than the lower limit of reference range as per lab
- Mean cell volume > 105 fL
- Creatinine increase > 30% over 12 months and/or calculated GFR < 60 mL/min
- Unexplained eosinophilia > 0.5 x 10^9/L
- ALT and/or AST > 100 U/L

	• Unexplained reduction in albumin < 30 g/L • Rash or oral ulceration • Abnormal bruising or **severe** sore throat (monitor FBC) • Patient is systemically unwell with significant infection – see above As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decreases in white blood cells or albumin, or increasing liver enzymes). If urgent clinical abnormalities arise emergency access to specialist advice should be sought. **Other adverse reactions:** • Decreased resistance to infection • Benign and malignant neoplasms • Nausea, anorexia, leukopenia, pancreatitis, alopecia, hepatic dysfunction This list is not exhaustive; please refer to SPCs and BNF.

References

1. Summary of product characteristics. Azathioprine 25mg film-coated tablets. Tillomed Laboratories Limited. Last updated on the EMC 11th February 2022. Accessed via: https://www.medicines.org.uk/emc/medicine/11142 [accessed online: 21st June 2022].
2. Summary of product characteristics. Azathioprine 50mg film-coated tablets. Tillomed Laboratories Limited. Last updated on the EMC 11th February 2022. Accessed via: https://www.medicines.org.uk/emc/medicine/11143 [accessed online: 21st June 2022].
3. Summary of product characteristics. Mercaptopurine 50mg tablets. Aspen. Last updated on the EMC 8th January 202. Accessed via: https://www.medicines.org.uk/emc/medicine/4655 [accessed online: 21st June 2022].
4. Ledingham et al. BSR/BHPR Non-Biologic DMARD Guidelines, June 2017. Accessed via: https://academic.oup.com/rheumatology/article/56/6/865/3053478
5. Flint et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding, January 2016. Accessed via: https://academic.oup.com/rheumatology/article/55/9/1693/1744535
6. Van der Woulde et al. The Second European Evidenced-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease. ***Journal of Crohn's and Colitis***, Volume 9, Issue 2, 1 February 2015, Pages 107–124
7. UK Health Security Agency. Immunisation Against Infectious Disease 'The Green Book', 2021. Department of Health and Social Care. London, UK.

RELEVANT CONTACT LIST

Speciality	
Name and Title	Tel. No.

East Lancashire Hospitals NHS
NHS Trust

Shared Care Agreement - Disease Modifying Drugs (DMARDs)

Request by specialist Clinician for the patient's GP to enter into a shared care agreement

Reference: **Date:**

Patient name: **RXR/NHS number:**

Patient address:

Diagnosis:_____

In accordance with the shared care guidelines I kindly request that you prescribe:

1. _____ **Dose** _____ **Frequency**_____
2. _____ **Dose**_____ **Frequency**_____
3. _____ **Dose**_____ **Frequency**_____

for the above named patient:

Shared care guidelines available @ http://www.elmmb.nhs.uk/policies-and-guidelines/shared-care-guidelines/

Last Prescription issued:_____ **Next prescription due:**_____

Date of last blood test:_____ **Date of next blood test**: _____

Frequency of Blood test:_____

I can confirm that the patient has been stabilised and reviewed on the above regime in accordance with the Shared Care guideline.

If this is a Shared Care Agreement for a drug indication which is unlicensed or off label, I confirm that informed consent has been received.

I will accept referral for reassessment at your request. The clinical team in the rheumatology department are available to give you advice.

Details of Specialist Clinician

Name:_____ Date:_____

Consultant/ Associate Specialist/ Specialist Registrar /Specialist Nurse (circle or underline as appropriate)

When the request for Shared Care is made by a specialist nurse, it is the supervising consultant who takes medicolegal responsibility for the agreement.

Consultant:_____

Contact details for rheumatology specialist nurses ELHT: elht.rheumatologynurses@nhs.net

Telephone number: 01254 734491 or 01254 734569

Unless we hear from you within 14 days, we will assume that the Shared Care agreement has been accepted.

Yours sincerely,

The Rheumatology Directorate, ELHT