National shared care protocol: Adapted for use as amber guidance for WY ICS

Azathioprine and mercaptopurine for patients within adult services (non-transplant indications)

Please ensure that summaries of product characteristics (SPCs), British National Formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites are reviewed for up-to-date information on any medicine.

Specialist responsibilities

- Assess the patient and provide diagnosis; section 2 and communicated to patient's GP practice..
- Use a shared decision making approach; discuss the benefits and risks of the treatment with the patient and provide the appropriate counselling (see section 11) to enable the patient to reach an informed decision. Obtain informed consent in line with current local processes. Provide an appropriate patient information leaflet.
- Discuss with the patient their responsibilities outlined below, confirm understanding and confirm that the patient is happy to adhere to them.
- Assess for contraindications and cautions and interactions.
- Conduct required baseline investigations and initial monitoring (see section 8).
- Initiate and optimise treatment as outlined in section 5.
- Continue to see the patient and prescribe azathioprine until the patient (and their condition) is stable (minimum period of two months). After this period the GP will be asked to take over prescribing, titration of dose (if required) and monitoring responsibilities within this amber drug guidance.
- Send information to the patient's GP practice detailing the current and ongoing dose, any relevant test results and when the next monitoring is required.

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- Conduct the required monitoring in section 8 and communicate the results to primary care. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.
- Give advice to primary care on continuing treatment if a woman becomes or wishes to become pregnant or breastfeed.
- Provide advice to primary care on the management of adverse effects if required

Primary care responsibilities

- Respond to the specialist in writing within 2 weeks if unwilling to take over prescribing and monitoring as requested by specialist. If accepted, prescribe ongoing treatment as detailed in the specialists request and as per section 5 taking into account any potential drug interactions in section 7.
- Adjust the dose of azathioprine or mercaptopurine prescribed as advised by the specialist.
- Conduct the required monitoring as outlined in section 9.
- Assess for possible interactions with azathioprine or mercaptopurine when starting new medicines (see section 7).
- Manage any adverse effects as detailed in section 10 and discuss with specialist team when required.
- Stop azathioprine or mercaptopurine and discuss urgently with the specialist if bone marrow suppression is suspected.
- Discuss other adverse effects with the specialist team as clinically appropriate (see section 10).
- Contact the specialist team for advice if the patient becomes or plans to become pregnant.
- Stop treatment as advised by the specialist.

Patient and/or carer responsibilities

- To agree and accept responsibility for taking azathioprine or mercaptopurine as prescribed, and not to stop taking it without speaking to their primary care prescriber or specialist.
- To understand how to take azathioprine or mercaptopurine safely.
- To understand the duration of treatment prescribed initially by the hospital specialist.
- To understand the most common adverse events/side effects and inform the specialist/primary care prescriber as soon as reasonably possible should they occur and significantly affect the use of the medicines.
- To understand the circumstances under which the medicines should be immediately stopped

and what action to take.

- To understand contents of written information provided by the specialist and in the patient information leaflet supplied with the medicines and to seek clarification if required.
- To attend for blood tests/disease monitoring on time.
- To check with the community pharmacist that there are no interactions with azathioprine or mercaptopurine and other medications taken including other prescribed medications, medicines bought over the counter and herbal/homoeopathic products.
- To check with dentists or other specialists who may prescribe medicines that there are no interactions with azathioprine or mercaptopurine.
- To contact the primary care prescriber, specialist or medicines information patient helpline if further information or advice is needed about this medication or if there is anything they do not understand. More information on asking about medication can be found in the Me & My Medicines Charter https://meandmymedicines.org.uk/the-charter/
- Use an appropriate form of contraception, as agreed with their doctor/nurse/sexual health service.
- Inform the specialist or primary care prescriber immediately if they become pregnant or wish to become pregnant.
- The NHS Website – NHS information on health link and medicines link

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1. Background

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Azathioprine and mercaptopurine are disease modifying anti-rheumatic drugs (DMARDs). They are used as immunosuppressant anti-metabolites either alone or, more commonly, in combination with other agents (usually corticosteroids) to influence the immune response. Therapeutic effect may be evident only after weeks or months and can include a steroid sparing effect, thereby reducing the toxicity associated with high dosage and prolonged usage of corticosteroids.

Azathioprine and mercaptopurine are not licensed for all the conditions they are used to treat, as noted below. However, their use for the indications below are established and supported by various sources and bodies including the BNF, NICE, British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR), British Association of Dermatologists (BAD), British Thoracic Society (BTS), Association of British Neurologists (ABN) and British Society of Gastroenterology (BSG).

2. Indications

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Azathioprine

The licensed indications for azathioprine include:

- Auto-immune chronic active hepatitis
- Auto-immune haemolytic anaemia
- Chronic refractory idiopathic thrombocytopenic purpura
- Dermatomyositis
- Inflammatory bowel disease (IBD)
- Pemphigus vulgaris
- Polyarteritis nodosa
- Polymyositis
- Pyoderma gangrenosum
- Rheumatoid arthritis
- Systemic lupus erythematosus (SLE)

Licensed indications vary with brand. See relevant summary of product characteristics (see SPC) for full details.

This guidance also includes treatment of chronic inflammatory conditions where off-label use of azathioprine is appropriate, including, but not limited to the following specialities and conditions:

- Dermatology (e.g. severe eczema)
- Neurology (e.g. myasthenia gravis, demyelinating conditions)
- Ophthalmology (e.g. uveitis, scleritis)
- Oral medicine (e.g. Behçet's disease, refractory inflammatory oral disease)
- Renal medicine (e.g. immune-mediated nephritis)
- Respiratory disease (e.g. interstitial lung disease)
- Rheumatology (e.g. inflammatory arthritis, connective tissue disease, vasculitis, giant cell arteritis)

These indications are off-label. The initiating specialist must specify the indication for each patient when initiating and clearly state when use is off-label.

Mercaptopurine

This amber guidance includes treatment of chronic inflammatory conditions where off-label use of mercaptopurine is appropriate, including, but not limited to the following conditions:

- Inflammatory bowel disease
- Autoimmune encephalitides
- Autoimmune hepatitis

These indications are off-label. The specialist must specify the indication for each patient when initiating and clearly state when use is off-label.

This amber guidance applies to adults aged 18 and over. It does not include use of azathioprine or mercaptopurine for transplant or oncology indications.

3. Locally agreed off-label use

See section 2

4. Contraindications and cautions

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Please see BNF & SPC for comprehensive information.

5. Initiation and ongoing dose regimen

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- Transfer of monitoring and prescribing to primary care is normally after the patient (and their condition) is stable (minimum period of two months)The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.
- Termination of treatment will be the responsibility of the specialist.

There is a wide dose range depending on the indication. The selected dose will be tailored to the individual patient and decided by the specialist.

The initial stabilisation period must be prescribed by the initiating specialist.

Maintenance dose (following initial stabilisation):

Usual dose range**:**

- **Azathioprine: 0.5–3 mg/kg daily**, adjusted according to response.
- **Mercaptopurine: 1-1.5mg/kg daily,** adjusted according to response.

Some patients may respond to lower doses. Please note patients may be initiated on more than one DMARD.

The initial maintenance dose must be prescribed by the initiating specialist.

Conditions requiring dose adjustment:

Lower doses may be required if there is significant renal or hepatic impairment, in elderly patients, and in patients with mild/moderately impaired bone marrow function, TPMT deficiency or NUDT15 mutation (see SPC) .

6. Pharmaceutical aspects

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Route of administration:	Oral
Formulation:	Azathioprine 25mg and 50mg tablets Azathioprine 10 mg/mL oral suspension (Jayempi®) Mercaptopurine 50mg tablets Mercaptopurine 20mg/ml oral suspension (Xaluprine®) • Mercaptopurine 10mg tablets (unlicensed import)
Administration details:	The tablets should be swallowed whole and not split / crushed. Can be taken either with or without food, but patients should standardise which method is chosen. Tablets should be taken at least 1 hour before or 2 hours after milk or dairy products. Taking with or after food may relieve nausea, however the oral absorption of azathioprine or mercaptopurine may be reduced. Consideration should be given to monitoring therapeutic efficacy more closely if patient is taking azathioprine or mercaptopurine consistently with food. For azathioprine or mercaptopurine oral suspension, the bottle should be shaken vigorously for at least 30 seconds to ensure the suspension is well

	mixed.
Other important information:	Providing the film coating of azathioprine tablets remains intact, there is no risk or additional precautions required when handling tablets. Azathioprine and mercaptopurine are cytotoxic. It is recommended that they are handled following local recommendations for the handling and disposal of cytotoxic agents. Mercaptopurine tablets and oral suspension are not bioequivalent with respect to peak plasma concentration; increased haematological monitoring is advised if switching between formulations. When prescribing mercaptopurine, remain vigilant with regards to the similarity in name with mercaptamine.

7. Significant medicine interactions

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The following list is not exhaustive. Please see BNF or SPC for comprehensive information and recommended management.

The following drugs must not be prescribed without consultation with the specialist:

- **Allopurinol** has the potential to cause thiopurine toxicity and should be avoided, except with specialist input. Allopurinol may be recommended in combination with thiopurines by the specialist for IBD patients, particularly in those who are unable to tolerate to or do not respond to treatment with a thiopurine alone. The dose of azathioprine or mercaptopurine should be reduced by 75% if used concurrently with allopurinol. If considering prescribing allopurinol, discuss with the specialist for advice and a dose adjustment.
- **Febuxostat** has the potential to cause thiopurine toxicity; avoid in combination with azathioprine or mercaptopurine.
- **Live vaccines** (e.g. oral polio, oral typhoid, MMR, BCG, yellow fever) can be given to patients on stable long term low dose corticosteroid therapy (defined as ≤20mg prednisolone per day for >14 days) alone or in combination with low dose non-biological oral immune modulating drugs (e.g. azathioprine up to 3mg/kg/day or mercaptopurine up to 1.5mg/kg/day). Clinician discretion is advised. Please refer to the Green Book Chapter 6 for current advice, and advice for patients taking higher doses.
- **Warfarin** – thiopurines may reduce anticoagulant effects of warfarin.
- **Co-trimoxazole / trimethoprim** – possible increased risk of haematological toxicity,

however evidence is conflicting and this combination is often used in practice.

- **Clozapine** - avoid due to increased risk of agranulocytosis.
- **Ribavirin** - increased risk of haematological toxicity when azathioprine given concurrently and this combination should be avoided.
- **Aminosalicylates** (sulfasalazine, mesalazine or olsalazine) - increased risk of haematological toxicity with concomitant thiopurine due to TPMT inhibition. Dose adjustment of azathioprine or mercaptopurine and additional monitoring of FBC may be required.

The following drugs may be prescribed with caution:

- **ACE inhibitors** - increase the risk of anaemia and or leukopenia.

Cimetidine and indomethacin - concomitant administration of thiopurines may increase the risk of myelosuppression.

8. Baseline investigations, initial monitoring and ongoing monitoring to be undertaken by specialist

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Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in immediate future will prescribing and monitoring be transferred to primary care.

Baseline investigations:

- Weight
- Full blood count (FBC)
- Urea and electrolytes (U&Es) & creatinine clearance (CrCl)
- LFTs
- Baseline thiopurine methyl transferase (TPMT) status (does not need to be repeated if already ever measured)

For azathioprine for autoimmune hepatitis: Consider Hepatitis B and C status (hepatitis B surface antigen, hepatitis B anti-core antibody, hepatitis C antibody)

Provide or request appropriate vaccination prior to treatment initiation, according to local arrangements (e.g. pneumococcal, shingles, influenza, COVID-19)

Most up to date information is in the Department of Health Green Book Website: https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

Initial monitoring and at dose change:
Repeat FBC and LFTs fortnightly for 8 weeks
(0-2 months post initiation), then monthly for 4 months (2 – 6 months post initiation), then quarterly;

Following dose change of patient already established on azathioprine or mercaptopurine recommend fortnightly blood test for 4 weeks and the recommencement of the usual monitoring schedule.

Following dose changes responsibility reverts back to secondary care until the month of 2 weekly tests completed. Change in dose to be documented in clinic letter to GP

More frequent monitoring is appropriate in patients at higher risk of toxicity.

Disease monitoring:

The specialist will retain the responsibility for monitoring the patient's ongoing response to treatment and advise if a dose change or treatment cessation is appropriate. This should usually be undertaken annually.

After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.

9. ngoing monitoring requirements to be undertaken by primary care

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See section 10 for further guidance on management of adverse effects/responding to monitoring results.

Monitoring and actions	Frequency
• FBC • LFTs	Repeat FBC and LFTs fortnightly for 8 weeks (0-2 months post initiation), then monthly for 4 months (2 – 6 months post initiation), then quarterly Following dose change of patient already established on azathioprine or mercaptopurine recommend fortnightly blood test for 4 weeks and the recommencement of the usual monitoring schedule. Following dose changes responsibility reverts back to secondary care until the month of 2 weekly tests completed. Change in dose will be documented in clinic letter to GP More frequently in patients at higher toxicity, as advised by specialist.

	The exact frequency of monitoring to be communicated by the specialist in all cases.
Patients aged 70-79 years old could be eligible for the shingles vaccine (varicella zoster). For patients taking prednisolone exceeding 20mg daily or azathioprine exceeding 3mg/kg/day a non-live vaccine should be used. Specialist input may be required. If patient is taking additional DMARDs, check advice for all drugs. Please refer to Green Book Chapter 6 and Chapter 28a (Shingles) for further details. **Annual** influenza (The Green Book, Chapter 19) vaccinations are recommended COVID-19 vaccination is safe and recommended (see The Green Book, Chapter 14a). Repeat pneumococcal vaccine may be indicated. See Green Book Chapter 25 for advice.	In line with Green Book
(If relevant) If monitoring results are forwarded to the specialist team, please include clear clinical information on the reason for sending, to inform action to be taken by secondary care.	

10. Adverse effects and other management

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Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard

For information on incidence of ADRs see relevant summaries of product characteristics

Result	Action for primary care
As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance	

Full blood count: • White blood cells less than $3.5x10^9$/L for all indications except for autoimmune hepatitis when the threshold is $<3.0x10^9$/L • Lymphocytes less than $0.5x10^9$/L • Neutrophils less than $1.6x10^9$/L for indications except autoimmune hepatitis when the threshold is $<1.0 \times 10^9$/L • Platelets less than $140x10^9$/L • Eosinophilia greater than $0.5x10^9$/L	Discuss urgently with specialist team, and consider interruption. NB: Isolated lymphopenia or eosinophilia is often a feature of the underlying autoimmune indication and is rarely an indication to discontinue azathioprine.
Mean cell volume >105 fl NB: Reversible, dose-related increases in mean corpuscular volume are a known effect of thiopurines.	Consider interruption in treatment if there is a significant increase from baseline. Check serum folate, B12, alcohol history and TSH and treat any underlying abnormality. If results of these additional investigations are normal discuss with specialist team urgently.
Signs or symptoms of bone marrow suppression, e.g. unexplained bleeding or bruising with or without sore throat, mouth ulcers	Consider interruption in treatment. Check FBC immediately and discuss with the specialist team. See haematological monitoring above.
Infections: Infection requiring antibiotics	Temporarily withhold thiopurine until the patient has recovered. Consider additional investigations (e.g. FBC), if clinically appropriate.
Liver function tests: AST or ALT > 3 times normal range, OR	Withhold and discuss with specialist team. When used for hepatology indications, continue treatment and discuss with specialist urgently.

Jaundice	Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.
Gastrointestinal disorders: Nausea	Review for reversible causes. Advise patient to take with food. If no improvement, contact specialist team.
Suspected pancreatitis	Withhold and discuss with specialist team.

11. Advice to patients and carers

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The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.

The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:

Signs or symptoms indicating haematological toxicity, e.g. sore throat, infection, unexplained or abnormal bruising or bleeding.

Signs or symptoms of pancreatitis, e.g. abdominal pain, nausea, or vomiting

Signs of symptoms of hepatic toxicity, e.g. Jaundice (yellowing of the skin or whites of the eyes)

The patient should be advised to:

- During a serious infection azathioprine or mercaptopurine should be temporarily discontinued until the patient has recovered from the infection or until discussed with specialist.
- That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended.
- Tell anyone who prescribes them a medicine that they are taking azathioprine or mercaptopurine. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe.
- To inform their specialist or primary care prescriber promptly if pregnancy occurs or is

planned.

- All women aged 25-64 years old should be encouraged to participate in national cervical cancer screening programmes. There is no need to attend more frequently than recommended.
- Patients have a small increased risk of skin cancers so should be advised to wear high factor sunscreen and to wear a hat and protective clothing when in strong sunshine. Sun beds should be avoided. Patients should be advised to carry out regular self-examination of the skin and report if there are any new lesions and/or changes to skin.
- Patients taking azathioprine at a dose of 3 mg/kg or more, or mercaptopurine at a dose of 1.5 mg/kg/day or more should be advised to avoid contact with people with chicken pox or shingles and report any such contact urgently to their primary care prescriber. If the patient is exposed, contact the specialist for advice. For detailed advice on risk assessment and post exposure prophylaxis following exposure to chicken pox and shingles, see:

  the Green Book (Chapter 34)

  UKSHA guidance: Guidelines on post exposure prophylaxis (PEP) for varicella/shingles April 2022

Patient information:

- General information: https://www.nhs.uk/medicines/azathioprine/
- General information: https://patient.info/medicine/azathioprine-azapress-imuran
- Rheumatology: https://www.versusarthritis.org/about-arthritis/treatments/drugs/azathioprine/
- Dermatology: https://www.bad.org.uk/for-the-public/patient-information-leaflets/azathioprine
- Patient information leaflets are also available from https://www.medicines.org.uk/emc/search?q=azathioprine

Gastroenterology:

- https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/azathioprine-mercaptopurine
- https://gutscharity.org.uk/advice-and-information/conditions/crohns-disease/
- https://gutscharity.org.uk/advice-and-information/conditions/ulcerative-colitis/

12. Pregnancy, paternal exposure and breast feeding

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It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist.

All patients should be informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The specialist team should be contacted if a patient becomes pregnant or is planning to become pregnant or breastfeed.

the following:

Pregnancy:

The BSR and BHPR guideline on prescribing DMARDs in pregnancy and breastfeeding advises that azathioprine is compatible throughout pregnancy at doses ≤2mg/kg/day.

Current available data do not suggest that mercaptopurine exposure during pregnancy increases the risk of miscarriage, congenital malformation, intrauterine death, fetal growth restriction, or preterm delivery but the data are limited for some outcomes. A careful assessment of risk versus benefit should be made before mercaptopurine is prescribed to patients who are pregnant.

The British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease advises that both maintenance and flares can be treated as normal with thiopurines (azathioprine and mercaptopurine) during pregnancy.

Information for healthcare professionals: https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-AZATHIOPRINE-OR-MERCAPTOPURINE-IN-PREGNANCY/

Information for patients and carers: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Azathioprinemercaptopurine/

Breastfeeding:

Azathioprine is compatible with breastfeeding, although the active metabolite mercaptopurine is present in breast milk. A risk versus benefit assessment is advised. If used during breastfeeding, monitor for signs of infection or immunosuppression. If high doses of azathioprine are used, monitor infant blood counts. If mercaptopurine is used, monitor infant's blood count and liver function.

Information for healthcare professionals:

- https://www.sps.nhs.uk/medicines/azathioprine/
- https://www.sps.nhs.uk/medicines/mercaptopurine/

Paternal exposure:

Azathioprine and mercaptopurine are compatible with paternal exposure. There is currently no evidence of adverse fetal effects relating to paternal use.

- Information for healthcare professionals: https://www.medicinesinpregnancy.org/bumps/monographs/PATERNAL-USE-OF-AZATHIOPRINE-OR-MERCAPTOPURINE/

13. Specialist contact information

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Contact the specialist who has initiated treatment as outlined in the letter to the GP