Azathioprine for the treatment of Rheumatology Conditions Information for GPs

Clinicians should also refer to the overarching DMARD shared care guideline document for details of the individual responsibilities for each group e.g. GP / Specialist Rheumatology team under the shared care agreement.

Clinicians should refer to the Summary of product characteristics (SmPC) and the eBNF for comprehensive drug information.

This information should be read **in conjunction** with the summary of product of characteristics (SmPC) **and** the overarching Rheumatology shared care guidance (SCG).

Background	• Azathioprine is a disease modifying anti-rheumatic drug (DMARD). It is used as an immunosuppressant anti-metabolite 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 is not licensed for all the conditions it is used to treat. However, its use for the rheumatology related 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).
Therapeutic indications	Licensed indications specific to rheumatology for azathioprine include: • Dermatomyositis • Polymyositis • Rheumatoid arthritis • Systemic lupus erythematosus (SLE) • Polyarteritis nodosa Licensed indications may vary with brand. See relevant summary of product characteristics (see SmPC) for full details. Azathioprine is also used **'off label'** to treat a variety of other rheumatology related chronic inflammatory conditions:- e.g. inflammatory arthritis, connective tissue disease, vasculitis, giant cell arteritis The initiating specialist must specify the indication for each patient when initiating treatment and should clearly state when use is off-label.

The following organisations contribute to and participate in the BLMK APC – Bedfordshire, Luton and Milton Keynes Integrated Care Board; Bedfordshire Hospitals NHS Foundation Trust; Cambridgeshire Community Services NHS Trust; Central and North West London NHS Foundation Trust; East London NHS Foundation Trust; Milton Keynes University Hospital NHS Foundation Trust

Pharmaceutical formulations	• Azathioprine 25mg and 50mg tablets (contains lactose) NB: 75mg and 100mg tablets should **not** be prescribed due to safety concerns relating to dosing errors and disproportionate cost.
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 may be reduced. Consideration should be given to monitoring therapeutic efficacy more closely if patient is taking azathioprine consistently with food. • Providing the film coating of azathioprine tablets remains intact, there is no risk or additional precautions required when handling tablets. • Azathioprine is cytotoxic. It is recommended that it is handled following local recommendations for the handling and disposal of cytotoxic agents.
Initiation and ongoing dosing information	• Azathioprine dosing is based on body weight with usual maintenance doses based between 1- 3mg/kg / day. • Typically, the Specialist Rheumatology team will initiate azathioprine therapy at 25mg once a day and escalate by 25mg every week until a maintenance dose is ach • ieved, usually up to 100mg – 200mg daily. • This dose escalation phase will be done by the Specialist Rheumatology Team. • Typical maintenance dose is 100-200mg daily (in divided doses). • Some patients may respond to lower doses. • Maximum daily dose is 250mg **NB: Please note patients may be initiated on more than one DMARD. Patients may also be taking other immunosuppressant medications e.g. a biologic, a JAK inhibitor which are prescribed by the specialist team.** **<u>Conditions requiring dose adjustment:</u>** • 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 SmPC) .
Time to response	• Approx. 6-8 weeks • Specialist Rheumatology team should consider withdrawal if no improvement occurs within 3 months.
Shared care Implementation	• The duration of treatment will be determined by the specialist based on clinical response and tolerability. • Prescribing and monitoring can be transferred to Primary care as per overarching Rheumatology shared care guidance (SCG).

Contra-indications	This information does not replace the Summary of Product Characteristics (SmPC) and should be read in conjunction with it. Please see eBNF & SmPC for comprehensive information. • Known hypersensitivity to the active substance or any excipients. • Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to azathioprine. • Absent or very low thiopurine methyltransferase (TPMT) activity – risk of life-threatening pancytopenia.
Cautions / Special considerations	• Live vaccines (see vaccinations section) • Patients with active/history of pancreatitis. • Concomitant prescribing of allopurinol: A 75% dose reduction of azathioprine is required, (see drug interaction section) • Patients receiving azathioprine are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers, sarcomas and uterine cervical cancer in situ. • Patients with low thiopurine methyltransferase (TPMT) activity are at increased risk of myelosuppression. Substantial dose reduction is generally required. • Severe infection. (see infections section) • Severely impaired hepatic or bone marrow function. • Pregnancy and breastfeeding (see pregnancy section) • Macrophage activation syndrome (MAS) – azathioprine could potentially increase susceptibility of developing MAS (a known life-threatening disorder which may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD). Clinicians should also be attentive for symptoms of EBV and cytomegalovirus (CMV), as these are known triggers for MAS • Patients with inherited mutated NUDT15 gene are at increased risk for severe azathioprine toxicity. • Lesch-Nyhan syndrome – use of azathioprine is not recommended. Treatment may need to be monitored **more frequently** in the following:- • Elderly patients • Impaired renal function • Mild/moderately impaired hepatic function • Mild/moderately impaired bone marrow function

Side effects and adverse effects	**Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit** www.mhra.gov.uk/yellowcard For full information regarding side effects and incidence of ADRs see relevant summaries of product characteristics (SmPC) Examples of some common side effects include: • nausea • vomiting • diarrhoea • loss of appetite (which may be alleviated by taking with food or last thing at night) • hair loss • skin rashes. Minor side-effects can sometimes be helped by reducing the dose – discuss with specialist team. **Adverse effects** As azathioprine is an immunosuppressant, clinicians should note to inform patients to contact their doctor immediately if they have any side effects, in particular – breathlessness, dry cough, whites of eyes becoming yellow, severe itching of skin, rash, dark urine, infections (including fever, chills or severe sore throats), new unexplained bleeding or bruising, mouth ulcers, vomiting and diarrhoea (particularly at the start of treatment, or if it is severe, at any stage in treatment). • Azathioprine should be stopped and discuss urgently with the specialist team if bone marrow suppression is suspected. **A list of adverse effects, blood tests results and the action that maybe required by primary care is detailed in appendix 1.**
Significant drug Interactions	The following list is not exhaustive. Please see eBNF or SmPC 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. The dose of azathioprine 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.

	• **Live vaccines** – **avoid**. Discuss with Specialist team (see vaccination section) • **Warfarin** – thiopurines may reduce anticoagulant effects of warfarin. • **Co-trimoxazole / trimethoprim** – possible increased risk of haematological toxicity – monitor closely. • **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 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.
Baseline investigations (To be done by the Specialist rheumatology team)	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:** • Height and weight • Blood pressure • Full blood count (FBC) • Urea and electrolytes (U&Es) & creatinine clearance (CrCl) • LFTs including alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), and albumin • Baseline thiopurine methyl transferase (TPMT) status • Screening for viral infections as per local policy, e.g. HIV, hepatitis B and C, varicella zoster, Epstein Barr virus, cytomegalovirus • Screening for lung disease, including tuberculosis, should be undertaken at clinician discretion on a case by case basis • Confirm cervical screening is up to date • Provide or request appropriate vaccination prior to treatment initiation, as per local arrangements (e.g. pneumococcal, shingles, influenza, COVID-19)

Blood Test Monitoring requirements *(Typically to be monitored by the GP from week 4 onwards as part of shared care guideline)* **(Ref: Based on British Society of Rheumatology Guidelines, 2017 and current clinical practise)**	Blood dyscrasias (e.g. leucopenia and neutropenia) and hepatocoxicity can occur hence the importance of regular blood tests. **Monitoring schedule** **To be repeated every 2 weeks until the dose has been stable for 6 weeks, then monthly for 3 months then at least every 12 weeks***. • FBC • U&Es, including creatinine and CrCl • LFTs, including AST and/or ALT, and albumin *More frequent monitoring is appropriate for patients at a higher risk of toxicity. **The exact frequency of monitoring to be communicated by the specialist in all cases**. **Following a dose increase:** • Repeat every 2 weeks until the dose has been stable for 6 weeks, then revert to previous schedule. NB: Monitoring of patients on more than one DMARD should be based on the DMARD which requires the most frequent monitoring - Contact the Specialist team for advice. 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. • **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.** See **appendix 1** for information relating to adverse effects / blood test results and the actions that should be taken in primary care.
Infections	• Azathioprine is an immunosuppressant and increases the patient's susceptibility to infections, including opportunistic infections. • Initiate prompt anti-infective treatment when indicated on the basis that the patient may be immunosuppressed to some degree. • During a serious infection*, azathioprine should be temporarily discontinued until the patient has recovered from the infection. (* Serious infection: warrants admission to hospital or requires parenteral anti-microbial therapy.) • If exposed to measles – contact specialist for advice.

	• If exposed, to chicken pox or shingles 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) and UKSHA guidance: Guidelines on post exposure prophylaxis (PEP) for varicella/shingles April 2022
Vaccinations for patients with rheumatological disease(s) who are receiving azathioprine	• A careful history should be checked to determine potential level of immunosuppression. • Factors affecting the degree of immunosuppression include the dosage (mg/kg) of azathioprine used, any concomitant use of other immunosuppressant agents e.g. steroids, an additional DMARD, a biologic, JAK inhibitor. • The immune response to vaccination may be impaired. • Live vaccines (e.g. oral polio, oral typhoid, MMR, BCG, yellow fever): should be **avoided.** • In certain circumstances, if a live vaccine is required – **contact Specialist team for advice.** • For further information regarding vaccines in patients taking immune modulators – see Green Book Chapter 6 • If azathioprine is stopped, live vaccines should also be avoided for a further 3 months. • Annual flu vaccination and Covid-19 vaccination (as per national schedule) are recommended. • Pneumococcal vaccination is recommended - repeat pneumococcal vaccine may be indicated. See Green Book Chapter 25 for details. • Shingles - depends on age of patient and degree of immunosuppression. If required, a **non-live vaccine** should be used. See green book Chapter 28a (Shingles) for details **Contact the specialist team if further guidance is required.**
Alcohol	• As both alcohol and azathioprine can affect the liver, patients should be advised to only drink alcohol in small amounts and stay within government guidelines, which state that adults should not drink more than 14 units per week and should have alcohol free days without 'saving units up' to drink in one go.
Elective Surgery	• **Contact the Specialist Rheumatology team for advice.** Generally, azathioprine should not routinely be stopped in the peri-operative period, although individualised decisions should be made for high-risk procedures (e.g. 'contaminated', or duration over 60 minutes), in which case it can be stopped 2 weeks prior to surgery and then restarted once wound healing is satisfactory. • Caution for early detection of infections.

Contraceptive Advise	• The Specialist Rheumatology team should discuss family planning before initiation of treatment. • GPs should refer any female or male patient who is wishing to start a family to the Specialist Rheumatology team.
Pregnancy and Breastfeeding	• 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. • It is important that the mother's health is maintained during pregnancy and disease flares are avoided by not stopping azathioprine. **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. **Information for healthcare professionals**: ukTIS monograph for azathioprine **Information for patients and carers:** Azathioprine -medicines in Pregnancy (Bumps) **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. **Information for healthcare professionals:** • https://www.sps.nhs.uk/medicines/azathioprine/ **Paternal exposure**: Azathioprine is compatible with paternal exposure. There is currently no evidence of adverse foetal effects relating to paternal use. **Information for healthcare professionals:** ukTIS Paternal use of azathioprine

Photosensitivity	• Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor to minimize the risk of skin cancer and photosensitivity.
Malignancies	• No good data to suggest any strong association with malignancies.
Advice to patients and carers	**As azathioprine is an immunosuppressant, the patient should be advised to report any of the following signs or symptoms to their primary care prescriber immediately without delay:** • Signs of breathlessness, dry cough • Signs or symptoms indicating haematological toxicity, e.g. sore throat, infection (including fever, chills), mouth ulcers, unexplained or abnormal bruising or bleeding. • Abdominal pain or jaundice ((yellowing of the skin or whites of the eyes) • Signs or symptoms of pancreatitis, e.g. abdominal pain, nausea, or vomiting • Signs of symptoms of hepatic toxicity, e.g. Jaundice, severe itching of skin, rash, dark urine **The patient should be advised:** • Taking azathioprine can mean they are more likely to get infections. They should contact their doctor for advice if they get an infection, such as coronavirus COVID -19. • Patients taking azathioprine should be advised to avoid contact with people with chicken pox or shingles or measles and report any such contact urgently to their primary care prescriber. • During a serious infection, azathioprine should temporarily be discontinued by the clinician until the infection resolves. • 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. 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. 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/

	• Patient information leaflets are also available from https://www.medicines.org.uk/emc/search?q=azathioprine
Practical points for GPs to note	• Advise patients to attend for a blood test approx. one week before their next prescription is due to ensure that the results can be reviewed before the next prescription is requested for issue. • Check the results of recent blood test **before** issuing a prescription. (click here for appendix 1) - This contains information regarding actions to take in the event of blood test abnormalities and side effects). • Increase blood test monitoring frequency after a dose increase as per specialist instructions. • Prescribers should note that whilst absolute blood test values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance.
References	1) National Shared care Protocol , Azathioprine and mercaptopurine for patients within adult services adults (non-transplant indications), RMOC azathioprine and mergacptopurine scg , accessed July 2024 2) eBNF – azathioprine entry , accessed July 2024 3) Summary of product of characteristics (SmPC) , azathioprine 50mg film coated tablets, Tillomed Laboratories , accessed July 2024

Appendix 1 – actions to be taken in primary care in response to abnormal blood tests results and/or adverse effects

Adverse effect / Blood Test Result	Action for Primary care
Full blood count: • White blood cells less than $3.5x10^9$/L • Lymphocytes less than $0.5x10^9$/L • Neutrophils less than $1.6x10^9$/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: ALT or AST >100 units/L, or any sudden increases (e.g. double of baseline), OR Unexplained fall in serum albumin <30g/L Jaundice	Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.
Renal function: Creatinine rise >30% or calculated GFR reduces to <60ml/min	Withhold and discuss with specialist team
Gastrointestinal disorders: • Nausea, vomiting, abdominal pain, diarrhoea, dyspepsia	Review for reversible causes. If simple nausea, advise patient to take with food. If no improvement contact specialist team. For all other symptoms – withhold and discuss with specialist team
Suspected pancreatitis	Withhold and discuss with specialist team.
Macrophage activation syndrome (MAS)	Evaluation and treatment should be started as early as possible, and treatment with azathioprine should be discontinued