SHARED CARE ARRANGEMENT AND PRESCRIBING INFORMATION FOR AZATHIOPRINE TABLETS (ADULTS) EXCLUDING RENAL TRANSPLANT

Clinicians must ensure they are referring to the correct SCA for specialty/situation.

This SCA is applicable for ALL conditions/specialities EXCLUDING RENAL TRANSPLANT PATIENTS.

Note: This document should be read in conjunction with the current Summary of Product Characteristics (SmPC).

Patient safety is paramount. The prescriber who prescribes the medicine legally assumes clinical responsibility for the drug and the consequences of its use.

GENERIC NAME (formulations and strength)

Name: Azathioprine

Formulation: Tablets

Strength: 25mg, 50mg

STATUS OF MEDICINE

Licence status: Licensed, indicated in combination with corticosteroids and/or other immunosuppressive agents and procedures.

Used across multiple specialities including rheumatology, gastroenterology, neurology, renal (excluding renal transplant) and dermatology (possible licensed and off-label indications).

Formulary status: Formulary – available for restricted use under specialist supervision.

Black triangle medicine: NO

Risk minimisation materials: NO

CONDITION(S) TO BE TREATED UNDER THIS SCA

Immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basic immunosuppression):

- To enhance the survival of organ transplants, e.g. liver transplant
- Moderate to severe inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis)
- Severe active rheumatoid arthritis
- Systemic lupus erythematosus
- Dermatomyositis and polymyositis
- Auto-immune chronic active hepatitis
- Pemphigus vulgaris
- Polyarteritis nodosa
- Auto-immune haemolytic anaemia
- Chronic refractory idiopathic thrombocytopenic purpura
- Anti-neutrophil cytoplasmic antibodies (ANCA) - associated vasculitis

- Sarcoidosis
- Steroid responsive inflammatory or autoimmune disorders of the central and peripheral nervous system including myasthenia gravis, autoimmune encephalitis, neuromyelitis optica (NMO) spectrum disorder/myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), neurosarcoid, chronic inflammatory demyelinating polyneuropathy, and myositis.

TYPICAL DOSAGE REGIME	
Licensed dose	See Specialist service/SmPC for advice – variable according to condition being treated
Route of administration	Oral
Recommended starting dose	See Specialist service for advice – variable according to condition being treated
Titration dose/increment	See Specialist service for advice
Maximum dose	See Specialist service for advice
Situations requiring dose adjustment	See Specialist service for advice and Monitoring Schedule for DMARDs
Duration of treatment	See Specialist service for advice

RESPONSIBILITY OF ACUTE CARE/SPECIALIST SERVICE

- Baseline as per Monitoring Schedule for DMARDs:
  - Full Blood Count (FBC), Liver Function Tests (LFTs), and Urea and Electrolytes (U&Es)
  - Thiopurine S-methyltransferase (TPMT). Azathioprine induced myelosuppression is linked to thiopurine methyl-transferase (TPMT) deficiency therefore the consultant will test for this prior to initiation of treatment.
    Any additional tests, e.g. Hep B core antibody, Hepatitis C, HIV and EBV as indicated, dependant on condition being treated and as determined by specialist service.
- Copy of baseline results to be shared with Primary Care.
- Request for initiation of therapy and recommendations for dose increments to Primary Care.
- Monitoring clinical response to treatment and advising on final dose required for the patient.
- Pneumococcal polysaccharide vaccine (PPV), COVID-19 vaccine and annual influenza vaccine should be given as per Joint Committee of Vaccination and Immunisation (JCVI)/The Green Book recommendations. Shingles vaccine should be given to those individuals who are severely immunocompromised, or anticipating immunosuppressive therapy, and eligible in line with JCVI/The Green Book recommendations and Scottish Government vaccination programme. Patients should be referred by specialist services to receive these vaccines in accordance with local protocol.
- Provide counselling, as appropriate, regarding pregnancy and breastfeeding.

RESPONSIBILITY OF PRIMARY CARE/PRESCRIBING CLINICIAN

A Practice agreeing to prescribe azathioprine should:

- Prescribe medication under the guidance of the Consultant from the relevant specialist service.
- Checking before prescribing each instalment of medication that the monitoring is up to date and results are within a satisfactory range.
- Note: for individuals referred for vaccinations by the specialist service it is ideal to wait for vaccinations before starting immunosuppressive treatments. However this risks not controlling the autoimmune condition quickly which can negatively affect long term prognosis. Therefore specialties do not insist on a delay in starting immunosuppressive treatment to allow for vaccinations and recommend vaccinations happen as soon as possible after starting immunosuppressive treatment.
- Ensure that the relevant monitoring requirements have been undertaken at the correct frequency.
- The Practice/General Practitioner (GP) has primary responsibility for monitoring according to the Monitoring Schedule for DMARDs and review of results.
- Only continue to prescribe medication if it is being satisfactorily monitored.
- Ensure the GP/prescriber is aware that the drug can cause:
  - Bone marrow suppression
  - Leucopenia
  - Increased risk of malignancy
  - Lymphomas and skin cancer
- Patients should be asked about the presence of sore throat, abnormal bruising or bleeding at each visit.
- Ensure when the patient has an inter-current illness FBC, U+Es and LFTs are done and abnormal results are acted upon promptly. If an intercurrent illness occurs, when completing laboratory request always include details of the patient's medication.
- If bloods are taken due to intercurrent illness, ensure they are monitored and action taken as per the Monitoring Schedule for DMARDs.
- Infection - During a serious infection azathioprine should be temporarily discontinued until the patient has recovered from the infection and is off antibiotics for 2 weeks with no recurrence of infection. (This excludes any transplant patients who should be discussed with specialist service).
  It can be considered appropriate to continue these drugs in patients with minor or uncomplicated viral infections or, if deemed clinically appropriate by the Specialist, in patients requiring long term antibiotic prophylaxis e.g. for prevention of recurrent UTIs.
- Contact the consultant in the event of a drug reaction, monitoring abnormality, or if you are concerned in any way regarding the current treatment regime.
- Be alert for any of the known adverse reactions.
- Ensure no interacting medications are prescribed in Primary Care
- Monitor for concordance with therapy
- The patient should be encouraged to ensure blood tests are undertaken at the correct intervals
- It is responsibility of Primary Care to ensure that the medication is recorded on the patient's clinical medication record. This will facilitate central searches for vaccinations in order to ensure patients receiving immunosuppressants are called by the HSCP teams for required vaccinations e.g. influenza and covid programmes.
- Report any adverse events to consultant and the MHRA using the Yellow Card System.

- Post exposure prophylaxis (PEP) should be considered in non-immune individuals if exposed to shingles or chickenpox as per The Green Book.
- If something unexpected occurs contact Consultant for the appropriate speciality.
- Notify consultant/specialist service if drug is stopped.

MONITORING

Refer to the NHSG Guidelines For The Monitoring of Disease Modifying Anti-Rheumatic Drugs (DMARDs) For Healthcare Professionals.

Primary Care are responsible to ensure results are reviewed and action taken as per monitoring guidance.

Note: In addition to absolute values for haematological or biochemical indices a rapid change or a consistent upward/downward trend in any value should prompt caution and extra vigilance.

RESPONSIBILITY OF THE PATIENT

- Take medication regularly as directed by the specialist/doctor.
- Attend hospital and GP clinic appointments as requested by specialist/GP practice. Failure to attend appointments may result in medication being reviewed/stopped.
- The patient should ensure all blood tests are undertaken at the correct intervals.
- Report any adverse effects/illness to the specialist/GP and present rapidly to specialist/GP should their condition significantly worsen.
- To minimise the risk of skin cancer, exposure to sunlight and Ultra Violet light should be limited by wearing protective clothing and using sunscreen with a high protection factor (minimum SPF 30).

PRESCRIBING INFORMATION

For specific product information consult the current summary of product characteristics (http://emc.medicines.org.uk/), the BNF/BNF for Children BNF (British National Formulary) | NICE

CONTRAINDICATIONS

- Hypersensitivity to azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any excipients listed in the SmPC.
- Severe infections - during a serious infection azathioprine should be temporarily discontinued until the patient has recovered from the infection and is off antibiotics for 2 weeks with no recurrence of infection. (This excludes any transplant patients who should be discussed with specialist service).
- Seriously impaired hepatic or bone marrow.
- Pancreatitis.
- It is recommended patients do not receive any live vaccines, especially BCG, smallpox, yellow fever until at least 3 months after the end of azathioprine treatment.

PREGNANCY

Women on azathioprine should be advised to adhere to their usual azathioprine monitoring, however no additional monitoring/change of therapy is required.

British Society for Rheumatology Guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids from April 2023 states that azathioprine is safe in pregnancy and can be continued.

BREAST-FEEDING

British Society for Rheumatology Guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids from April 2023 states that azathioprine is safe in breastfeeding (in a healthy, full term infant). This is outwith the product license which states patients should avoid breastfeeding while taking this medicine, but supported by specialist services.

COMMON SIDE EFFECTS

- Nausea
- Diarrhoea
- Vomiting
- Anorexia
- Abdominal discomfort
- Headaches
- Pancreatitis
- Mutagenicity and carcinogenicity increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma) sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ
- Macrophage activation syndrome
- Patients with NUDT15 variant gene are at increased risk for severe 6-mercaptopurine toxicity such as early leucopenia and alopecia, from conventional doses of thiopurine therapy.
- Viral, fungal, and bacterial infections in transplant patient receiving azathioprine in combination with other immunosuppressants. Increased sensitivity to infection in patients with inflammatory bowel disease.

Action abnormal monitoring results are per NHSG Disease Modifying Anti-Rheumatic Drugs (DMARDs) Monitoring Guidance.

The specialist service should be contacted if there are any patient specific issues or concerns regarding side effects or abnormal results.

COMMON DRUG INTERACTIONS (for a full list see SmPC)

- Live vaccines - should be avoided in patients taking azathioprine.
- Co-trimoxazole/trimethoprim - increased risk of haematological toxicity
- Allopurinol - do not prescribe (unless discussed/advised by a Renal Consultant).
- Warfarin - monitor concurrent use. Inhibition of the anticoagulant effect of warfarin, when administered with azathioprine has been reported.

- Surgery - Special care with neuromuscular blocking agents (e.g. rocuronium) anaesthetist to consider prior surgery.

This information is not intended to be a complete list of interactions. For further information consider appropriate reference sources such as SmPC/Vision system.

ADVERSE DRUG REPORTING

If an adverse reaction should occur, inform relevant medical practitioner as soon as possible.

Report to the MHRA using the Yellow Card System https://yellowcard.mhra.gov.uk/

REFERENCES

- Azathioprine 25mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- British Society for Rheumatology Guideline

ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION

In the event of a concern being raised, the Primary Care practitioner should contact the referring consultant for the appropriate specialist service via the hospital switchboard, via their secretary, by email or letter, whichever is more appropriate. If the concern is urgent, and out of hours advice is required, the on call Registrar for the speciality may be contacted via the switchboard.

<table>
<tr><td>Publish: Public</td><td>Applies to: NHS Grampian</td><td>Version: 4</td><td rowspan="3">NHS Grampian</td></tr>
<tr><td rowspan="2">Prepared by:

Medicines Management Team and specialities</td><td rowspan="2">Authorised for issue by:

Medicine Guidelines and Policies Group</td><td>Document no: MGPG/SCA_DMARD Azathioprine/1687</td></tr>
<tr><td>Effective Date: August 2025

Review Date: July 2028</td></tr>
<tr><td>Signature:
Dr Lindsay Robertson

Date: August 2025</td><td>Signature:
Lesley Coyle

Date: August 2025</td><td>Supersedes: MGPG1321, Version 3</td></tr>
<tr><td colspan="4">Review/Consultation Group: This document has been reviewed by rheumatology, gastroenterology, neurology, renal and dermatology consultants and pharmacists at ARI and approved by Medicines Guidelines and Policies Group.</td></tr>
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