NORTH AND EAST DEVON HEALTHCARE COMMUNITY SHARED CARE PRESCRIBING GUIDELINE

Azathioprine

Treatment of rheumatological conditions

Specialist: Please complete letter on page 6 before sending guideline to GP

GP: Please indicate whether you wish to share patient's care by completing letter on page 6 and return to specialist

Aim of treatment

Azathioprine is a disease-modifying antirheumatic drug.
Indication: Treatment of adults with severe rheumatoid arthritis, systemic lupus erythematosus and other rheumatological diseases.

A summary of prescribing information is provided on page 4.

Specialist responsibilities

- Initiate oral azathioprine, supply 28 days' medication.
- Discuss benefits and side effects of treatment with patient or patient's carers including where appropriate the risks associated with pregnancy and need for reliable method of contraception.
- Refer patient to specialist nurse service where appropriate (eg. new patient) for advice on taking the drug, its cautions, side effects associated with treatment, monitoring requirements and the timing of re-assessment and by whom.
- Ascertain immune status by enquiring about history of chickenpox. Measurement of antibodies to varicella-zoster virus is not recommended.
- Issue a booklet for recording test results to patient.
- Conduct baseline tests including full blood count, liver function tests, U&Es, serum creatinine and if appropriate, vitamin B12, folate and TSH. Copy test results to GP.
- Test for TPMT deficiency and if required, advise on alternative dosing and monitoring strategy.
- Specify review dates.
- Prompt verbal communication followed up in writing to GP of changes in treatment or monitoring requirements, results of monitoring, assessment of adverse events or when to stop treatment. Urgent changes to treatment should be communicated by telephone to GP.
- Reporting adverse events to MHRA.

General practitioner responsibilities

If GP has agreed to share care:

- Continue to prescribe oral azathioprine in accordance with these guidelines.
- Undertake monitoring during treatment as specified below. Review results and take any necessary action.
- Take appropriate action if patient reports sign(s) or symptom(s) specified under Monitoring.
- Be aware of criteria for referral to Rheumatology team.
- There is a significant interaction between azathioprine and allopurinol. Ensure that the patient is not taking allopurinol and be alert to the possibility of interactions when initiating new drugs. These drugs can be co-prescribed, but with great care – see Interactions section
- Respond to advice from secondary care on dose changes and frequency of monitoring.

- Report to and seek advice from specialist on any aspect of patient care of concern to GP which may affect treatment. Prompt referral to specialist if there is a change in patient's health status.
- Report adverse events to specialist.
- Stop treatment in case of a severe adverse event or as per shared care guideline.
- Offer influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check that the patient has had one dose of pneumococcal vaccine (revaccination is not recommended, except every five years in patients whose antibody levels are likely to have declined more rapidly e.g. asplenia) – see BNF or Green Book

Monitoring

1. Monitoring prior to starting therapy: rheumatology team

- Measure baseline height and weight, blood pressure, full blood count, LFTs, U&Es and creatinine and if appropriate, vitamin B12, folate and TSH.
- Chest x-ray
- Consider patient risk factors for viral infections and screen for occult viral infections (hepatitis B and C and HIV) where appropriate
- Pre-screening for TPMT deficiency will be conducted by the rheumatology team and if required, an alternative dosing and monitoring strategy will be recommended. This test is sent to an external laboratory and the result is available in 2-4 weeks.

2. Monitoring during treatment: General practice

Laboratory tests

<table>
<tr><th>Tests</th><th>Frequency of monitoring</th><th>Guidance</th><th>Action to be taken by GP</th></tr>
<tr><td>FBC</td><td rowspan="3">Every two weeks until on stable dose for 6 weeks, then every month for 3 months, then at least every 12 weeks.
Following dose increases, monitor every 2 weeks until on a stable dose for 6 weeks, then as above.

Patient factors where continued monthly monitoring is recommended (unless otherwise specified):
• Previous toxicity or deranged FBC or LFTs while on DMARDs
• Chronic kidney disease (CKD 3 or worse)
• Pre-existing liver disease

Additional urgent monitoring tests should be carried out within 24 hours for any patient with acute kidney injury (AKI).</td><td>WCC < 3.5 x10^9/L
Neutrophils < 1.6 x10^9/L
Eosinophils >0.5 x x10^9/L
Platelets < 140 x x10^9/L
MCV > 110fl</td><td rowspan="3">If results meet specified criteria, stop treatment and refer to specialist.
If isolated MCV rise, check for other causes (B12, folate, thyroid function and alcohol consumption). If results are normal, refer to specialist.
If concerned about sequential drops in FBC indices (possibly still within normal range), consider an early re-test/seek specialist advice.
If deterioration in renal function, dose adjustment may be necessary; if toxicity suspected or dosing advice required refer to specialist team.</td></tr>
<tr><td>Creatinine / eGFR</td><td>Creatinine increase >30% over 12 months and/or eGFR <60ml/min/1.73m2</td></tr>
<tr><td>ALT and/or AST and albumin</td><td>ALT and/or AST >100 U/L

Albumin unexplained reduction to <30g/L</td></tr>
</table>

Other factors that may increase risk of toxicity include moderate renal impairment, extremes of body weight, polypharmacy (especially other haematotoxic/ hepatotoxic/ nephrotoxic drugs), comorbidities, age > 80 years. Where more frequent ongoing monitoring is required due to a combination of patient factors this will be advised by the specialist prescriber.

Signs and symptoms

Patients MUST report mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding and any unexplained illness/infection.

Action to be taken by GP:

- **Review patient with any of the signs or symptoms listed above within 24 hours** for clinical assessment, full blood count and liver function tests. Signpost patient to alternative provider if this is not possible e.g. weekend/bank holiday
- **Stop treatment and refer if:**
  - Abnormal bruising
  - Severe sore throat
  - Rash
  - Severe oral ulceration
  - Unexplained illness including severe nausea, vomiting or diarrhoea

During a **serious** infection **STOP** treatment. During minor infections (e.g. uncomplicated UTI treated with a short antibiotic course) treatment can be continued.

Do not stop treatment prior to surgery unless significant risk of infection.

Contact Microbiology if a patient, not known to be immune to chickenpox, comes into contact with shingles or chickenpox, for advice on whether zoster immune globulin or other treatment is indicated.

In patients suffering from chickenpox or active skin lesions from shingles, withhold. Patients with chickenpox: contact microbiologist for consideration of admission to hospital for IV antivirals. Patients with shingles: if any vesicles are still present (regardless of the time of onset), treat with aciclovir (800mg five times a day for 7 days).

Patient/carer responsibilities

Patients (and/or their carers):

- MUST report mouth ulcers, sore throat, fever, epistaxis, rash, unexpected bruising or bleeding, and any unexplained illness/infection to their GP and/or specialist (or out of hours service e.g. NHS 111 if their GP practice is closed for weekend/bank holiday).
- Report any other adverse effect to their GP and/or specialist whilst being treated with azathioprine.
- Ensure that they have a clear understanding of their treatment.
- Ensure they attend for monitoring requirements.
- Be aware that treatment will be stopped if patient does not attend for monitoring.

Back-up advice and support

Contact details	Telephone No	E-mail address
Dr R Haigh Dr S Earl Dr M Brown Dr R Mascarenhas Dr M Abusalameh Dr M Cates Dr S Kyle Dr R Manhas Dr V Arya	(01392) 403705 (01392) 406351 (01392) 403567 (01392) 406355 (01392) 403772 (01392) 403707 (01271) 311571 (01271) 311571 (01271) 311571	richardhaigh@nhs.net Susannah.earl@nhs.net mary.brown11@rnhs.net r.mascarenhas@nhs.net m.abusalameh@nhs.net matthewcates1@nhs.net stuartkyle@nhs.net roopemanhas@nhs.net vivek.arya2@nhs.net
RD&E rheumatology dept NDHT rheumatology dept		rde-tr.rheumatology@nhs.net ndht.rheumatology@nhs.net

Please do not use rheumatology department emails for enquiries relating to patients receiving DMARDs under the care of other specialties e.g. dermatology, gastroenterology etc.

Supporting Information

This guideline highlights significant prescribing issues, not all prescribing information and potential adverse effects are listed. Please refer to SPC/data sheet for full prescribing data.

Dose

Dose: The normal dose range is 50mg to 200mg daily. The target dose will be clearly specified in the clinic letter.

Special patient groups: Use doses at the lower end of the range for the elderly and patients with hepatic or renal impairment.

Contraindications

- Hypersensitivity to azathioprine
- Hypersensitivity to mercaptopurine.
- Pregnancy. Patients of childbearing age should be advised to use a reliable method of contraception during treatment. When planning a pregnancy it is important that both men and women on this drug discuss medication with the Rheumatology team (at least six months before conception) since all drugs can potentially affect the unborn child.
- Live vaccines

Precautions

- Lactation: see SPC for further information.
- Patients with deficiency in the enzyme thiopurine methyltransferase (TPMT) as these patients have a higher risk of bone marrow toxicity.
- Renal or hepatic impairment – more frequent monitoring of FBC and LFTs if severe renal or hepatic disorder or high doses used
- 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 minimise the risk of skin cancer and photosensitivity.
- Varicella zoster – check if patient has history of varicella zoster before starting treatment. If no history of exposure, patient should avoid contact with individuals with chickenpox or herpes zoster. If exposed, passive immunisation with varicella zoster immunoglobulin may be considered. See local guidance page 3.
- Increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas and uterine cervical cancer in situ.

Side effects

Common and uncommon:

- Nausea – can be relieved by administering tablets after meals.
- Bone marrow depression, leucopenia, thrombocytopenia and anaemia.
- Hypersensitivity reactions.
- Cholestasis, abnormal liver function tests, pancreatitis.
- Increased susceptibility to infections.

Interactions

- ACE inhibitors – increased risk of anaemia when azathioprine given with captopril or enalapril especially in renal impairment and of leucopenia with co-prescribing of captopril
- Allopurinol – increased toxicity of azathioprine, reduce dose of azathioprine to one quarter of usual dose
- Aminosalicylates (e.g. mesalazine, olsalazine, sulfasalazine) – possible increased risk of leucopenia with concurrent use of azathioprine
- Antibacterials - Co-trimoxazole and trimethoprim – increased risk of haematological toxicity with concurrent use of azathioprine
- Anticoagulants – possible reduction in anticoagulant effect of coumarins

- Antivirals – myelosuppressive effects of azathioprine possibly enhanced by ribavirin.
- Febuxostat – concomitant use not recommended as may result in increased levels of azathioprine
- Vaccines – see below

Vaccines

- Live vaccines are contraindicated. These include measles, mumps and rubella; BCG; poliomyelitis – oral Sabin vaccine; yellow fever; typhoid – oral.
- Flu and pneumococcal vaccines may be given (see GP responsibilities).
- Shingles vaccination can be given to eligible patients on azathioprine monotherapy, seek specialist advice if used in combination with other DMARDs
- Passive immunisation should be carried out using Varicella Zoster Immunoglobulin (VZIG) in non-immune patients if exposed to chickenpox or shingles. See local guidance page 3.

For additional information refer to the British Society of Rheumatology guidance on vaccinations for immuno-suppressed patients at:
http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/v/vaccinations_in_the_immunocompromised_person.pdf

Pregnancy and lactation

See Contraindications section and SPC for further information

Important safety information

MHRA Drug Safety Update (May 2025): Thiopurines and intrahepatic cholestasis of pregnancy (ICP)

- Cholestasis of pregnancy has rarely been reported in association with azathioprine therapy
- This risk is believed to also apply to the other thiopurine drugs, mercaptopurine and tioguanine
- It may occur earlier in pregnancy than non drug-induced cholestasis of pregnancy, and it may not respond to ursodeoxycholic acid
- Withdrawal or dose reduction of the thiopurine drug may improve liver function tests
- Remain vigilant to signs and symptoms of ICP in pregnant patients taking thiopurines (intense itching without a rash, nausea, and loss of appetite) and discuss any concerns with clinicians managing the patient's immunosuppressant therapy and a hepatologist, as necessary
- If cholestasis of pregnancy occurs, a case-by-case assessment is required to determine the appropriate course of action. Consider the risks and benefits of remaining on the product against the risks and benefits of stopping.
- In patients with ICP, measure serum bile acids to identify pregnancies at particular risk of spontaneous preterm birth (≥40uM) or stillbirth (non-fasting serum bile acids ≥100uM)

Date ratified by Effective Practice Committee: April 2011
Partially updated: October 2019, March 2021
MHRA DSU added June 2025

Shared Care Agreement Letter - Consultant Request

To: Dr……

Practice Address: ……

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Patient Name:	
Hospital number:	
Date of birth:	
Address:	

DIAGNOSED CONDITION: **……..**

I recommend treatment with the following drug: **……**

I request your agreement to sharing the care of this patient according to the North and East Devon Health Community Shared Care Prescribing Guidelines for this drug.

Principles of shared care:
GPs are invited to participate. If GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug the GP should reply to this request as soon as practical. Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them.

The doctor who prescribes the medication has the clinical and legal responsibility for the drug and the consequences of its use.

Signed:		**Date:**	
Consultant name:			
Consultant email:			
Department email:			
Contact telephone:			

GP RESPONSE
I agree/ do not agree* to share the care of this patient in accordance with the Shared Care Guideline.

Signed: …….. **Date: ……**

GP name: …….. ***Delete as appropriate**