Specialised Medicines Service Guideline ~ Azathioprine and mercaptopurine for the treatment of inflammatory bowel disease in adults

This guideline highlights significant prescribing issues. Not all prescribing information and potential adverse effects are listed. Please refer to the BNF and individual product SPCs for full prescribing data.

Specialist: Please complete letter at the end of this document and send together with the shared care guideline to the GP.

GP: Please indicate whether you wish to share patient's care by completing letter at the end of this document and return to specialist.

GPs are invited to participate. If a 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.

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

Introduction and aims of treatment

Azathioprine and mercaptopurine are antimetabolite drugs that interfere with nucleic acid synthesis. Azathioprine is extensively metabolised to mercaptopurine in vivo. Mercaptopurine is an option where azathioprine has been beneficial, but side effects are affecting tolerability. Inflammatory bowel disease is a common but unlicensed use of these drugs.

This guideline covers the use of oral azathioprine and mercaptopurine for the treatment of inflammatory bowel disease (IBD) in adults.

Other indications are out of scope of this guideline. For shared care / Specialised Medicines Service (SMS) prescribing guidelines on the use of azathioprine & mercaptopurine for other indications, refer to the NHS Devon website (https://onedevon.org.uk/our-work/services-and-support/medicines-and-treatments/clinical-guidance-for-prescribers/) or the Devon Formulary website (https://devonformularyguidance.nhs.uk/).

The prescribing and drug safety monitoring of azathioprine for suppression of transplant rejection remains hospital only.

Specialist responsibilities

Consultants may decide to delegate some of these tasks to members of their team; however the responsibility for ensuring the following are undertaken remains with the consultant:

- Assess the patient, establish a diagnosis and the need for treatment with azathioprine or mercaptopurine.
- Update records with list of existing drugs from available resources and **ensure there are no drug interactions of clinical significance** with current medication.
- Discuss benefits and side effects of treatment with patient (and/or carer) including where appropriate guidance on pregnancy / contraception and cervical screening.
- Refer patient to specialist nursing service where appropriate (e.g. new patient, poor compliance) for advice on taking the drug, its cautions, side effects associated with treatment, monitoring requirements and the timing of re-assessment and by whom. Provide patients with written information regarding the benefits, risks, side effects and monitoring of treatment
- Ensure the patient understands that treatment may be stopped if they do not attend for monitoring & treatment review.

- Undertake baseline assessment and ongoing monitoring as specified (see monitoring section below).
- Prescribe azathioprine or mercaptopurine until patient is on a stable dose and then formally request shared care with GP. **The patient will have received at least 3 months of treatment and have been stabilised on a regular dose before sharing care.**
- Prescribing and monitoring will remain in secondary care until the patient is stable and GP agrees to share care.
- Ask the GP whether they are willing to participate in shared care. Include all relevant test results (GPs may not have access to these results in primary care) and confirm ongoing monitoring frequency.
- Continue to review the patient at agreed specified intervals, (including response to treatment and need to continue therapy), sending a written summary to the GP whenever the patient is reviewed, including the current dose to be prescribed.
- Advise the GP (in writing) of any 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 (and followed up in writing)
- Provide the GP with relevant contact information with clear arrangements for back-up advice and support should further assistance be required.
- Provide any other advice or information for the GP if required.
- Report adverse events to MHRA via yellow card scheme when appropriate (www.yellowcard.mhra.gov.uk/)

General practitioner responsibilities

- Ensure a timely reply is sent to specialist in response to request for shared care.

If GP has agreed to share care:

- Ensure there are no drug interactions with existing drugs and be alert to the possibility of interactions when initiating other medications (see supporting information below). **Note:** There is a significant interaction between xanthine oxidase inhibitors (allopurinol, febuxostat) & azathioprine / mercaptopurine. Allopurinol can be co-prescribed with azathioprine or mercaptopurine but with great care (normally dose reduction of azathioprine or mercaptopurine to 25-33%) – see supporting information. If the patient is on existing xanthine oxidase inhibitors, please liaise with gastroenterologist to ensure the correct dose.
- Continue to prescribe azathioprine or mercaptopurine in accordance with these guidelines, and on the advice of a specialist.
- Offer Pneumovax and annual influenza vaccines (except live nasal influenza).
- Offer shingles vaccination to all patients who are eligible under the national vaccination programme.
    - If treatment with azathioprine or mercaptopurine has already begun, contact specialist to discuss appropriateness of vaccination and which vaccine to use e.g. Zostavax or Shingrix (refer to green book for further information, including advice on immunosuppressed individuals)
- COVID-19 vaccine is recommended
- Contact microbiology to determine whether passive immunisation should be carried out in non-immune patients exposed to chickenpox or shingles, using Varicella Zoster Immunoglobulin.
- Undertake ongoing monitoring as specified below. Review and act on results or reported side-effects as described in monitoring section below.
- Be aware of criteria for referral to gastroenterology team.
- Respond to advice from secondary care on dose changes and frequency of monitoring.
- Stop treatment in case of a severe adverse event or as per prescribing guideline.
- Seek specialist advice if the patient becomes pregnant or wishes to become pregnant
- Report to and seek advice from specialist on any aspect of patient care or 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 and to MHRA via yellow card scheme when appropriate (www.yellowcard.mhra.gov.uk/).

Monitoring requirements

Assessment to be completed by the gastroenterology team:

- Before treatment:
  - Height and weight
  - Blood pressure
  - Full blood count (FBC), LFTs (including ALT and/or AST and albumin), U&Es and creatinine
  - Screen for Hep B surface antigen, Hep B core antibody, Hep C IgG and HIV (and VZV if no history of chicken pox, shingles or varicella vaccination)
  - TPMT
  - Consider NUDT15 testing if available
  - Where applicable, check cervical screening is up to date
- During initiation and dose stabilisation: at weeks 2, 4, 8, and 12, and then every three months until the GP takes over prescribing and monitoring:
  - FBC
  - LFTs (including ALT and/or AST, and albumin)
  - Creatinine and eGFR

Ongoing monitoring (and action to be taken) during treatment to be completed by the GP:

<table>
<tr><th>Test</th><th>Frequency of monitoring*</th><th>Guidance</th><th>Action to be taken by GP</th></tr>
<tr><td>Full blood count (FBC)</td><td rowspan="3">At least every 3 months.
Following dose increases, monitor every 2 weeks until on a stable dose for 6 weeks, then at least every 3 months.
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>If WCC falls on 3 successive occasions or <3.5 x 10^9/l
If neutrophils fall on 3 successive occasions or <1.6 x 10^9/l
If platelet count falls on 3 successive occasions or <140 x 10^9/l
If MCV >105fl
(if samples are being analysed by Derriford Hospital lab, MCV >108fl)</td><td rowspan="2">If any 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 >30% of baseline
and/or
eGFR <60ml/min/1.73m^2</td></tr>
<tr><td>LFTs
(ALT and/or AST, and albumin)</td><td>ALT or AST >100U/L
or
unexplained drop in serum albumin <30g/L</td><td>Look for alternative cause. Consider an early re-test/seek specialist advice.
If ALT or AST >3x ULN, stop treatment and refer to gastroenterology team</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, unexplained rash 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 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

Infections

Contact microbiology if a patient not known to be immune to chickenpox comes into contact with **shingles or chickenpox**, for advice on whether varicella-zoster immune globulin (VZIG) or other treatment is indicated.

In patients suffering from chickenpox or active skin lesions from shingles, withhold azathioprine / mercaptopurine. 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).

During a **serious infection** STOP azathioprine / mercaptopurine.

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 high-risk of infection where an individual patient plan should be made.

Patient responsibilities

- Ensure they understand the importance of monitoring treatment and attend specialist appointments and/ or GP appointments to ensure timely monitoring can be completed (in accordance with the prescribing guideline).
- Understand that treatment may be stopped if they do not attend for monitoring & treatment review.
- Ensure they have a clear understanding of the treatment, expected benefits and potential side effects.
- Take (or support administration of) medication as directed by the prescriber.
- Read the patient information leaflet regarding azathioprine / mercaptopurine.
- **MUST** report any of the following to their GP and/or specialist: mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding, unexplained rash and any unexplained illness/infection.
- Report any adverse effects to the GP and/or specialist regarding their treatment.
- Advise the GP and specialist immediately if pregnancy is suspected.
- Store their medicines safely and securely and dispose of any unused medication appropriately.

Supporting Information

Please refer to individual product SPCs for full prescribing data; these can be accessed at www.medicines.org.uk.

Dosage and administration

Refer to the current BNF and individual product SPCs

Doses are adjusted according to response; initiation and titration will be undertaken by the specialist.

Patient specific dosage guidance will be provided in writing to the GP by the specialist.

For azathioprine: The usual dose range is 2-2.5mg/kg daily.

For mercaptopurine: The usual dose range is 1-1.5mg/kg daily.

Doses reduced (usually to 25%-33% of usual) if used concomitantly with xanthine oxidase inhibitors e.g. allopurinol, febuxostat (see interactions below). Specialist to advise.

Use doses at the lower end of the range for patients with low TPMT, hepatic or renal impairment and monitor more closely.

Contraindications and precautions

Refer to the current BNF and individual product SPCs

Contraindicated in patients known to be hypersensitive to azathioprine or mercaptopurine

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, it is recommended that patients do not receive live organism vaccines until at least 3 months after the end of their treatment.

Pregnancy – see below

Patients with deficiency in the enzyme thiopurine methyltransferase (TPMT) have a higher risk of bone marrow toxicity.

Use with caution in renal or hepatic impairment – more frequent monitoring may be necessary if severe renal or hepatic disorder or high doses used (seek specialist advice).

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.

Increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (non-melanoma), sarcomas and uterine cervical cancer in situ.

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease, the SPCs indicate a potential for increased susceptibility for developing the condition with the use of **mercaptopurine**. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with mercaptopurine should be discontinued. Physicians should be attentive to symptoms of infection such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV), as these are known triggers for MAS.

Pregnancy and lactation

Refer to the current BNF and individual product SPCs

Pregnancy

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)

Seek specialist advice: Azathioprine / mercaptopurine should not be used during pregnancy without careful assessment of risks and benefit.

Adequate contraceptive precautions should be advised when either partner is receiving azathioprine or mercaptopurine (during treatment and for at least 3 months after receiving the last dose).

The UK Teratology Information Service (UKTIS) provides a national service on all aspects of the toxicity of drugs and chemicals in pregnancy (Tel: 0344 892 0909), and provides the 'best use of medicines in pregnancy' (bumps) website for supportive patient information relating to individual treatments. UKTIS information on azathioprine / mercaptopurine can be accessed here and bumps patient information leaflet here.

Lactation

Seek specialist advice: Manufacturers of mercaptopurine advise that mothers receiving mercaptopurine should not breast-feed. It is recommended that women receiving azathioprine should avoid breast-feeding unless the benefits outweigh the potential risks.

6-Mercaptopurine (the active metabolite of azathioprine) has been identified in the colostrum and breast-milk of women receiving azathioprine treatment. Available data has shown that the excreted levels in breast-milk are low. From the limited available data, the risk to newborns/infants is considered to be unlikely but cannot be excluded.

If a decision is made to breastfeed, because 6-mercaptopurine is a strong immunosuppressant, the breastfed infant should be closely monitored for signs of immunosuppression, leucopenia, thrombocytopenia, hepatotoxicity, pancreatitis or other symptoms of 6-mercaptopurine exposure.

UK Drugs in Lactation Advisory Service (UKDILAS) provides evidence-based information on the use of drugs during the breastfeeding period to all UK healthcare professionals. Further information relating to azathioprine and breastfeeding can be found here, and for mercaptopurine here

Adverse effects

This list is not exhaustive; only very common (greater than 1 in 10), common (1 in 100 to 1 in 10) and uncommon (1 in 1000 to 1 in 100) are listed below. Refer to the current BNF and individual product SPCs for further information and less frequent adverse effects. Seek specialist advice where necessary.

Frequency	Azathioprine	Mercaptopurine
Very common and common	Bone marrow depression (dose-related), leucopenia, thrombocytopenia, nausea (see additional information below), increased risk of infection, pancreatitis	Bone marrow depression (dose-related), leucopenia, thrombocytopenia, anaemia, decreased appetite, nausea (see additional information below), vomiting, diarrhoea, pancreatitis, hepatic disorders, hepatotoxicity (more common at high doses, see also interactions below)
Uncommon	Anaemia, hepatic disorders, hypersensitivity (see additional information below	Increased risk of infection, anorexia, arthralgia, fever, neutropenia, rash

The following adverse effects & additional information are also highlighted:

- Nausea is common early in the course of treatment and usually resolves after a few weeks without an alteration in dose. Moderate nausea can be managed by using divided daily doses, taking doses after food, prescribing concurrent antiemetics or temporarily reducing the dose (seek specialist advice).
- Hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and renal dysfunction) call for **immediate withdrawal**.
- Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life threatening or fatal have been reported very rarely with azathioprine treatment. If signs and symptoms suggestive of these severe skin reactions appear, **azathioprine should be withdrawn immediately**, and alternative treatment should be considered.
- Photosensitivity (refer to precautions above)
- Increased risk of malignancies (refer to precautions above)

Drug interactions

This list is not exhaustive; for additional information, and further interactions, consult the BNF and individual product SPCs. Seek specialist advice where necessary.

The following drug interactions are classified in the online version of the BNF as **severe** (the result may be a life-threatening event or have a permanent detrimental effect).

- **Allopurinol** potentially increases the risk of haematological toxicity when given with azathioprine or mercaptopurine. Manufacturer advises adjust azathioprine / mercaptopurine dose (seek specialist advice).
- **Baricitinib** is predicted to enhance the risk of immunosuppression when given with azathioprine. Manufacturer advises caution.
- **ACE inhibitors: Captopril**, **enalapril**, **fosinopril**, **imidapril**, **lisinopril**, **perindopril**, **quinapril**, **ramipril** and **trandolapril** are predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine. Manufacturers advise monitor.
- **Febuxostat** is predicted to increase the exposure to azathioprine or mercaptopurine. Manufacturer advises avoid.
- **Filgotinib** is predicted to increase the risk of immunosuppression when given with azathioprine. Manufacturer advises avoid.
- **Vaccines: Bacillus Calmette-Guérin (BCG) vaccine**, **herpes zoster vaccine (live)**, **influenza vaccine (live)**, **measles, mumps and rubella vaccine (live)**, **rotavirus vaccine**, **typhoid vaccine (oral)**, **varicella-zoster vaccine** and **yellow fever vaccine** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with azathioprine (high-dose) or mercaptopurine (high dose). UKHSA advises avoid (refer to Green Book)

The following drug interactions are classified in the online version of the BNF as **moderate** (the result could cause considerable distress or partially incapacitate a patient; they are unlikely to be life-threatening or result in long-term effects):

- Azathioprine and mercaptopurine decrease the anticoagulant effect of **acenocoumarol** and **warfarin**. Manufacturers advise monitor INR.
- Myelosuppression: There is an increased risk of myelosuppression when azathioprine or mercaptopurine are given with other medicines that may cause myelosuppression. The list of potentially interacting medicines is extensive, please refer to the BNF (here: AZA / 6-MP) for specifics.
- Hepatotoxicity: There is an increased risk of hepatotoxicity when mercaptopurine is given with **alcohol** and other medicines that can cause hepatotoxicity. The list of potentially interacting medicines is extensive, please refer to the BNF (here) for specifics

In addition, the SPCs note the following:

- Co-administration of **ribavirin** and azathioprine / mercaptopurine is not advised. Ribavirin may reduce efficacy and increase toxicity of azathioprine
- There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between azathioprine and **co-trimoxazole** (**trimethoprim** & **sulfamethoxazole**).
- There is *in vitro* and *in vivo* evidence that aminosalicylate derivatives (e.g. **olsalazine**, **mesalazine** or **sulfasalazine**) inhibit the TPMT enzyme. Lower doses of mercaptopurine may be needed.

Support

Contact details - North and East Devon:		
Consultants:		
Dr T. Ahmad	01392 406220	tariq.ahmad1@nhs.net
Dr T. Daneshmend	01392 402803	tawfique.daneshmend@nhs.net
Dr S. Prasad	01392 402818	shyamprasad@nhs.net
Dr N. Kennedy	01392 402783	nick.kennedy1@nhs.net
Dr J. Goodhand	01392 408456	james.goodhand@nhs.net
Dr C. Calvert	01392 406217	ccalvert@nhs.net
Dr O. Roy	01392 402818	ovi.roy@nhs.net
Dr J. Digby-Bell	01392 408407	j.digby-bell@nhs.net
Dr T. Shirazi	01392 408407	tarek.shirazi@nhs.net
Dr A Davis	01271 322447	andrew.davis3@nhs.net
IBD nurse specialists:		
Royal Devon & Exeter NHS Foundation Trust	01392 402728	rde-tr.IBDhelpline@nhs.net
Northern Devon Healthcare NHS Trust	01271 314005	ndht.ibdnurse@nhs.net
Contact details - West Devon:		
IBD nurse specialists:	01752 439224	plh-tr.ibd-advice@nhs.net
Consultants:		
Dr N. Bosanko	01752 433173	
Dr S. Cochrane	01752 431861	
Dr S. P. Dunlop	01752 430131	
Dr C. Suarez	01752 431860	
Dr M. Fung	01752 431865	
Dr C. M. Hayward	01752 431861	
Dr S. J. Lewis	01752 431863	
Dr K. Klimova	01752 433173	
Dr J. Gulliver	01752 430134	
Dr C. Spyridou	01752 431864	
Contact details - South Devon and Torbay:		
IBD nurse specialists (first port of call):	01803 655111	Ibdtorbay.sdhct@nhs.net
Support is also available via **advice and guidance** directed to the consultant responsible for patient, or		
access via Torbay Hospital switchboard to the gastroenterologist of the day (available 7 days per week)	0300 456 8000 or 01803 614567	

Date ratified: April 2022 (MHRA DSU added June 2025)

Shared Care Agreement Letter - Consultant Request

To:	**Dr:**
	Practice Address:
	Patient Name:
NHS Number:	
Date of birth:	
Address:	

Diagnosed condition: ……

I recommend treatment with the following drug: ……

At the following dosage: ……..……

I request your agreement to continue the care of this patient according to the Specialised Medicines Service Guidelines for this drug. The patient has been initiated on treatment and stabilised in accordance with the appropriate Specialised Medicines Service Guidelines.

The results of any relevant baseline tests and any additional supportive information (target range, date of last blood test etc.) are included below:

Principles:
GPs are invited to participate, but **if the GP is not confident to undertake these roles then they are under no obligation to do so.** If so, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If asked to prescribe this drug the GP should reply to this request as soon as practical. Continuing the care assumes communication between the specialist, GP and patient; the intention should be explained to the patient and accepted by them.

Remember: the clinician who prescribes the medication has the clinical and legal responsibility for the drug and the consequences of its use.

Signed:			**Date:**
Consultant name:			
Telephone number:		**Fax number**	
Email address			

Please sign below and return promptly. Remember to keep a copy of this letter for the patient's records. If this letter is not returned sharing of the care for this patient will not commence.

GP Response

I agree / do not agree* to share the care of this patient in accordance with the Specialised Medicines Guideline.

Signed: …….. Date: …….

GP name: …… *Delete as appropriate.

Patient agreement

I understand and agree to my responsibilities as described above.

Signed: …….. Date: …….

Name: