Northern Lincolnshire
Area Prescribing Committee

# Shared Care Guideline for the Treatment of Inflammatory Bowel Disease with Azathioprine or 6-Mercaptopurine in Adult Patients

**Patient Details** *(Attached patient label if appropriate)*
Patient Name: _____ NHS No: _____
Patient Address: _____ DOB: _____
_____
_____
_____

GP Name*: _____ Specialist Name: _____
GP Signature: _____ Specialist Signature: _____
Specialist Contact No: _____

*If the GP is unwilling to accept prescribing responsibility for this patient, the Secondary Care Specialist must be informed within one week of receipt of this document and letter from Secondary Care Specialist.

Points of Contact:
Cara Crisp, Inflammatory Bowel Disease Clinical Nurse Specialist; c.crisp@nhs.net ; 03033 303527 or Andrew Karvot, Northern Lincolnshire Interface Pharmacist; a.karvot@nhs.net 03033 302646

Gastroenterology Secretaries: 03033 306016

Produced by: Joy Ekpeh (Pharmacist), Dr P Mysore (consultant Gastroenterologist), Dr S Sarwar, Dr S K Roy, Sr Walduck (IBD Nurse), Dr Sami-ul Ahmad Gondal ( GP),
Approved by: Northern Lincolnshire Area Prescribing Committee
Approval Date: 10 February 2022 Review Date: 10 February 2025

# Shared Care Guideline for the Treatment of Inflammatory Bowel Disease with Azathioprine or 6-Mercaptopurine in Adult Patients


1. Introduction
2. Indication
3. Patient Inclusion and Exclusion Criteria
4. Form, Dose and Route of Administration
5. Contraindications
6. Interactions
7. Side Effect Profile
8. Clinician Responsibilities for Assessment, Prescribing and Monitoring for Primary and Secondary Care
9. Monitoring
10. Patient Information
11. Resources and Guidance
12. References


## 1. Introduction

This guideline aims to provide a framework for the prescribing of azathioprine or 6-mercaptopurine by GPs for patients with inflammatory bowel disease and to set out the associated responsibilities of GPs and hospital specialists who enter into the shared care arrangements.

This document should be read in conjunction with the guidance “Responsibility for prescribing between Primary & Secondary/Tertiary Care” https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf

The initiating clinician is responsible for ensuring that the patient receives relevant counselling, including warnings, potential side effects and interactions prior to initiating treatment. All baseline checks must be done by the specialist, prior to requesting shared care. Continued monitoring e.g. blood tests and ECGs remain the responsibility of the initiating clinician. A management plan for the duration of treatment must be created at the point of initiation, which the patient must be aware of and agree to.

The SCG should only be signed once maintenance phase is attained.

If the GP is unwilling to accept prescribing responsibility for the patient, under the SCG, the Secondary Care Specialist should be informed within **two weeks** of receipt of the Consultant’s letter. In such cases the GP must inform the Consultant of all relevant medical information regarding the patient and any changes to the patient’s medication, irrespective of the indication.

## 2. Indication

The indication that this SCG covers is:

Steroid dependant / resistant inflammatory bowel disease (Crohn’s disease, ulcerative colitis, microscopic colitis). This is an unlicensed indication.

## 3. Patient Inclusion and Exclusion Criteria

Inclusion

The patient will be diagnosed by a specialist, as suffering from inflammatory bowel disease (IBD), as outlined above.

Exclusion

Do not prescribe to patients with severe hepatic or renal impairment. Exclude patients with creatinine clearance of less than 30mL/minute.

Patients will not be pregnant or breast feeding when being treated as part of this Shared Care Guideline. (Treatment with azathioprine should not generally be initiated during pregnancy, but it may be reasonable to continue during pregnancy).

Patients over the age of 65 years are excluded from this Shared Care Guideline.

Patients with porphyria (acute or cutaneous) are excluded from this Shared Care Guideline.

Patients being prescribed warfarin are excluded from this Shared Care Guideline.

## 4. Form, Dose and Route of Administration

These medicines will be given in tablet form.

A blood sample to screen for thiopurine S-methyltransferase (TPMT) deficiency will be taken by the specialist, prior to commencing treatment.

- **Azathioprine** dosage: Usually 2mg/kg/day in a single dose; dosage range may vary from 1.5 to 2.5mg/kg/day in a single dose. The initial prescription is usually half of the target dose if the patient's TPMT level is unknown (typical initial dosage regimen: 50-100mg daily).

- **6-Mercaptopurine** dosage: A conversion factor of approximately 0.5 can be used when equating azathioprine doses to 6-mercaptopurine. i.e. usually 0.5 to 1.5 mg/kg/day in a single daily dose. The initial prescription is half the target dose if the TPMT is level unknown.

Treatment is usually continued subject to adequate response. Specialists will promptly provide advice to GPs on duration of treatment and any dose changes for each individual patient.

## 5. Contraindications

Not to be used in patients with hypersensitivity to azathioprine or 6-mercaptopurine.

Azathioprine is contraindicated in patients with severe hepatic impairment; severely impaired bone marrow function; severe infections; pancreatitis.

Use *with caution*, in mild to moderate hepatic and / or renal impairment and in the elderly. Avoid in porphyria.

There must be no contemporaneous use of live vaccines.

## 6. Interactions

**Allopurinol** significantly inhibits the metabolism of azathioprine; if it is co-prescribed the dose of azathioprine must be reduced by 75% (use one quarter of the original dose). Patients who are taking allopurinol are not excluded from this guideline. However, caution must be used in these patients and shared care arrangements made only when they are fully stabilised.

**Co-trimoxazole** or **trimethoprim**: there is an increased risk of haematological toxicity and therefore these must not be used whilst a patient is taking azathioprine.

The effects of **warfarin** may be potentially reduced and patients who are taking warfarin are excluded from this guideline.

**Febuxostat** – avoid concomitant use.

Patients taking aminosalicylates (e.g. **sulfasalazine** or **mesalazine**) have a theoretical risk of leukopenia.

Increased risk of side effects with **ACE inhibitors**, aminosalicylate derivatives, **cimetidine**, **indometacin** and other drugs with myelosuppressant properties – use with caution and monitor closely.

### Pregnancy and breast-feeding

Treatment with azathioprine should not generally be initiated during pregnancy, but it may be reasonable to continue during pregnancy.

**All patients wanting to become pregnant who are taking either azathioprine or mercaptopurine should discuss this with their specialist.**

Azathioprine has been reported to interfere with the effectiveness of intrauterine contraceptive devices. Therefore, it is recommended to use other or additional contraceptive measures.

**Breast-feeding:** present in milk in low concentration; no evidence of harm in small studies. BNF recommends use if potential benefit outweighs risk – this should be discussed with the patient.

**Further information on use in pregnancy and breastfeeding can be found at https://bnf.nice.org.uk/**or **https://www.medicines.org.uk.**

## 7. Side Effect Profile

**Patients with thiopurine methyl transferase (TPMT) deficiency may be more susceptible to delayed haematotoxicity including bone marrow toxicity.**

Hypersensitivity reactions: general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, myalgia, arthralgia, renal dysfunction and hypotension.

Mucocutaneous: urticaria, erythematous pruritus, oral ulceration, alopecia (rarely: erythema nodosum)

Haematological: Dose dependant, general reversible bone marrow suppression, usually seen as leukopenia, anaemia, thrombocytopenia, increases in MCV and haemoglobin content of red blood cells, megaloblastic anaemia, euthyroid hypoplasia.

Gastrointestinal: nausea (may be relieved by administering after food), vomiting, loss of appetite, diarrhoea, colitis.

Hepatic: deranged liver function tests, cholestatic hepatitis

Musculoskeletal: myalgia, arthralgia

Other: rare (but potentially serious) side effects include pancreatitis (reversible) pneumonitis, cardiac dysrhythmias, interstitial nephritis, opportunistic infections, alopecia.

Infection risk: opportunistic infections can occur, out with the context of leukopenia/neutropenia. These can require early and vigorous treatment; azathioprine 6-mercaptopurine may need to be stopped until the infection has cleared. Live vaccines are contra-indicated; vaccination against influenza is recommended.

## 8. Clinician Responsibilities for Assessment, Prescribing and Monitoring for Primary and Secondary Care

| Stage of Treatment | Hospital Specialist | General Practitioner |
|---|---|---|
| Pre-Initiation | TPMT, Hep B & C, HIV, EBV and HVZ serology may be done in advance if time permits, If not at initiation of treatment. | |
| Initiation | Initial supply via hospital for patient<br><br>Assess patient following referral from GP<br><br>Recommend appropriate treatment to the GP<br><br>Carry out baseline U&Es, LFTs and FBCs<br><br>FBC, LFT and U+E weekly for at least 8 weeks then fortnightly for 1 month. The patient must be stable for a total of 12 weeks before maintenance phase has started. | Maintain prescribing on FP10 after a period of stabilisation. |

# Shared Care Guideline for the Treatment of Inflammatory Bowel Disease with Azathioprine or 6-Mercaptopurine in Adult Patients

| Stage of Treatment | Hospital Specialist | General Practitioner |
|---|---|---|
| Maintenance | Assess clinical response to treatment<br><br>Provide adequate advice and support to GPs<br><br>Inform GP of dose amendments as appropriate | Prescribe suggested medication.<br><br>Monitor patients for adverse effects.<br><br>Ensure patient has bloods checked 3 monthly (FBC, U+E and FBC)– Patients are counselled at initiation by the hospital and informed if non - compliance with blood monitoring drug may be withdrawn. General practitioner may refer back to the consultant if any concerns around maintenance blood result abnormalities or patient compliance concerns.<br><br>Prescribe of medication under guidance of consultant<br>Check before prescribing medication that the monitoring is up to date and that results are within the normal range.<br><br>The GP should be aware that the drug can cause bone marrow suppression, leukopenia, increased risk of malignancy - lymphomas and skin cancer.<br><br>Patients should be asked about the presence of sore throat, abnormal bruising or bleeding at each visit.<br>Check for development of lymphomas and other malignancies particularly of the skin.<br><br>**When the patient has an intercurrent illness a FBC, U&E and LFTs should be done and any abnormal results including those noted above should be reported to the consultant.** |

# Shared Care Guideline for the Treatment of Inflammatory Bowel Disease with Azathioprine or 6-Mercaptopurine in Adult Patients

## 9. Monitoring

**Disease monitoring:**

Clinical response to therapy.

**Drug monitoring:**

Baseline

FBC, BCP (for renal function & LFTs) and TPMT assay.

On-going

FBC & LFT should be checked once weekly for at least 4 weeks then fortnightly for 2 months. If stable, the monitoring may be reduced to monthly. Once the dose, disease and blood monitoring are stable, the frequency of monitoring may be reduced to 3 monthly on advice of the specialist.

If doses are changed, then monitoring should be done as if the drug has been newly started.

| **Monitoring parameter** | **Recommended response** |
|---|---|
| WBC<br>3.0-3.5 x $10^9$/L<br>< 3.0 x $10^9$/L | Recheck FBC. Inform consultant within 72 hours.<br>Stop drug and refer back to consultant within 24 hours. |
| Neutrophils<br>1.5-2.0 x $10^9$/L<br><1.5 x $10^9$/L | Recheck FBC. Inform consultant within 72 hours.<br><br>Stop drug and refer back to consultant within 24 hours. |
| Platelets <100 x $10^9$/L | Stop drug and refer back to consultant within 24 hours |
| **ALT**> twice normal limit<br>(or if baseline ALT is abnormal, twice baseline level increase). | Recheck if not settling within two weeks or if worsening, refer back to consultant (initial temporary increase is normal) |
| **Alk Phos**>200 i.u./L | Stop drug and refer back to consultant within 24 hours |
| MCV<br>> 100 fl<br><br>> 105 fl | Check **serum folate** and **B12 & TSH**. and alcohol consumption.<br><br>Notify consultant within 72 hours. |
| Creatinine:<br>Increase above normal range, or above baseline in patients with renal impairment. | Stop drug and refer back to consultant within 24 hours. |
| Rash or oral ulceration. | Withhold **until discussed** with specialist team, within 24 hours. |
| Abnormal bruising or **severe** sore throat or throat ulceration. | Withhold **until FBC results** available & discuss with the specialist team within 24 hours. |
| Pregnancy. | Continue but refer to gastroenterologist within 72 hours. |

Refer back to the Consultant using the GI secretaries' number on the first page of this document.

Details of contraindications, cautions, drug interactions and adverse effects listed above are not exhaustive. For further information always check with BNF https://bnf.nice.org.uk/ or SPC (www.medicines.org.uk).

**10. Patient Information**

Patients should be informed about the benefits and risks of treatment and the need for monitoring.

Patients should report, immediately, any fever, rash, bruising, bleeding, sore throat, oral ulceration, jaundice, infection or new abdominal pain.

In the event of any serious concerns, abnormalities or symptoms not specified above, please contact the Gastroenterology Department.

Specific contact details for whom to contact within 24 hours if necessary: –

| | |
|---|---|
| **Scunthorpe**<br><br>IBD Advice Line<br><br>SAT 15<br>Outside of normal working hours (9am – 5pm) please contact Med Reg oncall for advice if needed. | **03033 306636 –** This is an automated voicemail service, calls are aimed to be returned within 24-48hrs, if URGENT advice needed contact SAT 15 who will be able to access an available nurse specialist/consultant. |
| **Grimsby**<br><br>Outside of normal working hours (9am – 5pm) please contact Med Reg oncall for advice if needed. | **03033 304543**<br><br>**IBD helpline.** |

**11. Resources and Guidance**

http://www.medicinescomplete.com/#/search/all/Azathioprine?offset=0

https://www.medicines.org.uk/emc/medicine/24688/SPC

https://www.medicines.org.uk/emc/product/3301/smpc

## 12. References

1. Muller, Dr A.F. (2012). Disease Modifying Drugs in Inflammatory Bowel Disease (IBD). *Inflammatory Bowel Disease Committee of the British Society of Gastroenterology (BSG)*.

2. National Institute for Clinical Excellence (NICE); *Crohn's disease, Management in adults, children and young people.*London: NG129, published May 2019.