# SHARED CARE PRESCRIBING GUIDELINE AZATHIOPRINE OR MERCAPTOPURINE for the treatment of Inflammatory Bowel Disease in ADULTS

## NOTES to General Practitioner

The information in the shared care guideline has been developed in consultation with CCGs in South East London and it has been agreed that it is suitable for shared care.

This document should provide sufficient information to enable you to make an informed decision regarding the clinical and legal responsibility for prescribing Azathioprine and Mercaptopurine (AZA/MP) for the treatment of Inflammatory Bowel Disease (IBD).

**AZA/MP should be regarded as identical** for the purposes of monitoring, adverse effects and drug interactions. AZA is metabolised to MP and then further to active and toxic metabolites. Gastrointestinal intolerance (nausea) is higher with AZA than MP and the latter may be used if a patient is unable to tolerate AZA due to this side effect (approx. 1 in 5 patients)

The questions below will help you confirm this:

- Is the patient's condition predictable or stable?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care prescribing guideline?
- Have you been provided with relevant clinical details including monitoring data?

**If you can answer YES to all these questions** (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility.

**If the answer is NO to any of these questions** you should contact the requesting consultant or your local CCG Medicines Management Team. There may be implications for the patient where the invitation to share care is declined. For example, the patient may need to be changed to an alternative treatment regimen. It would not normally be expected that shared care prescribing would be declined on the basis of cost.

Sharing of care assumes communication between the specialist, general practitioner (GP) and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. **It is important that patients are consulted about treatment and are in agreement with it**.

Prescribing should follow requirements in the South East London Interface Prescribing Policy.
**The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use. The patient's best interests are always paramount.**

**Note:** This shared care guideline was originally developed in 2013 and has been reviewed.

**Once you have read the shared care guideline and considered the information above, please complete the GP decision form on the next page and email back to the requesting clinician if you are in agreement to participate in shared care. If you are not in agreement, please include reasons for this.**

# GP DECISION FORM

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of Azathioprine and Mercaptopurine (AZA/MP) for Inflammatory Bowel Disease (IBD) can be shared between the specialist and general practitioner (GP). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is 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 practicable.

**AGREEMENT TO PARTICIPATE IN SHARED CARE**
**Azathioprine or Mercaptopurine for the treatment of Inflammatory Bowel Disease**

| | |
|---|---|
| **Consultant/Specialist Nurse Name:** | **Patient name:** |
| **Consultant/Specialist Nurse signature:** | **Patient Hospital Number:**<br><br>**Patient NHS Number:** |
| **Date completed:** | **Patient Agreement:**<br><br>Patient agrees to shared care ☐ |
| **Hospital requesting shared care:** | Patient does not agree to shared care ☐ |

This is to confirm that the above patient has been started on the following for inflammatory bowel disease:
Azathioprine ☐ **OR** Mercaptopurine ☐ (gastroenterology team to tick)

**GP Name:**

**This is to confirm that I agree to participate in shared care for ……. for the treatment of Inflammatory Bowel Disease for this patient as outlined in this shared care document.**

**GP Signature:**

**Date signed:**

**ACTION**

**1. HOSPITAL** **Tick to confirm**

- Explain shared care to patient and obtain agreement Date agreement obtained: _____ ☐
- Indicate requesting hospital ☐
- Complete and sign agreement ☐
- Email full shared care guideline (including signed agreement to GP) ☐
- Place original in patient's notes ☐

**2. GP PRACTICE**

- If **in agreement** to participate in shared care, sign and email (via secure NHS.net) back **within 2 weeks** of receipt **of request from specialist** to:
  - The appropriate IBD Team (see full contact details on page 8 of the document)
- If **you do not agree** to participate in shared care, contact consultant and local Primary Care CCG Medicines Management Team within 2 weeks of receipt to discuss. If after discussion it is agreed not to undertake shared care for this patient, both the consultant and the local Primary Care CCG Medicines Management team should be informed.
- Once decision reached file a copy in the Patient's medical notes.

# Azathioprine or Mercaptopurine for treatment of Inflammatory Bowel Disease in ADULTS

## CIRCUMSTANCES WHEN SHARED CARE IS APPROPRIATE

- Prescribing responsibility will only be transferred when the consultant and the GP are in agreement that the patient's condition is stable or predictable.
- The hospital will provide the patient with three months' supply of therapy

## 2. AREAS OF RESPONSIBILITY

### Consultant / Specialist Nurse responsibilities

- Ensuring patient fits criteria for use of this drug (e.g. no contraindications, cautions, fits local agreement for use of the drug)
- Baseline monitoring tests (see monitoring for full list). TPMT* must be checked before prescribing.
- To initiate, stabilise and supply treatment over the first **three months**.
- To inform patients of indication, therapeutic aims, adverse effects, monitoring requirements and special precautions.Patients should also be made aware of the need to limit exposure to sunlight (due to an increased risk of skin cancer) and use adequate sun protection measures. This risk is greater in patients who have a history of previous treatment with PUVA.
- Patients should be counselled on adverse effects and to report signs of bone marrow suppression.
- To inform patients of practical issues related to the use of Azathioprine and Mercaptopurine such as administration, storage and maximum dose – see "Information provided to patient" section on page 7.
- If patients have been prescribed allopurinol in combination with azathioprine or mercaptopurine they should be counselled appropriately on the nature of the interaction, the subsequent dose reduction in thiopurine and other possible adverse effects of allopurinol e.g. using: Crohn's and Colitis UK PIL
- At the time of initiating, notify GP in writing that Azathioprine or Mercaptopurine has been prescribed. The GP should be invited to share care once the patient is stable. Information provided to the GP should include:
  - A copy of the shared care guidelines
  - That a prescription for the first three months' supply has been given
  - Information on when the patient will next be reviewed and by whom.
  - A request that the GP continue prescribing after three months
- Any continuous monitoring that will remain under the consultant's responsibility
- To review patient at the request of GP should any problems arise (side-effects / lack of efficacy) within two weeks or as when appropriate as determined after discussion with the IBD Team..
- To communicate promptly (within two weeks) with the GP if treatment is changed.
- To report any suspected adverse effects to the MHRA: http://www.yellowcard.gov.uk

***TPMT** is an enzyme involved in the metabolism of AZA/MP to active and toxic metabolites. Its activity is controlled by genetic polymorphism and dictates what dose of AZA/MP is recommended by the hospital team.*

### General Practitioner responsibilities

- To consider shared care proposal within 2 weeks of receipt. If agreed to request to continue prescribing as detailed in shared care guideline. Confirmation to the requesting consultant is required **within 2 weeks** of receipt of this guideline by completing and returning the agreement on page 2
- If you do not agree to shared care, discuss with requesting consultant or local primary care medicines management team within 2 weeks of receipt of shared care request
- To provide ongoing prescriptions for Azathioprine or Mercaptopurine (with or without allopurinol), after three months. To adjust the dose as advised by the specialist.
- To agree monitoring requirements with specialist (IBD team) – see page 5 of this document for GP monitoring requirements.
- To advise/remind patients to report symptoms of bone marrow suppression, such as bruising, bleeding or severe sore throat/oral ulceration, immediately.
- To report and seek advice regarding any concerns, for example: side-effects, co-morbidities, pregnancy, or lack of efficacy to the specialist team
- Patients should be made aware of the need to limit exposure to sunlight (due to an increased risk of skin cancer) and use adequate sun protection measures. This risk is greater in patients who have a history of previous treatment with PUVA
- To advise the specialist if non-compliance is suspected
- To ensure compatibility with other concomitant medication
- To refer back to specialist if the patient's condition deteriorates
- To stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.
- To report any suspected adverse effects to the MHRA via the Yellow Card scheme:: http://www.yellowcard.gov.uk

## Patient's / Carer's responsibilities

- To contact the specialist (IBD Team) or GP if he or she does not have a clear understanding of any aspect of the treatment.
- To inform prescribing specialist, GP and other healthcare professionals of any other medication being taken, including over the counter products, alternative therapies or recreational drugs.
- To inform community pharmacists that they are using Azathioprine or Mercaptopurine before purchasing medication over-the-counter
- To attend all hospital and GP appointments including requests for blood test monitoring
- To take medicines as agreed and take steps to ensure that no doses are missed and not to share medicines with others
- To read the patient information leaflet included with the medication.
- To report any adverse effects or warning symptoms to GP or hospital specialist
- To report to GP and IBD/Gastro team if pregnant or breastfeeding.
- To inform GP and hospital of any changes in addresses or telephone contact numbers.

## 3. CLINICAL INFORMATION

**NOTE:** The information here is not exhaustive. Please also consult the current Summary of Product Characteristics (SPC) for **Azathioprine and Mercaptopurine** prior to prescribing for up to date prescribing information, including detailed information on adverse effects, drug interactions, cautions and contraindications (available via www.medicines.org.uk)

## Indication(s)

Inflammatory bowel disease (IBD) comprises Crohn's disease (CD) and ulcerative colitis (UC). Both are chronic, relapsing and remitting conditions that require anti-inflammatory or immunosuppressant medication. The inclusion of IBD within licensed indications varies within AZA branded (e.g. *Imuran*) and generic SPCs. All forms of MP used in IBD are off-label. These agents will be prescribed generically. In practice, all forms are indicated and their use is ratified by NICE guidance.

## Place in Therapy

NICE guidelines (CG152 and CG166), the British Society of Gastroenterology and European Crohn's and Colitis organisation recommends that AZA or MP be considered for patients who:

- require more than one full course of corticosteroids, to treat a flare of IBD, in any given 12 month period. A full course is regarded as 8 weeks of prednisolone starting at 40mg and reducing (once symptoms are controlled) by 5mg per week to zero
- suffer a disease relapse as the dose of corticosteroid (usually prednisolone) is reduced, or within six weeks of stopping
- require secondary prophylaxis after surgery for Crohn's (secondary care)

## Dose & route of administration

Dose may be altered according to the TPMT level.

- The usual dose of **AZA is 2.0 – 2.5 mg/kg/day** and **MP 1.0 – 1.5 mg/kg/day** (rarely above this level), given by mouth.
- TPMT low (carrier status): Start with 50% of normal dosage and monitor

TPMT absent: AZA/MP not to be used (see above), or by checking blood levels of AZA/MP metabolites (in secondary care).

Note: Dose reduction of the thiopurine to approximately 25% of the usual target dose is required to avoid dose-related toxicity when prescribed in combination with allopurinol.

## Duration of treatment

Long term

## Criteria for stopping treatment

Review by hospital specialist team

**Adverse Effects**

- Rash or oral ulceration: withhold AZA/MP until discussed with IBD specialist team
- Abnormal bruising or SEVERE sore throat: withhold AZA/MP until FBC results and discuss with specialist team
- Decreased resistance to infection: stop AZA/MP if patient systemically unwell with significant infection

## Monitoring Requirements including frequency

**Consultant:**

**IBD Team:**
FBC, U&E's, e-GFR, LFT's CRP will be checked at weeks 2, 4, 8 & 12 on initiation. , if stable – patients will be appropriate for shared care

**GP:**

FBC, U&E's, e-GFR , LFT's & CRP. should be checked **every 3 months**

- To report any concerns about side-effects (possible allergic reactions, excessive somnolence, dizziness), co-morbidities (seizures, severe cardiovascular disease, mental illness), pregnancy, overuse or lack of efficacy to the IBD specialist team (IBD nurse or consultant)
- Report any suspected adverse effects to the MHRA: http://www.yellowcard.gov.uk

## Management of blood test results

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| **Total white cell count <3.5**<br>**Neutrophil count 1.0-2.0** | Recheck FBC in one week. If stable, repeat in one month, and then return to 3-monthlymonitoring as usual. If falls further, stop medication and inform IBD Specialist Team |
| **Platelet count <100**<br>**Total white cell count <2.5**<br>**Neutrophil count <1.0** | Stop medication immediately and inform IBD Specialist Team |
| ***AST > 3x upper limit of normal*** | Reduce dose by half, inform IBD Specialist Team immediately |
| ***Derangement of lesser magnitude or of any other liver enzymes*** | Do not stop or change dose, recheck LFTs in one week<br>Contact IBD Specialist Team IBD for further advice with repeat result |
| ***Fall in eGFR of ≥30% from baseline*** | Inform IBD Specialist Team immediately for further advi |
| ***Sore throat with visible ulceration*** | Stop medication, check FBC<br>Inform IBD Specialist Team |
| ***Fever, vomiting or diarrhoea*** | Consider stopping medication<br>Discuss with IBD Specialist Team |
| ***Severe upper abdominal pain*** | Stop medication<br>Check LFTs (hepatitis) and amylase (pancreatitis).<br>Inform Gastroenterologist immediately |

**A rapid fall or consistent downward trend in any value should prompt caution and extra vigilance**

## Follow up arrangements

**Consultant**: Planned yearly follow-up with information provided from monitoring in GP practice. Urgent review in IBD clinic on request of GP or patient

**GP**: Monitor symptoms and requirement for steroids over the preceding 3 months. Faecal calprotectin is useful both as a diagnostic and monitoring tool to objectively assess disease activity and can be requested from primary care. This information should be provided to the patient or their hospital consultant for yearly review.

## Practical issues including other relevant advice/information

*Reminder: this list is not exhaustive - for full details of adverse effects and all potential drug interactions refer to latest Summary of Product Characteristics (SPC) for the drug, available via www.medicines.org.uk.*

**Use of allopurinol in combination with azathioprine or mercaptopurine:**

- Some patients may be prescribed allopurinol in combination with azathioprine or mercaptopurine due to hypermethylation of thiopurine (MeMP: TGN ratio >11:1), abnormal LFTs secondary to standard thiopurine treatment or other non-myelotoxic side-effects (excluding pancreatitis) on standard thiopurines, which limit dose optimisation.
- One in five people have high levels of enzymes that convert azathioprine and mercaptopurine to metabolites that can lead to side effects. Allopurinol can correct this imbalance, allowing a slightly larger number of people to tolerate thiopurines.
- Where this is the case, the dose of azathioprine or mercaptopurine in these circumstances will be **one quarter of normal dose to avoid dose related toxicity** – initiated by Gastroenterologist ONLY.
- The dose of allopurinol in these cases is 100mg daily.

**Important drug interactions (identical for both agents)**
Please also refer to SPC for full list: www.emc.medicines.org.uk

- Co-trimoxazole / trimethoprim - increases risk of haematological toxicity
- Warfarin – AZA and MP reduce anticoagulant effect
- Clozapine – increased risk of agranulocytosis
- Phenytoin – possible reduced absorption of phenytoin
- Digoxin – reduced absorption of digoxin
- ACE inhibitors - increased risk of leucopenia
- 5-ASA (mesalazine) – possibly increased risk of nephrotoxicity
- Febuxostat – avoid co-administration
- Allopurinol – enhanced effects and toxicity of allopurinol when taken together with azathioprine and mercaptopurine (**however, also see above**).

**Pregnancy and breastfeeding**
AZA/MP can be continued safely in pregnancy and breastfeeding

**Monitoring actions as part of the SCA**
Observational data suggest that most adverse reactions necessitating stopping medication will occur within the first three months of prescription (i.e. before this SCA comes into effect). However, some adverse events are idiosyncratic and a high level of vigilance must be maintained for these in all patients regardless of how long they have been on AZA/MP.

**AZA/MP should be regarded as identical** for the purposes of monitoring, adverse effects and drug interactions. AZA is metabolised to MP and then further to active and toxic metabolites. Gastrointestinal intolerance (nausea) is higher with AZA than MP and the latter may be used if a patient is unable to tolerate AZA due to this side effect (approx. 1 in 5 patients)

**Vaccinations**
Prior to starting therapy, patients receiving AZA/MP will be screened for Hepatitis B/C, HIV and for a history of chicken pox (VZV serology if available). A pregnancy test will be performed as appropriate. The following vaccination schedule should be considered for patients on AZA/MP (derived from British and American Consensus guidelines for vaccination):

- **VZV** (if not already given, serology negative and no reliable history of chicken pox, shingles) once, preferably before starting therapy
- **Influenza** (inactivated vaccine) every year
- **Pneumococcus** every 3-5 years
- **Hepatitis B** in seronegative patients
- **Human papilloma virus** vaccination is **not** required (unless within national guideline criteria), but regular cervical cancer screening is suggested by European Consensus guidelines.[6]

## Practical issues including other relevant advice/information

*Reminder: this list is not exhaustive - for full details of adverse effects and all potential drug interactions refer to latest Summary of Product Characteristics (SPC) for the drug, available via www.medicines.org.uk.*

***Live vaccines***

These include MMR, oral typhoid, yellow fever, BCG, oral polio, Varicella Zoster (VzV), cholera, flu-mist influenza (nasal spray only), adenovirus, small pox. (more information can be found at: www.ibdpassport.com/travelling-ibd/vaccinations/)

At present, the CDC (and therefore European Consensus guidelines) and SPCs recommend that **ALL live vaccines should be avoided in patients receiving AZA/MP**. If there are any queries regarding vaccination therapy please contact the IBD Team.

MMR has been given without complication in paediatric patients with rheumatoid arthritis receiving methotrexate, and those with liver transplant on tacrolimus or ciclosporin. The risk of MMR may, therefore, be overstated in the setting of AZA/MP. If appropriate, consideration should be given to administering MMR vaccination BEFORE starting AZA/MP.

Azathioprine at a dose of <3mg/kg/day and mercaptopurine at a dose of <1.5mg/kg/day are not (in absence of other immunosuppressing factors/medications) contraindications to shingles vaccine (Zostavax).

## Information provided to the patient

**Summary of Product Characteristics (SPC) for AZA and MP**

www.emc.medicines.org.uk

**Patient Information Leaflets**

https://www.crohnsandcolitis.org.uk/about-inflammatory-bowel- disease/publications/azathioprine-mercaptopurine

http://www.guysandstthomas.nhs.uk/resources/patient-information/gi/azathioprine-and-mercaptopurine-for-ibd.pdf

## Evidence Base for treatment and key references

**References**

1. British Society of Gastroenterology guidelines. www.bsg.org.uk/clinical-guidelines/ibd/index.html
2. NICE guidelines for Crohn's disease (CG152). www.nice.org.uk/CG152
3. NICE guidelies for ulcerative colitis (CG166). www.nice.org.uk/CG166
4. **Medicines Information Helpline –** 020 7188 8750 / 3849 / 3855
5. British National Formulary. www.BNF.org.uk
6. Rahier JF, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease, Journal of Crohn's and Colitis (2009)

## 4. COMMUNICATION AND SUPPORT

| **Guys & St Thomas' NHS Trust switchboard: 020 7188 7188** | |
|---|---|
| **Consultant / IBD nurse specialist team: via IBD helpline** (answer phone service only between 9am-5pm) | **IBD helpline:** 0207 188 2487 (answer phone service only between 9am-5pm) |
| **Email:** | ibdhelpline@gstt.nhs.uk |
| **Gastroenterology secretaries contact tel:** | 0207 188 2499/2492 |
| **Medicines Information Helpline contact tel:** (9am-5pm, Mon – Fri) | 0207 188 8748<br>Out of hours: via Accident and Emergency |
| **IBD helpline (Medication – interactions, availability of medicines, blood tests)** | **0900-1700:** 0207 188 2487<br>Or email ibdhelpline@gstt.nhs.uk |
| **King's College and Princess Royal Hospitals switchboard: 0203 299 9000** | |
| **Denmark Hill Consultant / IBD nurse specialist team contact tel no:** | **IBD helpline (8:30am-4:30pm)** 0203 299 1606 |
| **Email:** | kch-tr.IBDhelpline@nhs.net |
| **Denmark Hill Gastroenterology secretaries contact tel:** | 020 3299 3417<br>020 3299 5844<br>020 3299 6044 |
| **Princess Royal University Hospital (PRUH) Consultant / IBD nurse specialist team:** | **IBD helpline:** 01689 863000 Ext 63390 |
| **PRUH Gastroenterology secretaries contact tel:** | 01689 863741 |
| **Email:** | kch-tr.IBDnurse@nhs.net<br>Out of hours: via Accident and emergency |
| **Ms Alanna Johnston - Clinical Pharmacy Lead** | **Tel :** 020 3299 9000 / Ext 35704 / Bleep KH 8247 |
| **Medicines Information Helpline** | **Tel :** 020 7188 8750 / 3849 / 3855 |
| **Lewisham & Greenwich Trust switchboard: 020 8333 3000** | |
| **Queen Elizabeth Hospital Consultant / IBD nurse specialist team contact tel:** | **IBD helpline (9am-5pm):** 020 8333 3000 Ext 8167 |
| **Email:** | LG.IBD@nhs.net |
| **IBD nurse specialist nurse tel no:** | 0208 836 5546 |
| **Lewisham & Greenwich Gastroenterology secretaries contact tel:** | 0208 836 5580 |
| **Email:** | Elaine.baptiste@nhs.net OR A.mcnair@nhs.net<br>Out of hours: via Accident and emergency |
| **Medicines Information Helpline** | **Tel:** 020 7188 8750 / 3849 / 3855 |