Working in partnership

SHARED CARE PRESCRIBING GUIDELINE
For Azathioprine and Mercaptopurine Therapy in Inflammatory Bowel Disease (IBD)

NOTES to the GP

The expectation is that these guidelines should provide sufficient information to enable GPs to be confident to take clinical and legal responsibility for prescribing these drugs.

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 not accept prescribing responsibility. You should write to the consultant within 14 days, outlining your reasons for NOT prescribing. If you do not have the confidence to prescribe, we suggest you discuss this with the appropriate Milton Keynes Hospital specialist service who will be willing to provide training and support.

The patient's best interests are always paramount

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Approved by (date approved) : Milton Keynes Prescribing Advisory Group (Nov 2018)	

Original Author: Lianne Lewis - Inflammatory Bowel Disease & Research Nurse
Review Author: Quynh-Anh Nguyen - Principal Pharmacist, MKUH – Medicine
Reviewed/Edited – Christina Theophile-Clarke (inflammatory bowel disease nurse) **and**
Dr Conor Lahiff (Consultant Gastroenterology – IBD lead) – August 2018

Introduction and reason for shared care

This guideline has been developed in order to assist primary and secondary providers to monitor patients taking azathioprine or mercaptopurine for Inflammatory Bowel Disease (IBD). It was a recommendation of the 2nd National IBD Audit action plan to achieve Standard B local Care Delivery – develop shared care between hospitals and primary care, where care is delivered as locally as possible with rapid access to specialist services when needed (IBD Standards Group, 2013). This guideline seeks to establish a clear and comprehensive process to ensure a consistent standard is achieved.

It is the responsibility of General Practitioners, Gastroenterologists and IBD Specialist Nursing staff to follow the document. The professional whom prescribes the medication assumes legal clinical responsibility for the specific medication and consequences of its use.

This shared care agreement outlines suggested ways to which the responsibilities for managing the prescribing and monitoring of azathioprine and mercaptopurine with patients who have IBD can be shared between the hospital specialist team and general practitioner (GP).

Shared Care Guidelines for Azathioprine and Mercaptopurine Therapy in Inflammatory Bowel Disease (IBD)

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.
- Patients will only be referred to the GP once the GP has agreed in each individual case and the hospital will continue to provide prescriptions until successful transfer of responsibilities as outlined below.

1. Areas of Responsibility

Consultant

- The specialist will confirm the working diagnosis to the patient and/or carer as appropriate.
- Discuss treatment and monitoring with the patient, provide patient with patient information leaflet prior to commencement of therapy.
- The specialist and patient to complete patient education checklist.
- Perform baseline tests
- The specialist will provide the initial prescription for 28 days' supply. **FP10 (hospital) prescription**: Half the target dose for two weeks, then full dose for two weeks. GP to re-prescribe.
- Discuss rationale for commencement of therapy, risk v benefit approach, potential side effects including need to report untoward side effects.
- The specialist will suggest that shared care may be appropriate for the patient's condition.
- Request to GP via prescribing agreement form at the end of this document to continue treatment. Send hard copy of shared care guideline, including all completed information to GP.
- Annual review of the patient (minimum), the frequency may vary dependant on individual need.

IBD Nurse

- Educate on medication pre commencement to ensure informed decision regarding commencement of azathioprine or mercaptopurine is established.
- Potential calls via the telephone helpline may be in relation to side effects and can be dealt with over the telephone, a record of this information must be imported into the electronic patient record.
- All the correspondence in relation to outlining target dose, advice on frequency increase and other advice specific to azathioprine or mercaptopurine are recorded accurately.
- Adhere to suggestions as discussed in this document when giving patient advice in relation to adverse effects.
- Clarify with the patient, to ensure they are aware of the increase regime, blood monitoring and document in clinic letter when therapy commenced.
- If the patient is pregnant or planning to become, facilitate an outpatient appointment in the nurse led clinic. Advice should be to continue medication in the interim until discussed with the IBD team.
- Review blood monitoring results via telephone and advise accordingly, liaise with the IBD team as clinical need dictates.
- All patients are counselled that joint aches, nausea, and flu like symptoms may occur in the initial two weeks and will pass, it is important to determine and discuss whether the patient is able to continue taking the medication and bear the adverse symptoms.
- Support GPs, provide copy of all documents in shared care guideline, provide blood results and share information regarding patient treatment.
- Go through the patient information leaflet and patient record sheet to confirm retention of information and understanding.
- Complete and send GP invite letter
- Liaise with medicines information department as the need dictates.

GP

- Ensuring that he/she has the knowledge and information to understand the therapeutic issues in relation to the patient's clinical condition.
- Agreeing that the patient should receive shared care for the diagnosed condition unless there is a specific rationale for the patient management to remain within secondary care.
- Report to and seek advice on any aspect of the patient care that is of concern to the GP and may affect treatment.
- Ensure blood test results are checked prior to issuing a prescription for the medication.
- Prescribing the maintenance therapy in accordance with the written instructions within the GP letter, communicating any change of dosage with the patient.
- Report any adverse effects of the treatment to the specialist hospital team.
- The GP will ensure the patient is monitored as described in this protocol, and will take advise from the hospital specialist team if there are any amendments to the suggested monitoring schedule.
- Refer pregnant patients/breastfeeding or patients considering pregnancy to the hospital specialist team.
- The GP will ensure the patient is given appropriate appointments for follow up and monitoring. It is the GP's responsibility to decide to discontinue treatment in a non-compliant patient for follow up and monitoring. As a guide:
    - 1-2 weeks late - written or telephone reminder
    - 4 weeks late - telephone reminder
    - 6 weeks later - a written letter stating medication will be stopped and hospital specialist team informed.
- GPs should contact the hospital specialist team if any dose adjustments are required or if the need to discontinue the medication arises.

Patient

- To attend for regular blood tests.
- To report any side effects.
- To take their medication as agreed, unless otherwise advised by an appropriate health professional.
- Attend follow up appointments. If unable then inform health care professional to enable an alternative appointment to be scheduled.
- The patient will store medication securely.
- Read information provided by health care professional, and contact the relevant professional if they do not understand information provided.

2. COMMUNICATION AND SUPPORT

Hospital contacts: (the referral letter will indicate named consultant) **Milton Keynes University Hospital NHS Foundation Trust** Standing Way, Eaglestone, Milton Keynes, MK6 5LD Out of hours – contact Medical Registrar via switchboard	01908 660033
Dr. George MacFaul, Consultant Physician and Gastroenterologist	01908 997109
Dr. Conor Lahiff, Consultant Physician and Gastroenterologist - (IBD Lead)	01908 997060
Dr Ravi Madhotra, Consultant Physician and Gastroenterologist	01908 997103
Inflammatory Bowel Disease Nursing Team	01908 996955 Email: IBDNursingTeam@mkhospital.nhs.uk
Dr Prakash Gupta – Consultant Gastroenterologist and Hepatologist	01908 997061

Specialist support/resources available to GP including patient information:

This shared care guideline is available online at www.formularymk.nhs.uk then click on shared care guidelines.

A detailed guidance on prescribing and monitoring azathioprine and mercaptopurine in Inflammatory Bowel Disease is available on the Hospital Trust website.

Any dosage adjustments made by the hospital specialist team will be recorded in the electronic medical notes and full details sent to the GP.

Blood test results taken by the specialist hospital team will be available on the e-care system, the hospital specialist team will then send a paper copy of the blood test results to the GP in a timely manner.

GPs should contact the hospital specialist team if any dose adjustments are required or if the need to discontinue the medication arises.
The dosage regime and frequency of blood test monitoring should be clearly explained to the patient.

Further information sources:
ECCO e-guide www.e-guide.ecco-ibd.eu

3. CLINICAL INFORMATION

Indication(s):	**Azathioprine:** Maintenance therapy in steroid-dependent and steroid-refractory patients with Crohn's Disease and Ulcerative Colitis **Mercaptopurine (unlicensed indication):** Maintenance therapy in steroid-dependent and steroid-refractory patients with Crohn's Disease and Ulcerative Colitis

Place in Therapy:	Azathioprine or Mercaptopurine will be used following 2 or more steroid courses in 12 months; steroid-dependent patients; and those with severe disease especially with adverse prognostic factors. They are also used to enhance anti-TNF therapy, by reducing immunogenicity of biologic agents.
Therapeutic summary:	Azathioprine and Mercaptopurine are immune-modulators utilized to avoid prolonged steroid use by maintaining patients in remission.
Dose & route of administration:	Azathioprine PO 2-2.5mg/kg/day or Mercaptopurine PO 1-1.5 mg/kg/day. Doses should be reduced in renal impairment. GFR ml/min>50: no dose adjustment GFR ml/min 10-50: reduce dose by 25% GFR ml/min <10: reduce dose by 50%
Duration of treatment:	Consider stopping azathioprine and mercaptopurine after 4 years if patient is in remission. **Therapy will be stopped by the consultant specialist following review.** **Stopping therapy** Caution in withdrawal as may result in worsening of disease. Withdrawal should be a gradual process. Some patients will remain in long term remission. Remission can be reinduced by reinitiating thiopurines in most of those who, having previously responded, relapse.
Preparations available	Azathioprine comes as 25mg and 50mg tablets Mercaptopurine comes as 50mg tablets.

Summary of adverse effects: (See summary of product characteristics (SPC) for full list http://www.medicines.org.uk/emc/

Adverse effect (frequency)	**Management**
WBC (unknown)	<3.5X10^9/l Contact the hospital specialist team.
Neutropenia (unknown)	If the neutrophils <2 x 10^9/L contact the hospital specialist. If neutrophils <1.5 x 10^9/L, stop medication and contact hospital specialist.
Platelets (very common)	If <150 x 10^9/L contact hospital specialist.
Lymphocytes (very common)	<0.5 x 10^9/L contact hospital specialist.
Varicella (Unknown)	If in contact with the virus, non-immune patients require two weeks of oral Aciclovir 800mg 5 times daily and inform hospital specialist. Stop Azathioprine until lesions crusted over and Aciclovir completed.
Nausea, vomiting (common) **Diarrhoea** (Unknown)	Advice to take medication at night. If persists, identify and ensure that the patient is taking their tablets with food. Advise patient to divide dosage and take with food. If no improvement, reduce dosage and contact hospital specialist if reducing dose ineffective.
Abnormal bruising /bleeding/ fever/severe sore throat (very common)	Stop Azathioprine until recovery and check FBC and LFTs. Do not restart Azathioprine if blood tests abnormal – discuss with hospital specialist team.

Significant reduction in renal function (unknown)	Any abnormality, attempt to identify alternative cause. Repeat bloods and contact hospital specialist. If grossly abnormal (twice the normal range) Withhold and contact hospital specialist immediately for advice.
Flu like illness/ general aches and pains/general malaise (rare)	This could possibly part of a hypersensitivity reaction. Discuss with the gastroenterology specialist team.
Severe or persistent infection (Unknown)	Stop medication, take FBC, CRP and contact hospital specialist. Do not restart until results of FBC known (until it can be shown that there is no neutropenia).
MCV>105 fl (uncommon)	Check TSH, B12, Folate Start appropriate supplementation. Alert IBD Team
Rash or **Oral Ulceration** (Rare)	If rash is a significant new rash, stop treatment until resolved and check FBC. If FBC abnormal, contact hospital specialist. Wait until rash resolved and consider restarting at reducing dose provided no blood dyscrasias.
Liver impairment – Cholestatic Jaundice (common) Abnormal LFTs, ALT > x2 ULN (unknown)	Any abnormality, attempt to identify alternative cause. Repeat bloods and contact hospital specialist. If grossly abnormal (twice the normal range) ALP>250IU/L; ALT>100IU/L Withhold and contact hospital specialist immediately for advice.
Hair loss (rare)	Mild - consider dose reduction on advice of hospital specialist team. Severe - stop medication and discuss with hospital specialist team.
Severe abdominal pain (unknown)	Consider pancreatitis, obtain amylase and contact hospital specialist team.
Macrocytosis (unknown)	This typically does not signify a medical concern. Check serum folate and B12 & TSH. Treat any underlying abnormality. If results are within normal parameters discuss with hospital specialist team.
Hypersensitivity reactions- including dizziness, malaise, vomiting, diarrhoea, malaise, fever, rigors, myalgia, arthralgia, rash, hypotension.	Many respond to taking drug twice daily, dose reduction, or switching to alternative thiopurine.
Increased non-melanoma skin cancer. (unknown)	Advise patients to avoid excess exposure and use high-factor sunscreen.
Pancreatitis (rare)	Tends to occur within the first two months of use. Discontinue drug and do not re-challenge as pancreatitis often recurs

Many respond to taking drug twice daily, dose reduction, or switching to alternative thiopurine.

Other adverse effects:

- Increased risk of opportunistic infections
- Hepatotoxicity (hepatic necrosis, biliary stasis)
- Rarely gastrointestinal ulceration
- Interstitial nephritis, pneumonitis, hepatic veno-occlusive disease, lymphoma, red cell aplasia
- Increased risk of skin cancer
- Other malignancy
- Bone marrow suppression- leucopenia, anaemia, thrombocytopenia is common, and may be associated with improved drug efficacy.
- Severe leucopenia (neutrophil < 1x109/L or lymphocytes < 0.5x109/L) is associated with adverse outcomes (infection). Stop drug; consider lower dose and rechallenge once blood parameters have normalised.

Note: Hepatic toxicity can be abrogated taking 25% of the daily dose together with 100mg of allopurinol, which requires frequent blood monitoring (similar to those newly commenced on thiopurines +/- thiopurine metabolite monitoring); or switching to alternate thiopurine. This should be done at specialist level.

Switch to Mercaptopurine with intolerance / severe adverse effects to Azathioprine, unless these are severe pancreatitis or severe leucopenia.

The British National Formulary should be consulted to review adverse drug reactions and drug interactions.

Adverse effects and advised action to be taken:
Careful consideration has been given prior to initiation of therapy and the potential benefits are thought to outweigh any potential adverse effect.

In addition to absolute values for haematological indices a rapid fall or consistent downward trend in any values should prompt caution and extra vigilance. Any increase in LFTs should also be carefully monitored.

Monitoring Requirements by specialist:	FBC, U&Es, LFTs, varicella status and thiopurine methyltransferase (TPMT) assay prior to starting azathioprine or mercaptopurine.
Monitoring Requirements by GP:	Careful monitoring is essential during treatment, as this is a potentially toxic immunosuppressive drug. See table below for regimen

Time period of treatment	***Frequency of monitoring***	***Tests to be done***				
		FBC	*LFTs*	*Amylase*	*CRP*	*U&Es*
0-8 weeks	*2 Weekly*	✓	✓	*If symptomatic*	✓	✓
8 weeks-3months	*Monthly*	✓	✓		✓	✓
>3 months and stable dose for 6 weeks	*Every 3 months*	✓	✓		✓	✓
Any dose change	*2 weeks post dose change then monthly*	✓	✓		✓	✓

Situations where increased frequency of blood monitoring may be required:

- Downward trend in WBC or neutrophil count
- Renal impairment (dose should be adjusted accordingly)
- Following a dose change
- Mild to moderate hepatic impairment
- Concomitant drug therapy
- Increased frequency of blood monitoring should be effectively communicated.

Clinically relevant drug interactions:	**Allopurinol** - should be avoided where possible. If co-prescribed with azathioprine, the dose of azathioprine should be reduced to one quarter of the original dose. Due to the severity of interaction, GPs should contact the specialist hospital team for advice before commencing a patient on Allopurinol. **Aminosalicylate derivates (eg olsalazine, mesalazine, sulfasalazine)** - can increase the bioavailability of mercaptopurine, this would make the patients more susceptible to the toxic side effects and caution is advised by the manufacturers. **Co-trimoxazole/Trimethoprim** - close monitoring of FBC is required, as it increases the risk of haematological toxicity. **Warfarin** - the dose of Warfarin may require adjustment when initiating or discontinuing treatment with Thiopurine, as the anticoagulant effect of Warfarin and other derivatives may be possibly reduced. **Phenytoin, sodium valproate, carbamazepine** - the dose of these may require adjustment when initiating or discontinuing treatment with Thiopurine, as the absorption of may be reduced. **Febuxostat** - concomitant use should be avoided. **Ribavirin** - the mylosuppressive effects of Thiopurine are possibly heightened. **Clozapine** - concomitant use should be avoided, as there may be an increased risk of agranulocytosis (mercaptopurine). Close monitoring of FBC is required with concomitant use: • Allopurinol • Aminosalicylates • Indomethacin (contra-indicated in patients with inflammatory bowel disease) • Cytotoxic/myloesuppressive agents • ACE inhibitors • Cimetidine For more detailed information please refer to the BNF.
Clinically relevant Precautions and Contraindications: *See SPC for full details*	**Live vaccines** are contraindicated during and up to 3 months after treatment. If possible, vaccinate non-immune patients prior to immuno-suppressive treatment dependent on the results of the examinations. This will be performed by the specialist. **Pregnancy and lactation** Thiopurines are considered safe to use in pregnancy, following discussion as to their risk / benefit. Low dose excretion occurs into breast milk for four hours following ingestion; therefore consider advising expressing and wasting milk during this time period. **Surgery** Thiopurines do not increase the risk of peri- or post-operative complications. **Other contraindications** Ensure recent cervical screen performed – Cervical neoplasia is a contra- indication to thiopurine use.
Practical issues:	If the tablet needs to be halved, the tablet is required to be handled in accordance and guidance for handling cytotoxic agents and the patient should be advised accordingly.
Supply of ancillary equipment	N/A

Key references:	• Summary of Product Characteristics http://www.medicines.org.uk/emc/ • IBD Standards Group, 2013 update. Quality Care - Service standards for the healthcare of people who have Inflammatory Bowel Disease (IBD). Available online: http://www.bsg.org.uk/attachments/160_IBDstandards.pdf

Appendix 1: Letter to GP

Milton Keynes University Hospital NHS
NHS Foundation Trust

Department of Gastroenterology
Inflammatory Bowel Disease

Dr Conor Lahiff
Dr R Madhotra
Dr G MacFaul
Dr P Gupta

Date:

Surname:
Forename:
DOB:
Hospital No:
Or affix patient label

Diagnosis:
TPMT level:
Patient weight:

Re: Azathioprine or Mercaptopurine Monitoring

Dear Dr.

The above patient was seen in the Gastroenterology clinic today and treatment with **Azathioprine ☐ Mercaptopurine ☐** has been initiated. I am writing to invite you to participate in the shared care management of this patient. Please refer to the shared care guideline enclosed; you can also access an electronic copy at:
http://www.formularymk.nhs.uk/Shared-Care-Guidelines/

We have provided 4 weeks supply of …….. At the end of this period the patient's dose will be ……..
The risks and benefits of treatment have been discussed with the patient and counselling given regarding the importance of compliance with the blood monitoring programme during treatment. Treatment will be discontinued if not compliant with monitoring after 28 days.
We would be grateful if you can continue the prescribing with usual precautions. Clinical response can usually be expected by 6-12 weeks. The target doses are Azathioprine PO 2-2.5mg/kg/day or Mercaptopurine PO 1-1.5mg/kg/day.

We are grateful for your help in monitoring this patient. Thank you for your help in advance.

Yours sincerely

Print name ……..…; Designation: ……..……

Contact details:
Should you have any further questions or need advice, consult the specific health professional using the contact numbers below:

Inflammatory Bowel Disease Nursing team
Telephone: 01908 996955, Monday – Friday
Email: IBDNursingTeam@mkhospital.nhs.uk

Dr Conor Lahiff MD FRCP, Consultant Physician/ Gastroenterologist
Telephone/ facsimile: 01908 243867 (Secretary)
Dr Ravi Madhotra MD FRCP, Consultant Physician/ Gastroenterologist
Telephone / facsimile: 01908 243751 (Secretary)
Dr George MacFaul MD FRCP, Consultant Physician/ Gastroenterologist
Telephone / facsimile: 01908 243308 (Secretary)
Dr Prakash Gupta MD FRCP, Consultant Gastroenterologist/Hepatologist
Telephone / facsimile: 01908 243867 (Secretary)

NOTE: Secretary hours of working 8.00am to 4.00pm

To be completed by the GP and returned to the hospital consultant above
Please sign and return your agreement to shared care within 14 days of receiving this request (tick which applies)
☐ I accept sharing care as per shared care prescribing guideline and above instructions
☐ I would like further information. Please contact me on:……
☐ I am not willing to undertake shared care for this patient for the following reason:
……

GP name: ……..……

GP signature: ……Date: ……/……../……