NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT FRAMEWORK

Shared care guidelines for use of Azathioprine in Ulcerative Colitis & Crohn's Disease (within adult services)	
Monitoring level	**Amber Level 2 - Prescribe drug and perform intense level of monitoring, e.g. 3-monthly review**

Generic and Proprietary/Brand Name

Azathioprine (Imuran®, generics are also available)

Indications for shared care

Management of Ulcerative Colitis and Crohn's Disease

Summary of Specialist Prescribing and Monitoring Responsibilities	Summary of GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities

• To assess suitability of patient for treatment. Assess for contraindications, cautions and interactions.
• Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and provide the appropriate counselling to enable the patient to reach an informed decision. Obtain and document patient consent.
• Initiate treatment with Azathioprine and supply patient with necessary treatment information / appropriate patient information leaflet.
• Perform baseline investigations and initial monitoring, see specialist monitoring below.
• Specialist should prescribe until the patient has been **stable** on the dose for a period of **6 weeks**.
• Specialist should ensure they prescribe a sufficient quantity of medication to enable transfer to primary care.
• Send a letter to the patient's GP requesting shared care is agreed for the patient. The letter should contain the following information:
  ○ Diagnosis
  ○ Results of baseline and most recent blood tests
  ○ Results of other appropriate investigations
  ○ Dose and name of treatment
  ○ Confirm monitoring schedule and when next monitoring is required.
• Include contact information.
• Ensure clear arrangements for GP back up advice and support.
• All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.
	• Respond to the request from the specialist for shared care.
	• Prescribe ongoing treatment with Azathioprine as requested by specialist.
	• Perform ongoing monitoring, see GP monitoring below.
	• Assess for possible interactions with azathioprine when starting new medicines.
	• Manage any adverse effects as detailed and discuss with specialist team when required.
	
	GP monitoring
	Following the initial fortnightly blood tests requested by the specialist, the patient requires 3-monthly FBC and LFTs.
	
	The exact frequency of monitoring to be communicated by the specialist in all cases.
	Monitor for toxicity throughout treatment. Please see the table below in main body of document for further guidance on what to do if there are abnormalities with the blood tests, or if the patient reports an adverse event.

Contact for the TAG: jennifer.carroll@nhs.net

Specialist monitoring:

- Measure thiopurine methyl transferase (TPMT) level before initiation of Azathioprine.

- FBCs, LFTs should be done fortnightly for the first 8 weeks of treatment after which 3 monthly blood tests are carried out by the GP (see below).
- Blood tests are also needed 2 weeks after each dose increase.
- U+Es should be checked every 6 months or more frequently if there is any reason to suspect deteriorating renal function.

It may be more convenient for the patient to have the fortnightly blood tests carried out at the GP surgery.

The specialist will retain responsibility for monitoring the patient's response to treatment.

Patient Information

The film-coated tablets should be swallowed whole. Azathioprine is cytotoxic. It is recommended that azathioprine tablets are handled following local recommendations for the handling and disposal of cytotoxic agents. Please see the manufacturer's Patient Information Leaflet for further information.

Specialist Contact Details

JPUH: via Tel 01493 452 452
Consultants: Dr Aman Afridi (Clinical Lead), Dr Badreldin, Dr Banim, Dr Saleem

IBD Specialist Nurses: Trevor Hughes, Donna Barber

NNUH: via Tel 01603 286286
Consultants: Dr Anups de Silva, Dr Mark Tremelling Dr Richard Tighe, Dr Crawford Jamieson, Dr Simon Chan, Dr Ian Beales, Dr Leo Alexandre, Dr Andrew Douds, Dr Alvin Ochieng, Prof. Alastair Watson

IBD Specialist Nurses: Heather Simpson, Joan Murchie, Lyndsey Thorpe, Racheal Higgins

QEH: via switchboard Tel: 01553 613613. For Gastro Department Tel: 01553 214642. For Direct Dial Tel: 01553 61**** (ext number)

Consultants: Dr Khalid Yousif (extension 3939) Dr Shailesh Karanth (extension 3708) Dr Abhay Bagewadi (extension 3989) Dr Alan Wiles (extension 3004)

IBD Specialist Nurses: Jose Dias & Inah Cledera (extension 4642)

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, 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 practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment
An immunosuppressive agent that is metabolised to mercaptopurine. Azathioprine is used as a disease-modifying agent to induce and maintain remission in ulcerative colitis and Crohn's disease.
Licensed use and agreed local off-label use
Licensed indications vary with brand. See relevant summary of product characteristics (SPC) for full details. Azathioprine is used as an immunosuppressant anti-metabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and procedures which influence the immune response. Azathioprine is indicated for the treatment of moderate to severe inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis) in patients in whom corticosteroid therapy is required, in patients who cannot tolerate corticosteroid therapy, or in patients whose disease is refractory to other standard first line therapy. Azathioprine, in combination with corticosteroids and/or other immunosuppressive agents and procedures, is indicated to enhance the survival of organ transplants, such as renal transplants, cardiac transplants, and hepatic transplants; and to reduce the corticosteroid requirements of renal transplant recipients. Azathioprine, either alone or more usually in combination with corticosteroids and/or other drugs and procedures, has been used with clinical benefit (which may include reduction of dosage or discontinuation of corticosteroids) in a proportion of patients suffering from the following: • severe rheumatoid arthritis; • systemic lupus erythematosus; • dermatomyositis and polymyositis; • auto-immune chronic active hepatitis; • pemphigus vulgaris; • polyarteritis nodosa; • auto-immune haemolytic anaemia; • chronic refractory idiopathic thrombocytopenic purpura. Please note this shared care only covers the prescribing of Azathioprine for the treatment of Ulcerative Colitis & Crohn's Disease.
Criteria for Patient Selection
The main role for azathioprine is steroid sparing. It is considered for patients who require two or more corticosteroid courses within a calendar year; those whose disease relapses as the dose of steroid is reduced below 15 mg; relapse within 6 weeks of stopping steroids; or postoperative prophylaxis of complex (fistulating or extensive) Crohn's disease.
Form and strength of preparation
Film-coated tablets available as 25mg & 50mg
Side Effects – Refer to the SPC for full information
General side-effects:

- Common or very common - Bone marrow depression (dose-related); increased risk of infection; leucopenia; pancreatitis; thrombocytopenia
- Uncommon - Anaemia; hepatic disorders; hypersensitivity
- Rare or very rare - Agranulocytosis; alopecia; bone marrow disorders; diarrhoea; gastrointestinal disorders; neoplasms; photosensitivity reaction; pneumonitis; severe cutaneous adverse reactions (SCARs)
- Frequency not known - Nodular regenerative hyperplasia; sinusoidal obstruction syndrome.

Specific side-effects:

- Frequency not known - Nausea.

Further information:

- Side-effects may require drug withdrawal.
- **Hypersensitivity reactions** - Hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and renal dysfunction) call for immediate withdrawal.
- **Neutropenia and thrombocytopenia** - Neutropenia is dose-dependent. Management of neutropenia and thrombocytopenia requires careful monitoring and dose adjustment.
- **Nausea** - Nausea is common early during 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.

Drug Interactions - Refer to the SPC for full information

The following have potentially serious interaction with azathioprine and caution must be used when prescribing concurrently. Seek specialist advice before prescribing:

- Ribavirin; sulfamethoxazole (as co-trimoxazole); trimethoprim; warfarin or acenocoumarol (anticoagulant effect may be inhibited).
- Avoid concomitant use of azathioprine or mercaptopurine with: allopurinol (unless supervised by a specialist); clozapine; penicillamine.
- Aminosalicylate derivatives: Lower doses of azathioprine may need to be considered when administered concomitantly with olsalazine, mesalazine or sulfasalazine.
- Febuxostat is predicted to increase the exposure to Azathioprine. Manufacturer advises avoid.
- Filgotinib is predicted to increase the risk of immunosuppression when given with Azathioprine. Manufacturer advises avoid.
- Baricitinib is predicted to enhance the risk of immunosuppression when given with Azathioprine. Manufacturer advises caution.

The following drugs may be prescribed with caution:

- ACE inhibitors - increase the risk of anaemia and or leukopenia.
- Cimetidine and indomethacin - concomitant administration of thiopurines may increase the risk of myelosuppression.

Cautions and Contraindications - Refer to the SPC for full information

Cautions:

Reduce dose in elderly; reduced thiopurine methyltransferase activity.

Pregnancy: Azathioprine should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risk versus benefit.

Hepatic impairment: Manufacturer advises caution (impaired metabolism)—monitor liver function and complete blood count more frequently in those with severe impairment. Reduce dose if hepatic or haematological toxicity occurs.

Renal insufficiency: Caution (may result in slower elimination)—monitor complete blood count more frequently in those with severe impairment. Reduce dose for those patients with moderate to severe renal impairment (GFR<10ml/minute; serum creatinine >300micromol/litre)

Live vaccines: In general patients should avoid “live” vaccines such as influenza live vaccine, oral polio, MMR, BCG, shingles live vaccine, chicken pox live vaccine, typhoid oral vaccine, and yellow fever vaccine. See Immunisation Against Infectious Disease (Green Book). Contact the specialist if further guidance is required. Avoid contact with people who have active chickenpox or shingles.

Contra-indications:

Hypersensitivity to azathioprine / mercaptopurine

Absent or very low Thiopurine methyltransferase (TPMT) activity- risk of life-threatening pancytopenia

Initiation of therapy

Consultant Gastroenterologist

Initial dose and method of administration and supply

2mg to 2.5mg per kg daily by mouth.

The film-coated tablets should be swallowed whole where possible. Azathioprine is cytotoxic. It is recommended that azathioprine tablets are handled following local recommendations for the handling and disposal of cytotoxic agents. Please see the manufacturer's Patient Information Leaflet for further information

Maintenance Dose and Administration

The initial maintenance dose must be prescribed by the initiating specialist.
Due to the relatively slow onset of action, benefits may not be observed for 3 months.

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

On going treatment

Initial monitoring / baseline assessment – by Specialist

Thiopurine methyl transferase (TPMT) level assessed by initiating specialist, FBC, U+Es, LFTs.

The specialist will retain responsibility for monitoring the patient's response to treatment.

Specialist monitoring responsibilities

- FBCs, LFTs should be done fortnightly for the first 8 weeks of treatment after which 3 monthly blood tests are carried out by the GP (see below). Blood tests are also needed 2 weeks after each dose increase. U+Es should be checked every 6 months or more frequently if there is any reason to suspect deteriorating renal function. **It may be more convenient for the patient to have the fortnightly blood tests carried out at the GP surgery.**
- To send a letter to GP requesting shared care for a particular patient. The letter should contain the following information:
    - Diagnosis
    - Results of blood tests
    - Results of other appropriate investigations
    - Dose and name of treatment
    - Advice on dose alterations where appropriate
- To periodically review the patient

GP / Community Team or other Primary Care monitoring responsibilities

Following the initial fortnightly blood tests requested by the specialist, the patient requires 3-monthly FBC and LFTs. If there are abnormalities on these tests, or if the patient reports one of the adverse events below, these are recommendations for considering the withdrawal of azathioprine therapy.

The exact frequency of monitoring to be communicated by the specialist in all cases.

Monitor for toxicity throughout treatment. Please see the table below for further guidance. If there are abnormalities with the blood tests, or if the patient reports one of the adverse events below, these are recommendations for considering the withdrawal of azathioprine therapy:

Test/symptom	Result	Action
WBC	<4 x 10^9 per litre	Withhold drug and discuss with specialist
Neutrophils	<2 x 10^9 per litre	
Platelets	<150 x 10^9 per litre	
AST, ALT or Alk. Phos.	> 2-fold rise	
Rash or oral ulceration		
MCV	>105fL	Investigate and if B12 or folate low, start appropriate supplementation
Abnormal bruising, bleeding or sore throat, infection, fever, chills		Urgent FBC. Withhold until FBC result is available
Upper abdominal or back pain		Urgent amylase. Withhold until amylase result is available

Consultant / Specialist prescribing responsibilities

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• Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and provide the appropriate counselling to enable the patient to reach an informed decision. Obtain and document patient consent.
• Initiate treatment with Azathioprine and supply patient with necessary treatment information / appropriate patient information leaflet.
• Perform baseline investigations and initial monitoring, see specialist monitoring above.
• Specialist should prescribe until the patient has been **stable** on the dose for a period of **6 weeks**.
• Specialist should ensure they prescribe a sufficient quantity of medication to enable transfer to primary care.
• Send a letter to the patient's GP requesting shared care is agreed for the patient. The letter should contain the following information:
  ○ Diagnosis
  ○ Results of baseline and most recent blood tests
  ○ Results of other appropriate investigations
  ○ Dose and name of treatment
  ○ Advice on dose alterations where appropriate
• Confirm monitoring schedule and when next monitoring is required.
• Include contact information.
• Ensure clear arrangements for GP back up advice and support.
• All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.

GP prescribing responsibilities
• Respond to the request from the specialist for shared care. • Prescribe ongoing treatment with Azathioprine as requested by specialist. • Perform ongoing monitoring, see GP monitoring above • Assess for possible interactions with azathioprine or mercaptopurine when starting new medicines. • Manage any adverse effects as detailed and discuss with specialist team when required.
Indications for referral back to Specialist
See above under GP monitoring responsibilities.
Further information and supporting documents
Guidelines for management of inflammatory bowel disease in adults, Mowat et al, Gut 2011.

Author(s) and Organisation	Dr Anupama de Silva, Consultant Gastroenterologist, Norfolk and Norwich University Hospital
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Document history:

Version	Date	Author / Editor	Status	Comment
1	Sept 2007	Dr Anupama de Silva, Consultant Gastroenterology, David Todd Chief Pharmacist, JPUH / Fiona Marshall TAG Support Pharmacist	Superseded	Due for review Sept 2009
2	Sept 2009	Dr Anupama de Silva, Consultant Gastroenterology, David Todd Chief Pharmacist, JPUH / Fiona Marshall TAG Lead Pharmacist	Superseded	GP monitoring of FBC and LFTs revised to 3-monthly and 2-weekly after each dose change
3	Sept 2012	Dr Anupama de Silva, Consultant Gastroenterology, David Todd Chief Pharmacist, JPUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Changes to JPUH / NNUH consultant contacts. Approved by the TAG on 6th September 2012.
4	March 2013	Edited by Fiona Marshall TAG Lead Pharmacist	Superseded	QEH specialists' contacts added. Formatting corrected regarding hyphenation and superscripted numbers in units of measurement of blood tests. MCV units corrected to "fL". Footer updated.
5.1	July 2014	Dr Anupama de Silva, Consultant Gastroenterology, JPUH / Fiona Marshall TAG Lead Pharmacist	Draft	For review by author and consultation with local specialists.
5.2	Aug 2014	Dr Anupama de Silva, Consultant Gastroenterology, JPUH / Fiona Marshall TAG Lead Pharmacist	Draft	Amendments by Dr de Silva – update of key reference (2011) and JPUH specialist contacts. Text on the general principles of shared care added to the top of the document.

5.3	Sept 2014	Dr Anupama de Silva, Consultant Gastroenterology, JPUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Recommendation by the TAG to include shingles (varicella zoster vaccine) to the list of live vaccines that patients on azathioprine should avoid. Link to “Green Book” added.
5.4	Sept 2014	Dr Anupama de Silva, Consultant Gastroenterology, JPUH / Fiona Marshall TAG Lead Pharmacist	Superseded	v5.3 found to have incorrect names and contacts for NNUH – amended with details for NNUH IBD nurses, and consultants. Specialist nurse JPUH also added. Hyperlink to key reference inserted.
6.0 – 6.1	March – April 2017	Dr Anupama de Silva, Consultant Gastroenterology, JPUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Updated in line with current SPC – hyperlinks added to SPC and manufacturer’s PIL. Advice regarding handling tablets added under dosage and administration, and Patient Information. Additions to Side–effects and Drug Interactions made in line with SPC. For review by author and possible consideration by the TAG in May 2017.
6.2	May 2017	As for 6.0	Superseded	Supported by the TAG
7.0	Aug 2021	Jen Carroll, TAG Lead Technician	Superseded	Discussed at August 2021 TAG meeting. Review dates extended for a year from meeting due to covid pressures
7.1	Oct 2021	Jen Carroll, TAG Lead Technician	Superseded	QEH contact details updated on page 4, as per email request 18/10/2021
7.2	September 2023	Natalie Cunningham, Medicines Optimisation Pharmacist	Current	Reformatted as per the new ICS template for Shared Care Agreements. Specialist prescribing and monitoring responsibilities expanded and made clearer. Addition of ‘Specialist should prescribe until the patient has been stable on the dose for a period of 6 weeks.’ as per TAG guidance May 2016. Initial and ongoing monitoring changed to reflect national PGD, includes initial 2 weekly check and ongoing monitoring of U&E’s. GP prescribing and monitoring responsibilities expanded and made clearer also. Side effects updated as per current online BNF entry for Azathioprine. Contact information updated.
Dec 2023	7.3	Jen Carroll, TAG Lead Technician, NWICB	Final	Monitoring updated as per comments received at November TAG meeting