

Shared care guidelines for azathioprine in adults

General principles

This agreement outlines suggested ways in which the responsibilities for managing the prescribing of the drug treatment and clinical indication listed in the table below can be shared between the Specialist and General Practitioner (GP). The Specialist(s) is responsible for initiating treatment, prescribing the drug and monitoring of therapy until such a time as when the patient is deemed to be stable. If GPs are 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.

If a Specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the Specialist, the GP and the patient. The intention to undertake shared 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. Patients on Azathioprine are under regular follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

Indications

Azathioprine is an immunosuppressant antimetabolite used either alone or in combination with other agents (usually corticosteroids). It is commonly used as disease modifying drug or steroid sparing drug. It is used in many conditions, some of which are not mentioned in the product literature. This guideline covers its use in the following areas:

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 Ulcerative colitis and Crohn's disease (unlicensed)
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Azathioprine is converted in the body to mercaptopurine. This is an anti-metabolite interfering with nucleic acid synthesis. It is metabolised by the enzyme thiopurine methyltransferase (TPMT). Patients with intermediate or low TPMT activity and are at greater risk of adverse drug reactions on standard doses and are at risk of suffering life-threatening complications even when treated with low doses of azathioprine. TPMT activity should be measured before a patient is prescribed azathioprine.

Presentation/Dose/Administration

Oral: 25mg and 50mg tablets

Taken with or after food and the dose can be divided if preferred.

- Starting dose from 1mg to 3 mg/kg/day, and should be adjusted within these limits depending upon clinical response. The maintenance dose may range from <1mg/kg/day to 3mg/kg/day.

Responsibility for monitoring azathioprine

There is no evidence that regular monitoring of FBC prevents myelotoxicity. It is important that patients are counselled to report symptoms of infection promptly, which should be reinforced in writing. However, FBC should be monitored at least every 3 months in stable patients.

See table below for detailed monitoring information.

MONITORING	RESPONSIBILITY	CONDITIONS	TESTS
Pre-treatment	Hospital team	All	FBC, U&Es, LFTs, TPMT Results to be known before drug is commenced
Initiation to stabilisation	Hospital team	All	FBC, LFTs Weekly for the first 8 weeks of therapy, or more frequently if high dose or if patient has severe renal or hepatic impairment.
Ongoing	GP	All	FBC, LFTs every 1 to 3 months according to specialist advice U&E's 6 monthly

Criteria for managing events & symptoms occurring during azathioprine therapy in primary care

LABORATORY EVENTS	VALUES	ACTION
MCV	> 110 fl	Check B12 and folate – supplementation may be required if low. Also check TSH. If these are all normal, seek Specialist advice.
WBC	< 3.5 x 10 ⁹ /L	Withhold and seek Specialist advice, repeat FBC in 1 or 2 weeks.
Neutrophils	< 2.0 x 10 ⁹ /L	
Platelets	< 150 x 10 ⁹ /L or bleeding	
Significant deterioration in renal function	Creatinine >30% of baseline.	Seek Specialist advice. Caution: dose reduction advised in renal impairment
Elevation in liver enzymes (or falling albumin)	>2 fold rise in AST, ALT or Alk Phos (from upper limit of reference range).	Withhold and seek Specialist advice.
Serial decrease in WBC and/or platelets within normal range	E.g. 6.0→5.0→4.5 over 3 occasions	

SYMPTOMS	MANAGEMENT
Rash, oral ulceration, stomatitis.	Stop azathioprine , repeat FBC immediately and discuss with Specialist.
Cough, dyspnoea, infection, fever, rigors.	
Abnormal bruising or bleeding or severe or persistent sore throat.	
Abdominal pain suggestive of pancreatitis, jaundice.	
Nausea, vomiting and diarrhoea.	Withdrawal of drug may be necessary if persistent or severe.
Pneumonitis.	Rare, but stop and discuss with Specialist.
Hair loss	Rare - discuss with Specialist

Key adverse drug reactions (ADRs)

- Bone marrow suppression (leucopenia, thrombocytopenia).
- Hepatotoxicity (hepatic necrosis, biliary stasis).
- Anorexia, nausea, vomiting.
- Oral ulceration, rarely gastrointestinal ulceration.
- Hypersensitivity reactions (fever, rigors, rash).
- Pancreatitis (rare).
- Alopecia.

NB: Patients should be advised to report any mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding and any unexpected illness or infection and should be seen URGENTLY for a full blood count, liver function tests, urea and electrolytes.

This document only lists the key important ADRs-For comprehensive information on adverse drug reactions, cautions, contra-indications and interactions, please refer to the current British National Formulary and Summary of Product Characteristics.

Contraindications & precautions

Contraindications

- Hypersensitivity to azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any of the Excipients (see SPC).
- Pregnancy: Azathioprine should not be given to patients who are pregnant or who are likely to become pregnant, unless the benefits outweigh the risks after discussion with clinical team. In this situation, prescribing responsibility resides with the Specialist. Adequate contraceptive precautions should be advised when either partner is receiving azathioprine.
- Breastfeeding: Not recommended.

Precautions

- Inherited thiopurine methyltransferase deficiency (TPMT) - these patients are at an increased risk of bone marrow toxicity. Dose reduction and more regular monitoring of FBCs may be required in accordance with Specialist advice.

- Malignancies: patients receiving immunosuppressive regimens involving combination of drugs, including azathioprine, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. **Patients should be advised to wear protective clothing and use sunscreen with a high protection factor (ie SPF 50).**
- Patients with renal/hepatic impairment (see above).
- Extreme caution in blood disorders.
- Vaccinations: live vaccines should be **AVOIDED** (i.e. oral polio, MMR, BCG, yellow fever and oral typhoid). Passive immunization should be carried out using Varicella zoster immunoglobulin (VZIG) in non-immune patients exposed to active chickenpox or shingles. **Pneumococcal and annual flu vaccination is recommended.**
- Lesch-Nyhan Syndrome.

Drug interactions

- Allopurinol: Reduce azathioprine dose to one-quarter (25%) of original dose.
- Febuxostat: use is not recommended in patients concomitantly treated with azathioprine
- Co-trimoxazole/trimethoprim: increased risk of haematological toxicity.
- Warfarin: anticoagulant effect possibly reduced.
- Clozapine: increased risk of agranulocytosis.
- ACE inhibitors: co-prescription of azathioprine may cause anaemia. If significant, consider alternative to ACE inhibitor or different DMARD.
- Aminosalicylates i.e mesalazine, olsalazine, balsalazide or sulfasalazine: may contribute to bone marrow toxicity.
- Methotrexate: when azathioprine is administered with high dose methotrexate, dose of azathioprine may require adjustment to maintain suitable white blood count (in accordance with Specialist advice)

See [BNF](#) and manufacturer's SPC [Home - electronic Medicines Compendium \(eMC\)](#) for up-to-date advice.

Consultant /Specialist responsibilities

- Identify those patients who will benefit from treatment with azathioprine.
- Undertake pre-treatment monitoring of FBC, U&Es, LFTs and TPMT phenotype
- Ensure that the patient/carer is an informed recipient in therapy, provide necessary education on their treatment regimen and any monitoring or follow up that is required, and issue local patient information leaflets where applicable.
- Initiate the prescribing of azathioprine and stabilise patient on a therapeutic dose of azathioprine before referral to the GP.
- Send a letter to the GP requesting a formal agreement to share care and transfer care to GP only after receipt of a completed and signed agreement from the GP.
- Ensure prior dissemination of sufficient information to patient's GP and patient/carers.
- Inform the GP that azathioprine has been commenced, the dose and future plans for dose changes in keeping with the shared care agreement.
- Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis.
- Send a letter/results notification to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
- Evaluation of any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent

action is required following tests the hospital team will inform the patient and GP as required.

- Inform GP of patients who do not attend clinic appointments.
- Counsel the patient on contraception and what to do if pregnancy occurs. Document in the notes.
- Provide access to backup advice and support facilities at all times.
- Discuss with patient re: Varicella, flu vaccine and pneumococcal vaccine status.

GP responsibilities

- Reinforce the patient’s understanding of the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the Specialist for clarification where appropriate.
- Prescribe azathioprine at the dose recommended by the hospital Specialist once the patient is stabilised on treatment and side effects have been excluded as far as possible by the hospital. Any decision to alter treatment should usually be taken by the hospital Specialist.
- Monitor blood results (FBC, LFT U&E) in line with recommendations in this document.
- Check for possible drug interactions when newly prescribing or stopping concurrent medication.
- Monitor patient’s overall health and well-being.
- Report any adverse events to the Consultant/Specialist, where appropriate.
- Report any adverse events to the CSM, where appropriate.
- Stop Azathioprine if serious adverse drug effect/reaction and contact Specialist team
- Help in monitoring the progression of disease.

CCG responsibilities

- To provide feedback to trusts via South West Essex Medicines Management Committee
- To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
- To support trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer responsibilities

- Report any adverse effects to their GP and/or Specialist.
- Ensure they have a clear understanding of their treatment.
- Report any changes in disease symptoms to GP and/or Specialist.
- Alert GP and/or Specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy.
- Take/ administer the medication as prescribed.
- Undertake any monitoring as requested by the GP and/or Specialist.

Contact details

Consultant, medical staff and nurse practitioners at the Basildon and Thurrock University Hospitals NHS Foundation Trust (BTUH) are available to give advice and can be contacted either through the main hospital switchboard or direct.

Department / Specialist	Contact Telephone Number
Hospital switchboard – ask for Specialist or On-Call Specialist (Rheumatologist/Dermatologist/Gastroenterologist) out-of-hours	01268 524900
Rheumatology	
Dermatology	
Gastroenterology	

Document Control	
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Shared Care Guidelines are also available electronically via: to insert website link after approval	
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AZATHIOPRINE PATIENT INFORMATION LEAFLET

This form will be completed by the Hospital Specialist and given to the patient once stabilised and a fax back has been received from the GP accepting the transfer of responsibility to primary care.

You have been prescribed **Azathioprine** tablets

for.....

This **treatment** will continue until stopped by your doctor

Your GP has been given all the necessary information regarding your condition and treatment.

The success and safety of your treatment also **depends on you.**

- You will have been given information, which tells you about your treatment and condition.
- Avoid excessive alcohol consumption.
- Do not take any over-the-counter medicines, herbal, complementary or alternative medicines and treatments without getting advice from your doctor.
- Avoid contact with chicken pox or shingles.
- Avoid driving and hazardous work until you have learned how azathioprine affects you, as these drugs can occasionally cause dizziness.
- Azathioprine can increase the skin’s sensitivity to

sunlight and the risk of developing some forms of skin cancer. Use sun block and wear a hat and light clothing when out in strong sunshine.

- Do **not** use sunlamps or sun beds.
- You will need to have blood tests at least every three months.
- Your GP/ Practice Nurse needs to see you everymonths

If you experience any of the following side-effects, urgently see your GP:

- Mouth ulcer, sore throat, sore mouth.
- Feeling generally unwell.
- Feeling sick, upset stomach, diarrhoea.
- Rashes – new rash or severe itching anywhere on the body.

Stop treatment and get immediate medical advice if you develop:

- An infection with fever and or chills or a severe sore throat.
- Sudden shortness of breath (breathlessness).
- The whites of your eyes or skin become yellow.
- Severe itching of the skin.

- New unexplained bleeding or bruising.
- Severe and continuing abdominal pain or diarrhoea or vomiting.
- If you think you are pregnant contact the IBD nurse or Specialist.
- If you have any concerns about your treatment contact your GP or the hospital.

The direct-dial telephone numbers for the department are.....

GP AZATHIOPRINE SHARED MONITORING AGREEMENT 1ST LETTER

Name of GP

Address

Drop code of GP.....

Dear Dr

Re: Patient's name.....

Date of birth.....

Hospital number.....

NHS number.....

I have seen this patient and believe that he/she is suitable for treatment with Azathioprine for:

.....

I have initiated the patient on **Azathioprine**mg tablets

Take..... tablets (.....mg) times per day.

I will be prescribing and monitoring this patient at our clinic until such a time that the patient is deemed stable, which is likely to be in the region of months.

I would like to seek your agreement to take over the prescribing and monitoring of this patient's treatment after this stabilisation period as per agreed shared care guideline which is enclosed for your information.

Please complete, sign and fax back the form below to stated safe haven fax.

If you decide not to accept monitoring responsibility you must ensure your drop code is written in the patients hand held monitoring book to ensure you receive the blood results to enable you to prescribe further azathioprine.

I thank you in anticipation.

Yours sincerely

Dr
(Consultant)

AZATHIOPRINE SHARED CARE GP/PRACTICE FAX BACK FORM

Patient name..... Hospital number.....

Dear GP

You will take over monitoring of the patient including responsibility for organising blood tests and other tests required in accordance with the shared care guidance (enclosed). You will be responsible for reviewing underlying disease including complications and efficacy of therapy.

PLEASE COMPLETE, SIGN AND FAX BACK TO CLINIC/HOSPITAL:

I agree to take over the prescribing and monitoring of this medication and disease.

Signed by (GP).....

Name of GP

Address

or

I am not willing to undertake shared care for this patient
because.....
.....

.....
.....
Signed by (GP).....

Name of GP

Address

Please return to

Or Faxback to:.....

References:

1. NHS ONEL and BHRuT NHS Trust Shared Care Guidelines: Mercaptopurine & Azathioprine in Inflammatory Bowel Disease. Approved September 2013, review date November 2015.
2. City & Hackney NHS AND Homerton University Hospital: Azathioprine shared care guideline. Approved January 2009. Review date January 2010.
3. BNF 70
4. Azathioprine® (Sandoz Limited) Summary of Product Characteristics accessed on Electronic Medicines Compendium (eMC). Last Updated on eMC 29-JuApril-2014. Last accessed November 12, 2016.
5. NICE Clinical Knowledge Summaries: DMARDs (<https://cks.nice.org.uk/dmards>). Last accessed November 17, 2016.