Specialised Medicines Service Guideline ~ Azathioprine for the treatment of autoimmune chronic active hepatitis (AIH) in adults (South and West Devon)

This guideline highlights significant prescribing issues. Not all prescribing information and potential adverse effects are listed. Please refer to the BNF and individual product SPCs for full prescribing data.

Specialist: Please complete letter at the end of this document and send together with the shared care guideline to the GP.

GP: Please indicate whether you wish to share patient's care by completing letter at the end of this document and return to specialist.

GPs are invited to participate. If a GP is 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.

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

Introduction and aims of treatment

Azathioprine is an immunosuppressive agent that is used to suppress the body's immune system. It is mainly used in conditions where the immune system is overactive and reacting against the body. Azathioprine may be used either alone or in combination with corticosteroids and/or other immunosuppressive medications.

This South and West Devon guideline applies to the use of oral azathioprine for the treatment of autoimmune chronic active hepatitis (AIH) in adults under the care of specialist teams at Torbay and South Devon NHS Foundation Trust or University Hospitals Plymouth NHS Trust.

Other indications are out of scope of this guideline; for shared care / Specialised Medicines Service (SMS) prescribing guidelines on the use of azathioprine for other indications, refer to the NHS Devon ~~CCG~~ website (https://onedevon.org.uk/our-work/services-and-support/medicines-and-treatments/clinical-guidance-for-prescribers/), or the Devon Formulary website (https://devonformularyguidance.nhs.uk/).

The prescribing and drug safety monitoring of azathioprine for suppression of transplant rejection remains hospital only.

Specialist responsibilities

Consultants may decide to delegate some of these tasks to members of their team; however the responsibility for ensuring the following are undertaken remains with the consultant:

- Assess the patient, establish a diagnosis and the need for treatment with Azathioprine.
- Update records with list of existing drugs from available resources and **ensure there are no drug interactions of clinical significance** with current medication.
- Discuss with the patient (and/or carer) the benefits, side effects, frequency of dosing and monitoring requirements of treatment; provide relevant supporting information in writing. Ensure the patient understands that treatment may be stopped if they do not attend for monitoring & treatment review.
- Undertake baseline assessment and ongoing monitoring as specified (see monitoring section below).
- Screen patient for Varicella Zoster, Hepatitis B and Hepatitis C before commencing treatment and refer patient to GP for vaccination when appropriate.
- Prescribe azathioprine and stabilise the patient on a therapeutic dose. **The patient will have received at least 3 months of treatment and have been stabilised on a regular dose before sharing care.**

- Prescribing and monitoring will remain in secondary care until the patient is stable and GP agrees to share care.
- Ask the GP whether they are willing to participate in shared care. Include all relevant test results (GPs may not have access to these results in primary care).
- Continue to review the patient at agreed specified intervals, (including response to treatment and need to continue therapy), sending a written summary to the GP whenever the patient is reviewed, including the current dose to be prescribed.
- Advise the GP (in writing) of any dose changes required.
- Provide the GP with relevant contact information with clear arrangements for back-up advice and support should further assistance be required.
- Provide any other advice or information for the GP if required.

General practitioner responsibilities

- Ensure a timely reply is sent to specialist in response to request for shared care.

If GP has agreed to share care:

- Ensure there are no drug interactions with existing drugs and be alert to the possibility of interactions when initiating other medications.
- Continue to prescribe azathioprine in accordance with these guidelines, and on the advice of a specialist.
- Offer Pneumovac and annual influenza vaccines (except live nasal influenza).
    - Refer to green book chapter 25 for pneumococcal vaccine / green book chapter 19 for influenza vaccine
- Offer shingles vaccination to all patients who are eligible under the national vaccination programme.
    - If treatment with azathioprine has already begun, contact specialist to discuss appropriateness of vaccination and which vaccine to use e.g. Zostavax or Shingrix (refer to green book chapter 28a for further information, including advice on immunosuppressed individuals)
- COVID vaccine is recommended as per national schedule (refer to green book chapter 14a)
- Contact microbiology to determine whether passive immunisation should be carried out in non-immune patients exposed to chickenpox or shingles, using Varicella Zoster Immunoglobulin.
- Undertake ongoing monitoring as specified below. Review and act on results or reported side-effects as described in monitoring section below.
- Respond to advice from secondary care on dose changes and frequency of monitoring.
- Stop treatment in case of a severe adverse event or as per prescribing guideline.
- Seek specialist advice if the patient becomes pregnant or wishes to become pregnant.
- Report to and seek advice from specialist on any aspect of patient care or concern to GP which may affect treatment.
- Report adverse events to specialist and to MHRA via yellow card scheme when appropriate.

Monitoring requirements

Assessment to be completed by the specialist service provider:

- Before treatment:
    - Height & weight
    - Blood pressure
    - Full blood count (FBC)
    - U&Es, creatinine and eGFR
    - ALT and/or AST, and albumin
    - Consider chest x-ray (e.g. if any concern re latent TB)
    - Ensure a non-invasive liver screen has been completed and that Varicella Zoster Virus and Hepatitis B core antibody have been tested. Refer for treatment as appropriate

- Pre-screening for thiopurine methyltransferase (TPMT) deficiency and, if required, recommend an alternative dosing and monitoring strategy. This test is sent to an external laboratory and the result is available in 2-4 weeks

- Weekly for the first month and then every two weeks for the second month, then monthly until on stable dose for 6 weeks, then every 3 months:
  - FBC
  - ALT and/or AST, and albumin
  - Creatinine and eGFR

Ongoing monitoring (and action to be taken) during treatment to be completed by the GP:

- Every three months:
  - FBC
  - ALT and/or AST, and albumin
  - Creatinine and eGFR

Test	Action
Abnormal Full Blood Count Results	
DO NOT withhold in liver disease unless on advice of hepatologist. If concerned about sequential drops in FBC indices (possibly still within normal range), consider an early re-test/seek specialist advice.	
White Cell Count <3.5 x 10^9/L	Discuss with hepatology department as soon as possible (ideally within 24 hours)*
Neutrophils <1.6 x 10^9/L	
Platelet count <140 x 10^9/L	If remains low discuss with hepatology department
MCV >105 fl *(if samples are being analysed by Derriford Hospital lab, MCV >108 fl)*	Check B12, folate and TFTs. If abnormal start appropriate treatment. Check alcohol status. If no cause found discuss with hepatology department
Lymphocytes <0.5 x 10^9/L	Discuss with hepatology department as soon as possible (ideally within 24 hours)*
Abnormal Renal Function Results	
Creatinine increase >30% over 12 months and/or eGFR <60ml/min/1.73m^2	Discuss with hepatology department (risk of toxicity, dose adjustment may be required)
Abnormal LFT Results	
AST or ALT >2x upper limit of normal, or Unexplained fall in serum albumin	Look for alternative cause Repeat LFTs, if abnormal discuss with hepatology department
Abnormal symptoms	
Rash (significant new) or oral ulceration. Hypersensitivity reactions - fever, malaise, rash, vomiting, muscle/bone pain, dizziness.	**Withhold** and discuss with hepatology department as soon as possible (ideally within 24 hours)* Treat oral ulceration
Severe or persistent infections, fever, chills and/or persistent sore throat	**Withhold** until urgent FBC result available and discuss with hepatology department as soon as possible (ideally within 24 hours)*
Abnormal bruising or bleeding	
Gastrointestinal symptoms – nausea, diarrhoea, vomiting, abdominal discomfort	Advise patient to divide dosage and take with food. If no improvement, reduce dose and contact hepatology department

* There is a gastroenterology / hepatology consultant on call 24/7. The specialist teams would prefer emails and calls are made in working hours, when the blood tests and letters are available. However, if there is significant concern or there will be a long delay e.g. Bank holiday weekend, the on call consultant can be contacted through the relevant Hospital switchboard (see “Support” section on page 6 below).

Infections

Contact microbiology if a patient not known to be immune to chickenpox comes into contact with **shingles or chickenpox**, for advice on whether varicella-zoster immune globulin (VZIG) or other treatment is indicated.

In patients suffering from chickenpox or active skin lesions from shingles, withhold. Patients with chickenpox: contact microbiologist for consideration of admission to hospital for IV antivirals. Patients with shingles: if any vesicles are still present (regardless of the time of onset), treat with aciclovir (800mg five times a day for 7 days).

During a **serious infection** STOP azathioprine.

During **minor infections** (e.g. uncomplicated UTI treated with a short antibiotic course) treatment can be continued.

Do not stop treatment prior to surgery unless significant high-risk of infection where an individual patient plan should be made.

Patient responsibilities

- Ensure they understand the importance of monitoring treatment and attend specialist appointments and/ or GP appointments to ensure timely monitoring can be completed (in accordance with the prescribing guideline).
- Understand that treatment may be stopped if they do not attend for monitoring & treatment review.
- Ensure they have a clear understanding of the treatment, expected benefits and potential side effects.
- Take (or support administration of) medication as directed by the prescriber.
- Read the patient information leaflet regarding Azathioprine.
- **MUST** report any of the following to their GP and/or specialist: mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding, unexplained rash and any unexplained illness/infection.
- Report any adverse effects to the GP and/or specialist regarding their treatment.
- Advise the GP and specialist immediately if pregnancy is suspected.
- Store their medicines safely and securely and dispose of any unused medication appropriately.

Supporting Information

Available as tablets containing 25mg and 50mg Azathioprine.

Azathioprine injections should not be prescribed or administered within primary care.

Dosage and administration

In general, starting dose is from 50mg once per day to 1 to 2mg/kg body weight/day, and should be adjusted, within these limits, depending on the clinical response (which may not be evident for weeks or months) and haematological tolerance.

Use doses at the lower end of the range for patients with low TPMT, hepatic or renal impairment and monitor more closely.

Contraindications and precautions

Refer to product SPC for azathioprine.

Contraindications include:

- Hypersensitivity to azathioprine, 6-mercaptopurine (metabolite of azathioprine).
- Severe infections.
- Seriously impaired hepatic or bone marrow function.
- Pancreatitis.
- Any live vaccine, especially BCG, smallpox, yellow fever.

Patients with deficiency in TPMT have a higher risk of bone marrow toxicity.

Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with high protection factor to minimise the risk of skin cancer and photosensitivity.

Increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas and uterine cervical cancer in situ.

Pregnancy and lactation

Important safety information

MHRA Drug Safety Update (May 2025): Thiopurines and intrahepatic cholestasis of pregnancy (ICP)

- Cholestasis of pregnancy has rarely been reported in association with azathioprine therapy
- This risk is believed to also apply to the other thiopurine drugs, mercaptopurine and tioguanine
- It may occur earlier in pregnancy than non drug-induced cholestasis of pregnancy, and it may not respond to ursodeoxycholic acid
- Withdrawal or dose reduction of the thiopurine drug may improve liver function tests
- Remain vigilant to signs and symptoms of ICP in pregnant patients taking thiopurines (intense itching without a rash, nausea, and loss of appetite) and discuss any concerns with clinicians managing the patient's immunosuppressant therapy and a hepatologist, as necessary
- If cholestasis of pregnancy occurs, a case-by-case assessment is required to determine the appropriate course of action. Consider the risks and benefits of remaining on the product against the risks and benefits of stopping.
- In patients with ICP, measure serum bile acids to identify pregnancies at particular risk of spontaneous preterm birth (≥40uM) or stillbirth (non-fasting serum bile acids ≥100uM)

Azathioprine must not be used during pregnancy without careful assessment of risks and benefit.

6-Mercaptopurine, the active metabolite of azathioprine, has been identified in the colostrum and breast-milk of women receiving azathioprine treatment. Breast-feeding and concomitant use of azathioprine are contra-indicated.

Adverse effects

Refer to SPC for further information

Common:

- Nausea, diarrhoea, vomiting, anorexia, abdominal discomfort, headaches.

Uncommon:

- Bone marrow suppression: patient should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. inexplicable bruising or bleeding, infection.
- Hypersensitivity reactions (fever, rigors, rash, myalgia, arthralgia, hypotension, dizziness).
- Skin photosensitivity.
- Hair loss.

Drug interactions

This list is not exhaustive, for additional information, and further interactions, consult the BNF and individual product SPCs.

Common/important to primary care

The following drugs have potentially serious interactions with Azathioprine and caution must be used when prescribing concurrently:

- Allopurinol: it has an inhibitory effect on the metabolism of azathioprine by blocking the enzyme xanthine oxidase. If allopurinol is administered concomitantly with azathioprine, the dose of azathioprine must be reduced to a quarter of the original dose.
- ACE inhibitors e.g. Captopril or Enalapril: increased risk of leucopenia or anaemia.
- Clozapine: increased risk of agranulocytosis.
- Co-trimoxazole or trimethoprim: increased risk of haematology toxicity.
- Febuxostat: increased exposure to azathioprine. Avoid.
- Sulfasalazine: inhibits TPMT enzyme; risk of bone marrow suppression and leucopenia with concurrent use of azathioprine.
- Warfarin: reduced anticoagulant effect.

Support

Contact details

University Hospitals Plymouth NHS Trust

For advice and support, GPs can contact the Hepatology department*

- Hepatology Department email: plh-tr.HepatologySecretaries@nhs.net
- Hepatology department telephone line: 01752 439002
- Switchboard: 01752 202082
- Medicines Information: 01752 439976

* There is a Hepatology Consultant on call 24/7. The hepatology department would prefer calls are made in working hours, when the blood tests and letters are available. However, if there is significant concern or there will be a long delay e.g. Bank holiday weekend, the Hepatology Consultant can be contacted through the Hospital switchboard

Torbay and South Devon NHS Foundation Trust

Clinical questions about azathioprine should be directed to the Liver Nurse email inbox (below), which is monitored within working hours; responses will often be available in 24 hours (following consultation as needed with consultant team).

Support is also available via **advice and guidance** directed to the consultant responsible for patient.

There is a gastroenterology consultant on call 24/7. If queries are more urgent (or bank holiday periods where the wait may be longer), contact on call gastroenterologist via Torbay Hospital switchboard.

- Hepatology nurse specialists: tsdft.livernurses@nhs.net
- Switchboard: 0300 456 8000 or 01803 614567

NHS Devon Medicines Optimisation Team

01752 398800

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Shared Care Agreement Letter - Specialist Request to GP

To	**GP name**	
	Practice address	
Patient name		
Hospital number		
NHS number		
Date of birth		
Address		

GPs are invited to participate in shared care agreements, but if the GP is not confident to undertake these roles then they are under no obligation to do so. If so, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If asked to prescribe this drug the GP should reply to this request as soon as practical. Continuing the care assumes communication between the specialist, GP and patient; the intention should be explained to the patient and accepted by them.

The prescriber has the clinical and legal responsibility for the drug and the consequences of its use. Responsibility for drug monitoring and acting on results remains with the prescriber.

NHS England 'Responsibility for prescribing between Primary & Secondary/Tertiary care' guidance (2018) states that "when decisions are made to transfer clinical and prescribing responsibility for a patient between care settings, it is of the utmost importance that the GP feels clinically competent to prescribe the necessary medicines. It is therefore essential that a transfer involving medicines with which GPs would not normally be familiar should not take place without full local agreement, and the dissemination of sufficient, up-to-date information to individual GPs."

I have discussed and agreed the following treatment with the patient:

Azathioprine *(state dose and frequency)*

……...

For the treatment of autoimmune chronic active hepatitis (AIH)

Treatment was started on ……..

The patient has been on the optimised dose stated for ……...

This patient is now suitable for prescribing to move to primary care. The patient fulfils criteria for shared care therefore I am writing to request your agreement to continue the care of this patient according to the Specialised Medicines Service (SMS) Guideline for azathioprine for the treatment of autoimmune chronic active hepatitis (AIH) in adults (South and West Devon).

In accordance with the SMS Guideline the transfer of monitoring and prescribing to the GP is after at least 3 months, or once the patient's condition/dose is stabilised whichever is longer.

I have provided the patient with sufficient medication to last until ……..

Please undertake prescribing and monitoring from …… in line with the SMS Guideline.

The next monitoring is due on ……..

I have arranged a follow up with this patient in ……

I can confirm that the following has happened with regard to this treatment:

	Specialist to complete (YES / NO)
Baseline investigation and monitoring as set out in the SMS Guideline have been completed and were satisfactory	
The condition being treated has a predictable course of progression and the patient can be suitably maintained by primary care	
The risks and benefits of treatment have been explained to the patient	
The roles of the Specialist / GP / Patient have been explained and agreed	
The patient has agreed to this shared care arrangement, understands the need for ongoing monitoring, and has agreed to attend all necessary appointments	
I have enclosed a copy of the SMS Guideline which covers this treatment. The guideline can also be found here	
I have included with this letter copies of the information the patient has received	

The results of baseline tests, early monitoring and any additional supportive information are included below and/or attached:

GP please sign response letter and return promptly (where possible this should be within 14 days of the request being made).

Specialist signature		**Date**	
Specialist name, role, speciality			
Daytime telephone number			
Email address			
Alternative contact **e.g. clinic or specialist nurse**			
Out of hours contact details **e.g. duty doctor**			

Remember to keep a copy of this letter for the patient's records.

Shared Care Agreement Letter – GP Acceptance Letter to Specialist

To **Specialist name**	
Patient name	
Hospital number	
NHS number	
Date of birth	
Address	

GPs are invited to participate in shared care agreements, but if the GP is not confident to undertake these roles then they are under no obligation to do so. If so, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If asked to prescribe this drug the GP should reply to this request as soon as practical. Continuing the care assumes communication between the specialist, GP and patient; the intention should be explained to the patient and accepted by them.

The prescriber has the clinical and legal responsibility for the drug and the consequences of its use. Responsibility for drug monitoring and acting on results remains with the prescriber.

NHS England 'Responsibility for prescribing between Primary & Secondary/Tertiary care' guidance (2018) states that "when decisions are made to transfer clinical and prescribing responsibility for a patient between care settings, it is of the utmost importance that the GP feels clinically competent to prescribe the necessary medicines. It is therefore essential that a transfer involving medicines with which GPs would not normally be familiar should not take place without full local agreement, and the dissemination of sufficient, up-to-date information to individual GPs."

Thank you for your request for me to accept prescribing responsibility for this patient under a shared care agreement and to provide the following treatment for autoimmune chronic active hepatitis (AIH):

Medicine	Route	Dose and frequency
Azathioprine	Oral	

I can confirm that **I am willing to take on this responsibility** from ……and will maintain the prescribing and monitoring responsibilities as set out in the Specialised Medicines Service (SMS) Guideline for azathioprine for the treatment of autoimmune chronic active hepatitis (AIH) in adults (South and West Devon).

GP signature		**Date**	
GP name			
Practice address			
Telephone number			
Email address			

Remember to keep a copy of this letter for the patient's records. If this letter is not returned sharing of the care for this patient will not commence.

Shared Care Agreement Letter – GP Refusal Letter to Specialist

To **Specialist name**	
Patient name	
Hospital number	
NHS number	
Date of birth	
Address	

GPs are invited to participate in shared care agreements, but if the GP is not confident to undertake these roles then they are under no obligation to do so. If so, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If asked to prescribe this drug the GP should reply to this request as soon as practical. Continuing the care assumes communication between the specialist, GP and patient; the intention should be explained to the patient and accepted by them.

The prescriber has the clinical and legal responsibility for the drug and the consequences of its use. Responsibility for drug monitoring and acting on results remains with the prescriber.

NHS England 'Responsibility for prescribing between Primary & Secondary/Tertiary care' guidance (2018) states that "when decisions are made to transfer clinical and prescribing responsibility for a patient between care settings, it is of the utmost importance that the GP feels clinically competent to prescribe the necessary medicines. It is therefore essential that a transfer involving medicines with which GPs would not normally be familiar should not take place without full local agreement, and the dissemination of sufficient, up-to-date information to individual GPs."

In the interest of patient safety NHS Devon, in conjunction with local acute trusts have classified guanfacine as a "shared care" drug which requires a number of conditions to be met before transfer can be made to primary care.

Thank you for your request for me to accept prescribing responsibility for this patient. I regret to inform you that in this instance **I am unable to take on responsibility** due to the following:	**Tick which apply**
The prescriber does not feel clinically confident in managing this individual patient's condition, and there is a sound clinical basis for refusing to accept shared care. As the patients GP I do not feel clinically confident to manage this patient's condition. I have consulted with other GPs in my practice who support my decision. This is not an issue which would be resolved through adequate and appropriate training of prescribers within my practice. **I have discussed my decision with the patient and request that prescribing for this individual remain with you as the specialist, due to the sound clinical basis given below.**	

The condition does not fall within the criteria defining suitability for inclusion in a shared care arrangement. As the condition requested to be treated is not included on the locally recognised list of indications for shared care for azathioprine, I am unable to accept clinical responsibility for prescribing this medication at this time. **Until this condition is identified locally as requiring shared care with azathioprine the responsibility for providing this patient with their medication remains with you.**	
Initiation and optimisation by the initiating specialist. It is the specialist's responsibility to prescribe guanfacine and continue to monitor the patient for the first 3 months of treatment or until the patient's condition/dose is stabilised whichever is longer. As the patient has not been optimised on this medication I am unable to take clinical responsibility for prescribing this medication at this time. Therefore, can you please contact the patient as soon as possible in order to provide them with the medication that you have recommended. **Until the patient is optimised on this medication the responsibility for providing the patient with their medication remains with you.**	
A minimum duration of supply following initiation and optimisation by the initiating specialist. Following the request to the patient's GP to participate in a shared care agreement, the specialist must ensure that the patient has an adequate supply of medication (usually 28 days) until shared care arrangements are in place. As the patient has not had the minimum supply of medication to be provided by the initiating specialist, I am unable to take clinical responsibility for prescribing this medication at this time. Therefore, can you please contact the patient as soon as possible in order to provide them with the medication that you have recommended. **Until the patient has had the appropriate length of supply the responsibility for providing the patient with their medication remains with you.**	
Other (GP to complete if there are other reasons why shared care cannot be accepted):	

I would be willing to consider prescribing for this patient once the above criteria have been met for this treatment.

Please do not hesitate to contact me if you wish to discuss any aspect of my letter in more detail and I hope to receive more information regarding this shared care agreement as soon as possible.

GP signature		**Date**	
GP name			
Practice address			
Telephone number			
Email address			

Remember to keep a copy of this letter for the patient's records.