

OPT-OUT SHARED CARE GUIDELINE

It is assumed that shared care **will** be accepted unless the specialist is informed otherwise within 28 days of receipt of the request at the end of this document.

MEDICATION NAME: Azathioprine

INDICATIONS COVERED: Rheumatoid Arthritis and other inflammatory conditions in adults

NHS Brighton and Hove CCG, Crawley CCG and Horsham and Mid-Sussex CCG
Traffic Light System Classification: Amber

NOTES to the general practitioner (GP) or primary care prescriber

For medicines which require specialist initiation and/or dose titration and specific ongoing monitoring. For initiation, dose stabilisation and prescribing (including monitoring) by a specialist until the patient is stabilised (usually for 3 months) after which the GP may be asked to work under shared care through the use of approved shared care guidelines.

The expectation is that these guidelines should provide sufficient information to enable GPs or primary care prescribers to be confident to take clinical and legal responsibility for prescribing these medicines.

The questions below will help you confirm this:

- Is the patient currently under your care (e.g. shared care should not be agreed if the patient is currently in intermediate care following hospital discharge)?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care 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. It is assumed that shared care will be accepted unless the specialist is informed otherwise within 28 days of receipt of this request.

If the answer is NO to any of these questions, you should not accept prescribing responsibility. You should inform the consultant or specialist within 28 days, outlining your reasons for NOT prescribing. If you do not have the confidence to prescribe, we suggest you discuss this with your local Trust or specialist service, who will be willing to provide training and support. If you still lack the confidence to accept clinical responsibility, you still have the right to decline. Your CCG medicines management pharmacist will assist you in making decisions about shared care if you are unsure.

Prescribing unlicensed medicines or medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber's professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.

The GP or primary care prescriber has the right to refuse to agree to shared care, in such an event the total clinical responsibility will remain with the consultant or specialist.

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Approved by (Specialist or Consultant): Kelsey Jordan on behalf of SMSKP Rheumatology Consultants		
Approved by (Chief Trust Pharmacist): Iben Altman Chief Pharmacist SCFT		
Approved by (CCG Medicines Management Pharmacist): Via APC		
Approved by Brighton and Hove and HWLH CCG on: 27/2/2018		
Approved by Crawley CCG, Horsham and Mid-Sussex CCG on: 27/04/2018		

Information

This information sheet does not replace the Summary of Product Characteristics (SMPC), which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF.

1. **Link to the relevant SMPC website:** <http://www.medicines.org.uk/emc/> .

2. **Background to use for the indication(s), including licence status:**

Azathioprine tablets are used as an immunosuppressant antimetabolite either alone or in combination with other agents which influence the immune response.

This guideline covers the treatment of rheumatoid arthritis and inflammatory myopathies as per marketing authorisation.

Unlicensed indications include ANCA-associated vasculitis, and connective tissue disease. A significant body of evidence exists for its use in these indications outlined.

3. **Dose & administration:**

1-3mg/kg/day, though actual dose to be set by specialist team during initiation period.

When a therapeutic response is evident, consideration should be given to reducing the maintenance dose.

A therapeutic response may not be evident for 6 to 12 weeks. Consider withdrawal of treatment if no response after 3 months.

4. **Cautions:**

- Elderly – doses should be at the lower end of dosage range.
- Patients with impaired renal function – doses should be at the lower end of dosage range. Dosage should be further reduced if haematological toxicity occurs.
- Patients with impaired hepatic function – metabolism of azathioprine may be impaired, dosage should be reduced if hepatic or haematological toxicity occurs.
- Patients with thiopurine methyl transferase (TPMT) deficiency – may be associated with delayed haematotoxicity including bone marrow toxicity.
- Avoid excessive unprotected sun exposure, and advise the patient to use a high factor sunscreen
- Patients receiving multiple immunosuppressive agents – treatment should be maintained at lowest effective level.
- Varicella Zoster Virus Infection – in patients with severe exposure to chickenpox or shingles consider passive immunization with varicella zoster immunoglobulin (VZIG) – see Green Book Chapter 34 for further details.
- All patients contemplating becoming pregnant are advised to contact the rheumatology department at the earliest opportunity to discuss therapy with azathioprine.
- All patients contemplating breast feeding are advised to contact the rheumatology department at the earliest opportunity to discuss therapy with azathioprine

This list is not exhaustive; refer to the Summary of Product Characteristics (SmPC) or BNF for further guidance.

5. Contraindications:

- Patients with known hypersensitivity to azathioprine, its metabolites or any of the excipients.
- Patients with known hypersensitivity to mercaptopurine.
- Patients with hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome). Patients with absent thiopurine S-methyltransferase (TPMT) activity.
- If the formulation contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
- Severe infections.
- Seriously impaired hepatic or bone marrow function.
- Pancreatitis.

This list is not exhaustive; refer to the Summary of Product Characteristics (SmPC) or BNF for further guidance.

6. Side effects:

The most common side effects are:

- Flu-like symptoms, affecting approximately 20% of patients (myalgia, headache, diarrhoea) which characteristically occur 2-3 weeks after initiating treatment and usually subside if treatment is continued.
- Nausea, may be relieved by taking the tablets after food.
- Bone Marrow suppression causing leucopenia or thrombocytopenia (both more likely to occur in those with low TPMT activity).
 - It is important that patients are informed that they should consult either their GP or specialist team should they develop symptoms of possible myelosuppression such as sore throat (or other signs of infection) or easy bruising. In the case of such presentation an urgent FBC should be carried out.
- Other side effects include hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis—calling for immediate withdrawal); liver impairment, cholestatic jaundice, hair loss and increased susceptibility to infections and colitis in patients also receiving corticosteroids; nausea; rarely pancreatitis, pneumonitis, hepatic veno-occlusive disease, lymphoma, red cell aplasia.

This list is not exhaustive; refer to the Summary of Product Characteristics (SMPC) or BNF for further guidance.

7. Notable Drug Interactions

Prescribers are advised to check the BNF or ask a pharmacist for advice where required. This is not a comprehensive list

DO NOT GIVE ALLOPURINOL TO PATIENTS ON AZATHIOPRINE UNLESS EXPRESSLY DIRECTED BY SPECIALIST

- Trimethoprim and co-trimoxazole cause an increased risk of haematological toxicity; avoid using these antibiotics if possible.
- Other interactions of note include coumarins and febuxostat.
- Contact the appropriate specialist for advice if above drugs are considered essential for patient.

Vaccines

- Live vaccines are not generally recommended in patients on immunosuppression. This is relevant for patients seeking vaccination for foreign travel (e.g. yellow fever vaccination) if considering the shingles vaccine discuss with specialist.^{2,3}
- Inactivated vaccines such as influenza vaccine are safe to use although they may elicit a lower response.

8. Criteria for use:

Chronic inflammatory conditions as determined by the appropriate specialist according to this shared care guideline.

Specialist has initiated and dose stabilised (usually for a minimum 3 months).

GP or Primary Care Prescriber confident to take clinical and legal responsibility for prescribing this drug.

9. Any further information (e.g. supporting therapies):

Prior to starting azathioprine, best practice recommends checking the TPMT activity; this enzyme is involved in the metabolism of 6-mercaptopurine (a metabolite of azathioprine) and its activity is controlled by a genetic polymorphism. TPMT testing, initial dosing and subsequent dose adjustments will be the responsibility of the specialist team.

10. References:

1. Guidelines for the management of inflammatory bowel disease in adults. Mowat C, et al. Gut (2011).

2. BSR and BHR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. 2017 Jo Ledingham et al.
http://www.rheumatology.org.uk/includes/documents/cm_docs/2017/f/full_guideline_dmards.pdf
(accessed 9/10/17)

3. Immunisation of individuals with underlying medical conditions
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/566853/Green_Book_Chapter7.pdf (accessed 09/10/2017)

4. Handbook of systemic drug treatment in dermatology 2nd edition (2015) S Wakelin et al British Society for Rheumatology, Immunisation against shingles in people with inflammatory rheumatic disease. Available at
http://www.rheumatology.org.uk/includes/documents/cm_docs/2013/i/immunisation_with_zostavax_f_or_people_with_inflammatory_rheumatic_disease.pdf (accessed 13/10/17).

5. Summary of Product Characteristics, Azathioprine. Available at: <http://www.medicines.org.uk/emc/> (accessed 13/10/17).

6. UKMI. *Suggestions for Drug Monitoring in Adults in Primary Care*. February 2014. Available at <http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Drug%20monitoring%20document%20Feb%202014.pdf> (accessed 13/10/17)

RESPONSIBILITIES and ROLES

Consultant or specialist responsibilities

- Confirm diagnosis and indication for treatment with azathioprine.
- To discuss fully the aims, benefits, risks and side effects of treatment and a treatment plan with the patient and/or carer and written information to be supplied to the patient and/or carer.
- Prior to treatment ask GP whether patient has had pneumococcal vaccination and flu vaccination and, if not, immunise (unless contra-indicated).
- Inform GP when initiating treatment so the GP is aware what is being prescribed and can add to GP clinical record.
- Undertake baseline monitoring as required (specific to the medication).
- Record other medications and address potential medicine interactions before starting therapy.
- Discuss the potential implications of pregnancy and breastfeeding in women of child bearing potential and agree a strategy.
- To initiate treatment by prescribing and monitoring usually for a minimum of 3 months.
- Undertake monitoring if dose changed.
- Monitor and prescribe according to guidelines until handover is appropriate (including when dose changes are made).
- Discuss the possibility of shared care with the patient and/or carer and ensure that they understand the plan for their subsequent treatment.
- Supply GP with a summary of the patient's review (including anticipated length of treatment) and a link to, or a copy of, the shared care guideline when requesting transfer of prescribing to GP or primary care prescribers.
- Advise GP if treatment dose changes or treatment is discontinued.
- Inform GP if patient does not attend planned follow-up.

GP or primary care prescriber responsibilities

- Continue prescribing at the dose recommended and undertake monitoring requirements.
- Undertake all relevant monitoring as outlined in the monitoring requirements section below, and take appropriate action as set out in this shared care guideline.
- Monitor for adverse effects throughout treatment and check for medicine interactions on initiating new treatments.
- Add information about the medicine to the patient record, initially as "hospital prescribed", and highlight the importance that this medicine is only to be prescribed under a shared care guideline in primary care.
- Perform an urgent FBC on any patient on azathioprine who becomes unwell to check for myelosuppression.
- Report any adverse events to the MHRA and specialist team.
- Refer patient back to the Consultant/Specialist if any concerns.
- Provide patient with pneumococcal polysaccharide vaccine and flu vaccination unless contra-indicated.
- Ensure that if care of the patient is transferred to another prescriber, that the new prescriber is made aware of the shared care guideline (e.g. ensuring the patient record is correct in the event of a patient moving surgery).

Patient and/or carer role

- Make sure that you understand the treatment and ask for more information, if needed.
- Share any concerns in relation to treatment with whoever is prescribing this medicine for you.
- Tell the prescriber of this medication about any other medication being taken, including over-the-counter products.
- Read the patient information leaflet included with your medication and report any side effects or concerns you have to whoever is prescribing this medicine for you.
- Report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding.
- Attend any follow up appointments with the consultant or specialist.

Monitoring Requirements

Monitoring schedule²

Test	Frequency	Duration
FBC	Every 2 weeks	For first six weeks and until on stable dose for 6 weeks
Creatinine/ calculated GFR	Monthly	For three months
ALT and / or AST Albumin	3 Monthly	To continue

More frequent monitoring (monthly) is appropriate in patients at higher risk of toxicity. Following a dose increase monitoring should revert to 2 weekly until on stable dose for 6 weeks then revert back to previous schedule.

Contact specialist team urgently and consider interruption in treatment if any of the following develop:

White Cell Count $<3.5 \times 10^9/l$	Mean cell volume $>105 f/l$
Neutrophils $<1.6 \times 10^9/l$	Creatinine increase $>30\%$ over 12 months and/or calculated GFR $<60ml/min/1.73m^2$
Unexplained eosinophilia $>0.5 \times 10^9/l$	ALT and/or AST $>100 U/l$
Platelet count $<140 \times 10^9/l$	Unexplained reduction in albumin $<30 g/l$

Whilst absolute values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance.

A FBC must also be performed on any patient on azathioprine who becomes unwell as profound myelosuppression can develop between routine blood tests. If a patient is found to be myelosuppressed azathioprine therapy should be stopped immediately and medical advice should be sought.

This list is not exhaustive; refer to the Summary of Product Characteristics (SmPC) or BNF for further guidance.

Other Warning Signs

- Rash or oral ulceration: Check FBC and withhold treatment until results available
- Abnormal bruising or severe sore throat: Check FBC and withhold treatment until results available

This list is not exhaustive; refer to the Summary of Product Characteristics (SMPC) or BNF for further guidance.

SHARED CARE GUIDELINE

MEDICATION NAME: Azathioprine

INDICATION: Rheumatoid Arthritis and other inflammatory conditions in adults

DATE OF REQUEST:

Agreement to transfer prescribing to general practice or primary care prescriber:

Patient details:

Name:
Address:
DoB:
NHS No:
Hospital No:

Medication name, form and strength:

The following tests and investigations have been carried out:

Date treatment initiated:

At the last patient review the medication appeared to be effectively controlling symptoms or providing benefit:

Yes/No

The patients has now been stabilised on a dose of:

The patient has been given written information about their medication:

Yes/No

The patient understands that this medication is being prescribed under a shared care agreement between their GP and specialist and that they have responsibilities under the agreement to ensure they attend their GP to be regularly monitored.

Yes/No

The patient has been informed that the GP can opt-out of taking on prescribing responsibility if they do not feel clinically able to prescribe or if the patient persistently does not attend for monitoring:

Yes/No

Date of next clinic appointment:

If the practice declines shared care, then the named consultant or specialist should be informed within 28 days of receipt of this request. Forms used to decline prescribing can be found here:

Brighton and Hove CCG:

<http://www.gp.brightonandhoveccg.nhs.uk/prescribing/joint-formulary-supporting-information>

Crawley CCG, Horsham and Mid Sussex CCG:

<http://www.horshamandmidsussexccg.nhs.uk/EasySiteWeb/GatewayLink.aspx?allid=415216>

BACK-UP ADVICE AND SUPPORT

	Name and position	Telephone	Email
Specialist or Consultant			
Alternative specialist (e.g. departmental contact)			

Specialist pharmacist			
Out of hours (e.g. medical team on call)			

Link to full SCG: <http://>