Sussex MSK Partnership

WORKING IN PARTNERSHIP WITH

NHS
Brighton and Hove Clinical Commissioning Group
Crawley Clinical Commissioning Group
Horsham and Mid Sussex Clinical Commissioning Group
High Weald Lewes Havens Clinical Commissioning Group

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 TABLETS**

INDICATIONS COVERED: **Rheumatoid Arthritis, Systemic Lupus Erythematosus and other chronic inflammatory conditions in Adults**

NHS Brighton and Hove CCG, Crawley CCG, Horsham and Mid-Sussex CCG and High Weald Lewes Havens 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 effective 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 with 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.

Reason for update: New	**Prepared by:** Dr.U.Davies, D.Finney, Dr.S.Griffith, Dr.J.Kelsey, Dr.R.Makadsi, Dr.S.Mohamed, Dr.G.Papasavvas, Dr.W.Shattles, SCT Medicines Management Team	**Updated by:** N/a
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Approved by NHS Brighton and Hove and High Weald Lewes Havens CCG on: 22.09.2015		
Approved by Crawley CCG, Horsham and Mid-Sussex CCG on: 22.09.2015		

Information

This information sheet does not replace the Summary of Product Characteristics (SPC), 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 SPC website**: http://www.medicines.org.uk/emc/ .

2. **Background to use for the indications, including licence status:**

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

It has a marketing authorisation for the treatment of rheumatoid arthritis and systemic lupus erythematosus.

3. **Dose & administration:**

1mg to 3mg per kg bodyweight per day. Dose to be set by consultant or specialist 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 to12 weeks. Consider withdrawal of treatment if no response after 3 months.

4. **Cautions (including pregnancy and lactation):**

- 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 hematological toxicity occurs.
- Patients with thiopurine methyl transferase (TPMT) deficiency – may be associated with delayed haematotoxicity including bone marrow toxicity.
- 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 must be seen by a Consultant at the earliest opportunity to discuss the complex issues surrounding therapy with azathioprine.
- All patients contemplating breast feeding must be seen by a Consultant at the earliest opportunity to discuss the complex issues surrounding therapy with azathioprine.

This list is not exhaustive; refer to the Summary of Product Characteristics (SPC) 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.
- Live vaccines (see medicine interactions section).

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

6. **Side effects:**

The most common side effects are:

- Flu-like symptoms (myalgia, headache, diarrhoea) which characteristically occur 2-3 weeks after initiating treatment and usually subside if treatment is continued.
- Nausea – which can usually 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).

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 (SPC) or BNF for further guidance.

Table 1. Side effects and actions to take for abnormal results

SIDE EFFECT	ACTIONS
WBC < 3.5 x 10^9/l, or Neutrophils <1.5 x 10^9/l, or Platelets <150 x 10^9/l	Discuss with specialist (note frequently used in connective tissue disease where values may be low).
Liver Function AST/ALT > twice upper limit of reference range	Withhold and discuss with specialist.
MCV > 105fl	Check folate, B12 & TSH and treat if appropriate. If normal results, continue treatment.
Rash	Withhold and seek urgent specialist (preferably dermatological) advice.
Oral Ulceration	Withhold and discuss with specialist.
Abnormal bruising, sore throat, unexplained bleeding	Withhold and check FBC urgently. Discuss with specialist.

Please note that in addition to absolute values, a rapid fall/rise or consistent downward/upward trend in haematological or biochemical index should prompt caution and extra vigilance.

7. Notable drug interactions:

- Allopurinol / xanthine oxidase inhibitors – avoid concomitant use if possible. If concomitant use, it is essential that only 25% of the usual dose of azathioprine is given since allopurinol decreases the rate of catabolism of azathioprine.
- Aminosalicylates & derivatives (i.e. mesalazine, olsalazine or sulfasalazine) - may increase risk of bone marrow toxicity when used concomitantly with azathioprine.
- Anticoagulants – azathioprine reduces the effect of warfarin.
- Angiotensin-converting enzyme (ACE) Inhibitors – concomitant use may cause anaemia.
- Co-trimoxazole & Trimethoprim – Increased risk of haematological toxicity. Avoid concomitant use.
- Cytostatic/myelosuppressive agents – where possible avoid concomitant administration of cytostatic drugs, or drugs which may have a myelosuppressive effect, such as penicillamine.
- Febuxostat – avoid concomitant use.
- Methotrexate – when azathioprine is administered concomitantly with high dose methotrexate, the dose should be adjusted to maintain a suitable white blood cell count.
- Phenytoin, sodium valproate, carbamazepine: Azathioprine reduces the absorption of these drugs.
- Ribavirin – avoid concomitant use.
- **Live Vaccines** – should **NOT** be administered to patients receiving treatment with azathioprine.
  Herpes zoster vaccine is not contraindicated in these patients. Please see http://tinyurl.com/nvdeqp2 .

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

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:

Prior to starting azathioprine, best practice recommends checking the TPMT (thiopurine methyltransaminase) 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 adjustments will be the responsibility of the specialist team.

10. References:

- Brighton and Hove CCG, *Effective Shared Care Agreement (ESCA): Azathioprine Tablets.* March 201. Available at:http://www.brightonandhoveccg.nhs.uk/sites/default/files/resources/ch_10_musculoskeletal_cp.pdf (accessed 24.03.15).
- 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_for_people_with_inflammatory_rheumatic_disease.pdf (access 11.08.15).
- Chakravarty, K. et al, *BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists, British Society for Rheumatology*, Oxford University Press, 2008. Available at: http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmar

d_therapy.pdf (accessed 24/03/15).

- Crawley CCG, Horsham and Mid-Sussex CCG, Effective Shared Care Agreement (ESCA): azathioprine. August 2011. Available at: http://www.horshamandmidsussexccg.nhs.uk/intranet/clinical/programmes/medicines-management/ (accessed 09.04.15).
- Immunisations against infectious diseases (Green Book online), *Chapter 34: Varicella.* Updated April 2013. Available at Varicella: the green book, chapter 34 - Publications - GOV.UK (accessed 26.03.15).
- Joint Formulary Committee. *British National Formulary; Azathioprine,* March 2015, British Medical Association and Royal Pharmaceutical Society. London. Available at: https://www.medicinescomplete.com/mc/bnf/current/index.htm (accessed 24.03.15).
- Summary of Product Characteristics, *Imuran®25mg Tablets.* Aspen. Last update 09.12.14. Available at: http://www.medicines.org.uk/emc/medicine/2881 (accessed 24.03.15).
- Summary of Product Characteristics, *Azathioprine 25mg Tablets.* Sandoz Limited. Last update 29.04.14. Available at: http://www.medicines.org.uk/emc/medicine/26877 (accessed 24.03.15).
- 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 26.03.15).

RESPONSIBILITIES and ROLES

Consultant or Specialist responsibilities	
1	Confirm diagnosis and indication for treatment with azathioprine.
2	To discuss fully the aims, benefits, risks and side effects of treatment and a treatment plan with the patient and/or carer and for written information to be supplied to the patient and/or carer.
3	Inform GP when initiating treatment so the GP is aware what is being prescribed and can add to GP clinical record.
4	Prior to treatment ask GP whether patient has had pneumococcal vaccination and flu vaccination and, if not, immunise (unless contra-indicated). Inform patient not to start medication until after immunisation.
5	Undertake baseline monitoring as required and record varicella status.
6	Record other medications and address potential medicine interactions before starting therapy.
7	Exclude existing pregnancy in women with child bearing potential.
8	To discuss the potential implications of pregnancy and breastfeeding in women of child bearing potential and agree a risk minimisation strategy where appropriate.
9	To initiate treatment by prescribing and monitoring usually for a minimum of 3 months.
10	Undertake monitoring if dose changed.
11	Inform patient to report immediately any exposure to Varicella Zoster Virus.
12	Monitor and prescribe according to guidelines until handover is appropriate (including when dose changes are made).
13	Discuss the possibility of shared care with the patient and/or carer and ensure that they understand the plan for their subsequent treatment.
14	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.
15	Advise GP if treatment dose changes or treatment is discontinued.
16	Inform GP if patient does not attend planned follow-up.

GP or Primary Care Prescriber responsibilities	
1	Continue prescribing azathioprine at the dose recommended and undertaken monitoring requirements.
2	Undertake all relevant monitoring as outlined in the monitoring requirements section below, and take appropriate action as set out in this shared care guideline.
3	Monitor for adverse effects throughout treatment and check for medicine interactions on initiating new treatments.
4	Add information about the medicine to 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.
5	Inform the consultant or specialist of any issues that may arise.
6	Inform patients to report immediately any unexplained bleeding, bruising, purpura, sore throat, fever, pallor, jaundice or malaise and take the actions outlined in this shared care guideline.
7	Inform patients to report immediately any exposure to Varicella Zoster Virus.
8	Refer patient back to the consultant or specialist if any concerns.
9	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).

Monitoring requirements and appropriate dose adjustments	
1	Pre-treatment: FBC, U&Es, creatinine, LFTs, ESR and / or CRP and TPMT assay.
2	Initiation: Weeks 2, 4, 6, 8, 10, 12: FBC, U&Es, LFTs, ESR and / or CRP.
3	Weeks 18 and 24: FBC, U&Es, LFTs, ESR and / or CRP.
4	Maintenance: Every three months thereafter: FBC, U&Es, creatinine, LFTs, ESR and / or CRP.
5	Dose increase when on maintenance: Recheck FBC, LFTs, ESR and / or CRP 2 weeks after dose change.
6	Monitor for adverse drug reactions throughout treatment.
7	Check for medicine interactions on initiating new treatments.
8	Elderly – doses should be at the lower end of the dosage range.
9	Hepatic &/or Renal impairment – doses should be at the lower end of the dosage range.
10	Pregnancy – dose reduction at 32 weeks of gestation may prevent neonatal leucopenia.

Patient's or Carer's role	
1	Make sure that you understand the treatment and ask for more information, if needed.
2	Share any concerns in relation to treatment with whoever is prescribing this medicine for you.
3	Tell the prescriber of this medication about any other medication being taken, including over-the-counter products.
4	Report immediately any exposure to Varicella Zoster Virus.
5	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.
6	Attend the follow up appointments with the consultant or specialist.
7	Attend any monitoring appointments (e.g. blood tests).

SHARED CARE GUIDELINE
MEDICATION NAME: Azathioprine
INDICATION: Rheumatoid Arthritis, Systemic Lupus Erythematosus and other chronic inflammatory conditions in Adults
Agreement to transfer prescribing to general practice or primary care prescriber:

Patient details:

Name:

Address:

DoB:

NHS No:

Hospital No:

Medication name and strength: Azathioprine

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 and High Weald Lewes Havens 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?alId=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://