Azathioprine

Shared Care Agreement for the treatment of Ulcerative colitis and Crohn’s disease with azathioprine, a copy of which must be supplied by the specialist to the GP at commencement, which will not be before the patient is stabilised on and tolerating treatment.

Areas of responsibility for the sharing of care
This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing and monitoring of azathioprine for patients with Ulcerative colitis and Crohn’s disease will be shared between the specialists, the general practitioner (GP) and the patient.

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 good communication between the specialist, GP and patient. The intention to share 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.

The overall clinical responsibility for the diagnosed condition and treatment remains with the specialist; however, the primary care doctor who provides repeat prescriptions shares responsibility for the medicine and the consequences of its use.

RESPONSIBILITIES and ROLES

<table>
<thead>
<tr>
<th>Specialist responsibilities</th>
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<tbody>
<tr>
<td>1 Discuss with the patient the benefits and side effects of treatment and the importance of blood tests.</td>
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<td>2 To check any interactions between azathioprine and the patient’s medications of which they are currently taking and aware of.</td>
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<td>3 Send letter to GP requesting shared care.</td>
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<td>4 Initiation of treatment, and supply of hospital prescriptions for suitable quantities of drug until at least the transfer of monitoring to the primary care (6-8 weeks).</td>
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<td>5 Baseline monitoring of the patient as outlined overleaf</td>
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<td>6 Regular review of patient’s condition and of response to treatment</td>
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<td>7 Communication with GP once the patient is established on azathioprine about the transfer of prescribing and monitoring under this shared care arrangement.</td>
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<td>8 Notification to the GP if the patient changes dose or stops therapy with azathioprine.</td>
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<td>9 Inform GP of patients that don’t attend out patient appointments.</td>
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<tr>
<td>10 Reporting any significant or unexpected adverse events to the CSM.</td>
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<td>11 Ensure clear arrangements for back-up, advice, and support.</td>
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<th>General Practitioner responsibilities</th>
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<tr>
<td>1 Monitor patients overall health and wellbeing.</td>
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<tr>
<td>2 To make sure the specialist is aware of all patient’s regular and acute medication.</td>
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<td>3 To check for interactions with azathioprine of any new medications they may initiate.</td>
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<tr>
<td>4 Reporting to and seeking advice from the specialist on any aspect of patient care which is of concern to the GP and may affect treatment.</td>
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<tr>
<td>5 Prescribe and monitor azathioprine after a formal handover by the specialist as per guidelines</td>
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<tr>
<td>6 Reporting any significant or unexpected adverse events to specialist and CSM.</td>
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Azathioprine, March 2012
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7 Change dose or stop treatment on the advice of the specialist.
8 Request input from the hospital specialist as appropriate.

**Patient’s role**

1. Alert clinical staff to the treatment they are receiving either bought or prescribed.
2. Agree to attend for regular clinic appointments and to have regular blood tests.
3. Report any adverse effects to the specialist, IBD Nurses or GP whilst taking azathioprine.
4. Share any concerns in relation to treatment with azathioprine.
5. Report to the specialist or GP if they do not have a clear understanding of their treatment.

**BACK-UP ADVICE and SUPPORT**

<table>
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<tr>
<th>Contact details</th>
<th>Telephone</th>
<th>Fax</th>
<th>For any emergency / urgent advice outside normal office hours inc. weekends</th>
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<tbody>
<tr>
<td>Specialists:</td>
<td></td>
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<td>Contact on call medical team via hospital switchboard 01733 687000</td>
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<tr>
<td>Dr Nair</td>
<td>01733 677526</td>
<td>01733 676786</td>
<td></td>
</tr>
<tr>
<td>Dr Das</td>
<td>01733 677527</td>
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<td></td>
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<tr>
<td>Dr Kumar</td>
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<tr>
<td>Dr Ninkovic</td>
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| IBD Specialist Nurses: Gill Anderson & Elaine Marsden (Help line) | 01733 673876 | 01733 676786 |

| Hospital Pharmacy Dept: PCH Medicines Information Helpline | 01733 677303 | Weekdays 9am-5pm |

**Azathioprine monitoring information**

A. **Indications:** (unlicensed) Ulcerative colitis and Crohn’s disease. However, use for Inflammatory Bowel Disease is widespread (BNF Section 1.5).

B. **Dose:** Grade of evidence: C
   The initial oral dose is 50mg once daily for 2 weeks, and then gradually increased in 50mg increments every 2 weeks to 2 – 2.5 mg/kg daily, if tolerated. Occasionally the start dose may be 25mg.

C. **Route of administration:** Oral

D. **Time to response:** 6-12 weeks.

E. **Cautions:** Grade of evidence: C
   (1) Thiopurine methyl transferase (TPMT) reduced activity (– only in patients with extensive problems.)

   (2) Sunscreens and protective covering should be encouraged to reduce sunlight exposure

   (3) Renal or liver impairment

   (4) Localised or systemic infection including hepatitis B or C and history of tuberculosis.

   (5) Patients should avoid ‘live’ vaccines typhoid, MMR, BCG and yellow fever, whilst
on immunosuppressive therapy. Contact hospital specialist for advice on any vaccinations if required.

(6) Patients should try to avoid contact with people who have active chickenpox or Shingles and should report any such contact to their GP or hospital specialist immediately.

(7) Patients receiving azathioprine should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or other manifestations of bone marrow depression.

(8) Careful assessment of risk versus benefit should be carried out before use during pregnancy and breastfeeding. Consult hospital specialist clinician or IBD nurse.

(9) Patients on multiple immunosuppressants at risk of over immunosuppression, therefore azathioprine therapy should be maintained at the lowest effective level.

F. Contraindications: Grade of evidence: C

(1) TPMT deficiency

(2) Individuals with Lesch-Nyhan Syndrome – due to congenital hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency.

(3) Significant haematological impairment

(4) Hypersensitivity to azathioprine or 6-mercaptopurine (6-MP)

G. Notable drug interactions (please refer to latest edition of BNF)

(1) Allopurinol, oxipurinol and/or thiopurinol: enhanced effects and increased toxicity of azathioprine. Azathioprine dose should be reduced to 25% of the original dose.

(2) Warfarin: azathioprine possibly inhibits the anticoagulant effects of warfarin. Monitor INR, consider increasing the dose of warfarin if necessary.

(3) Neuromuscular blocking agents: azathioprine can potentiate the effects of depolarising agents such as succinylcholine and reduce the effects of non-depolarising agents such as tubocurarine. The potency of this interaction can vary significantly.

(4) Febuxostat: avoidance of azathioprine advised by manufacturer.

(5) Ribavirin: myelosuppressive effects of azathioprine possibly enhanced by ribavirin.

(6) Angiotensin-converting enzyme (ACE) inhibitors: co-prescribing of azathioprine may cause haematological abnormalities.

(7) Aminosalicilates e.g mesalazine, olsalazine, balsalazide or sulfasalazine, may contribute to bone marrow toxicity.
(8) Sulfamethoxazole and trimethoprim can cause life threatening haematoxicity.

H. Monitoring schedule: Grade of evidence: C

(a) Pre-treatment Assessment
FBC, U&E, Creatinine, LFTs, varicella status and TPMT assay

(b) Monitoring
FBC and LFT’s weekly for 8 weeks; then monthly
If maintenance dose is achieved and stable for 6 months consider discussing with patient to reduce monitoring to 3 monthly.

CRP every 3 months to access response to treatment
(In people heterozygote for TPMT, monitoring should continue at monthly intervals at minimum.)

(c) Following changes in dose
Repeat FBC and LFT’s 2 weeks after dose change and then monthly

(d) Regular review
U&E and Creatinine should be repeated 6 monthly

(Please note – other medications may increase need for monitoring e.g. concomitant use of 5ASA)

I. Actions to be taken: Grade of evidence: C

Lymphocytes <0.5 X10⁹/L
Discuss with IBD nurse or specialist hospital clinician.

Neutrophils > 1.5 but < 2.0 x 10⁹/L
Discuss with IBD nurse or specialist hospital clinician.

Neutrophils < 1.5 x 10⁹/L
Stop and discuss with IBD nurse or specialist hospital clinician.

LFTs >2 fold rise in AST, ALT (from upper limit of reference range)
Contact IBD nurse or specialist hospital clinician. Consider Halving the dose

4 fold rise in AST, ALT (from upper limit of reference range)
Stop Azathioprine and contact IBD nurse or specialist hospital clinician immediately.

Rash (significant new)
Stop Azathioprine and check FBC.
If FBC abnormal contact IBD nurse or specialist hospital clinician.
Severe or persistent infections, check fever, chills and/or persistent sore throat

Severe or persistent infections, check fever, chills and/or persistent sore throat

Stop Azathioprine
FBC and contact IBD nurse specialist hospital clinician

Do not restart until results of FBC known
For sore throats, take FBC, and contact specialist hospital clinician

Abnormal bruising or bleeding

Stop Azathioprine until recovery and check FBC

Do not restart if blood test abnormal, contact IBD nurse or specialist hospital clinician

Nausea

Advise patient to divide dosage and take with food.

If no improvement, reduce dosage or stop and contact IBD nurse or specialist hospital clinician if reducing dose ineffective.

J. Caveats:

(1) Immunisation:

(a) Patients receiving azathioprine must not receive immunisation with live vaccines.

(b) Annual flu vaccination is recommended.

(c) In patients receiving azathioprine exposed to chickenpox or shingles, passive immunisation should be carried out using varicella zoster immunoglobulin (VZIG).

(2) Pregnancy and breast feeding:

(a) Adequate contraceptive precautions should be advised when either partner is receiving azathioprine. Evidence of mutagenicity is equivocal. In most cases, azathioprine should not be prescribed if there is a possibility of pregnancy. However, there may be some circumstances where the benefit of treatment outweighs the possible risks related to the unborn child. There have been reports of spontaneous abortion following both maternal and paternal exposure. Haematological abnormalities have been observed in neonates following maternal exposure. Therefore extra care in haematological monitoring is advised during pregnancy.

(b) Azathioprine is present in milk in low concentration; no evidence of harm in small studies—use if potential benefit outweighs risk

(3) TPMT assay: This assay provides additional information of risks related to treatment but does not replace routine monitoring. However, for those with higher levels of serum TPMT, higher doses of azathioprine may be required. Homozygous deficiency is associated with serious and fatal toxicity that may occur within 6 weeks of starting azathioprine. Heterozygous deficiency is also linked to serious adverse events, although the symptoms may not be evident until 6 months after commencing treatment.
Minor unrecognised infections or drug interactions, particularly when co-prescribed with aminosalicylates, such as sulfasalazine, mesalazine or olsalazine, may precipitate fatal toxicity. Heterozygous individuals should be prescribed azathioprine with caution and, in particular, reduced drug dosage.

This guideline was prepared by Poonam Dhokia Medicines Information Pharmacist.

The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics and British National Formulary.

Date ratified at Peterborough & Stamford Hospitals NHS Foundation Trust Formulary Committee Meeting: March 2012

Review date: March 2014