

Shared Care Agreement

AZATHIOPRINE / MERCAPTOPURINE (MP)

Referral Criteria

- These guidelines are for patients over 16 years of age.
- Shared Care is only appropriate if it provides the optimum solution for the patient.
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patients' GP
- Safe prescribing must be accompanied by effective monitoring
- When transfer is agreed, the patient will be given a supply of azathioprine/mercaptopurine (MP) sufficient for 4 week maintenance therapy
- **The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.**

SHARED CARE RESPONSIBILITIES

Consultant

1. Undertake the necessary testing to confirm a diagnosis for which azathioprine / MP treatment is recommended.
2. Ensure the patient's concurrent drug therapy is stabilised and there are no contra-indications to treatment with azathioprine / MP
3. Ensure that patient is aware of risks and benefits of medication and has read appropriate information leaflet.
4. Ensure the patient understands the shared care agreement and has signed the Patient Agreement Letter (page 8-9)
5. Perform baseline tests (see Monitoring section) including TPMT and provide results to GP
6. Initiate treatment and prescribe until the patient has been on a stable dose for minimum of SIX weeks
7. Send a letter to the GP requesting shared care for this patient.
8. Review the patient in outpatients as clinically appropriate and advise the GP promptly after these reviews on when to adjust the dose, stop treatment or consult with the specialist.
9. Inform GP, by letter, of each clinic attendance and action taken for the management of the patient ensuring current dose, most recent blood results and frequency of monitoring are stated.
10. Evaluate any reported adverse effects by GP or patient.
11. Inform GP of patients who do not attend clinic appointments, admin to contact patient to rearrange.
12. Ensure that backup advice is available at all times. (see Contacts section) and respond to any GP queries as soon as practicable.
12. To report any adverse events to the CHM and GP (see link)

<https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>

General Practitioner

1. Monitor patient's overall health and well-being.
2. Consider request to prescribe under shared care arrangements and reply only if you **do not agree** to share care, in a timely manner within 14 days as outlined on page 7 with clinical reasons and return to Consultant and Pharmacy department.
3. Ensure compatibility with other concomitant medication.
4. Prescribe at the dose recommended.
5. Monitor U&E, creatinine, FBC and LFTs at recommended frequencies (see monitoring section) and refer if abnormal.
6. Adjust the dose as advised by the specialist.
7. Stop treatment on advice of specialist or immediately if any urgent need to stop treatment arises (see monitoring section).
8. Report any adverse events to the specialist and CHM.
9. <https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>
10. Inform specialist of any change in the medical condition of patient which may have effect on disease / medications.
11. Ensure patient is offered an annual flu vaccination and a one off pneumococcal vaccination

Patient

1. Report to specialist or GP if there is not a clear understanding of their treatment and discuss any concerns in relation to treatment

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2. Report any adverse effects to their Specialist whilst taking Azathioprine / MP, especially unexplained bruising/bleeding, fever, infections or mouth ulcers which should be reported immediately.
3. Report any changes in disease symptoms to Specialist whilst taking Azathioprine / MP.
4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy whilst taking Azathioprine / MP.
5. Inform GP or specialist of any other medicines being taken including over-the-counter products.
6. Do not use sunbeds, and avoid strong sunlight or use a sun cream with a high sun protection factor (SPF of at least 15).
7. Attend for regular reviews and blood monitoring tests.

CONTACT NUMBERS FOR ADVICE AND SUPPORT

| Princess Alexandra Hospital NHS Trust - Gastroenterology | |
|--|--|
| Consultant: Clare Macpherson Specialist Gastroenterology Pharmacist | 01279 444455 Ext 7424 / 7821 Bleep 272 Direct dial: 01279 278224 (voicemail if not answered) |
| IBD Specialist Nurse | Direct dial:01279 278223 (voice mail only) |

| Princess Alexandra Hospital NHS Trust - Rheumatology | |
|---|--|
| Consultant: Nicola McCutcheon Specialist Rheumatology Pharmacist | 01279 444455 Ext 7434 / 7420 Ext 7819 Direct dial 01279 827819 (voicemail) |
| Rheumatology Specialist Nurse | 01279 444455 Ext 7434 |

| Princess Alexandra Hospital NHS Trust - Dermatology | |
|--|--|
| Consultant: Medicines Information | 01279 444455 Ext 7431 / 7421 01279 827054 |
| Clinical Nurse Specialist Dermatology | 01279 444455 Ext 7431 / 7421 |

| Princess Alexandra Hospital NHS Trust - Neurology | |
|--|-----------------------|
| Consultant: | 01279 444455 Ext 7422 |

| Princess Alexandra Hospital NHS Trust - Haematology | |
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| Consultant: | 01279 444455 Ext 7035 |

| Princess Alexandra Hospital NHS Trust - Pharmacy | |
|---|--------------|
| Medicines Information (for medicines related queries) | 01279 827054 |

CLINICAL INFORMATION

Prescribed Indications covered by this Shared Care Agreement

Azathioprine

All licensed indications:

- 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

and the following unlicensed autoimmune disorders:

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Severe eczema¹
Vasculitis¹
Crohn's Disease and Ulcerative Colitis²
Psoriatic arthritis³
Myasthenia gravis⁴
Chronic inflammatory demyelinating polyneuropathy⁴
Autoimmune mediated neurological disorders⁴

6-Mercaptopurine

Unlicensed Indications - Crohn's Disease and Ulcerative Colitis²

Therapeutic Summary

Azathioprine is used as a disease-modifying agent to induce and maintain remission in several inflammatory and autoimmune conditions. Azathioprine is a pro-drug, which is cleaved rapidly in the liver to MP. The predominant toxic effect is myelosuppression, although hepatotoxicity is also well recognised. Azathioprine is metabolised by the enzyme thiopurine methyl transferase (TPMT). It has been established that approximately 90% of the population have a Normal TPMT activity and may require standard doses of azathioprine, 11% have intermediate TPMT activity and are at a higher risk of adverse drug reactions on standard doses of azathioprine and 0.3% are deficient or have no detectable TPMT activity and are at risk of suffering life-threatening complications even when treated with low doses of azathioprine. TPMT activity can be measured phenotypically and genotypically.

For rheumatoid diseases improvement may take 2 to 3 months to occur.

Note: Mercaptopurine is the active metabolite of Azathioprine, with the same mechanism of action, the same risk/benefit profile and the same monitoring requirements. However, MP may be better tolerated than Azathioprine. **The dose of MP is approximately half that of Azathioprine.**

Dose and Route of Administration

Azathioprine

In general, the dosage range is 1-3 mg/kg bodyweight/day orally, and should be adjusted according to the clinical response (which may be evident only after weeks or months) and haematological tolerance. For the treatment of chronic active hepatitis the dosage is usually between 1.0 and 1.5 mg/kg bodyweight/day and for IBD up to 2.5mg/kg body weight/day.

Starting typically at 1mg/kg and increasing after 4-6 weeks to 2-3 mg/kg/day according to response.

When the therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with maintenance of the response.

Mercaptopurine

0.75 to 1.5 mg/kg daily by mouth.

See SPC for more details

<http://www.medicines.org.uk/emc/medicine/2882>

azathioprine

<http://www.medicines.org.uk/emc/medicine/24688>

mercaptopurine

Duration of Treatment

Indefinite but may be withdrawn after a prolonged period of remission in selected cases.

It is also used as a rotational treatment in eczema.

Adverse Effects and Management

Undesirable effects may vary in their incidence depending on the indication.

- Bone marrow suppression (leucopenia, thrombocytopenia)
- Hypersensitivity reactions including malaise, rash, dizziness, vomiting, diarrhoea, fever, rigors, nephritis requires immediate withdrawal.
- Hepatotoxicity (hepatic necrosis, biliary stasis, hepatic veno-occlusive disease)

Written by: Clare Macpherson, Senior Pharmacist

References: Draft SCG for Azathioprine in Gastroenterology by Dr Lakshmana Kumar, Consultant, Rheumatology Department guidelines for prescribing Azathioprine

Adapted from Derbyshire Joint Area Prescribing Committee Guidelines for Azathioprine/6-Mercaptopurine

Approved Oct 2017. Review date Oct 2019. 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.

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- Anorexia, nausea, vomiting
- Oral ulceration, rarely gastrointestinal ulceration
- Rarely pancreatitis
- CNS disturbances (headache, drowsiness, blurred vision)
- Alopecia
- Increased susceptibility to infection
- Oligospermia
See BNF and SPC for comprehensive list and details

Skin Care: There is an increased risk of skin cancer. Patients should be aware of the need for adequate sun protection measures. This risk is greater in patients who have a history of previous treatment with PUVA

IMMUNOSUPPRESSION

Patients who have not had chicken pox and are in contact with anyone with the virus are advised to contact either their own GP or the specialist department to have VZ antibody status checked. If antibodies are negative it is recommended for these patients to have VZ immunoglobulin.

[Please see Human Varicella-Zoster Immunoglobulin \(VZIG\) Doc for further information and contact details.](#)

TPMT Assay:

Individuals with severely reduced TPMT activity (**homozygous**) **should not be prescribed AZATHIOPRINE** as serious and fatal toxicity may occur within 6 weeks of starting the drug. For mild/moderate (heterozygous) deficiency serious adverse events may occur anytime and as late as 6 months after treatment commences. Serious Adverse Events can be exacerbated by minor infections or drug interactions (See Drug Interactions & contra-indications). **Heterozygous individuals should be prescribed Azathioprine/MP with caution and reduced drug dosage.**

Cautions

- Patients should try to avoid contact with people who have active chickenpox or shingles and should report any such contact urgently to their GP or specialist. Passive immunisation should be carried out using Varicella zoster immunoglobulin (VZIG) in non-immune patients if exposed to chickenpox or shingles.
- Anticoagulant effect of warfarin possibly reduced by Azathioprine / MP.
- Sunscreens and protective covering should be encouraged to reduce sunlight exposure.
- Infection with hepatitis B or C and history of TB

Contraindications

- Moderate/severe renal or liver impairment
- Hypersensitivity to azathioprine, MP (metabolite of azathioprine) or to any of the excipients.
- Severe infection
- Severely impaired hepatic or bone-marrow function.
- Pancreatitis
- Pregnancy unless the benefits outweigh the risks (see below)
- Lactation
- Low or marginal TPMT levels.
- Patients should avoid 'live' vaccines such as oral polio, MMR, BCG and yellow fever. An inactivated form of polio is readily available.
- Increased risk of haematological toxicity with co-trimoxazole/trimethoprim. Avoid concomitant use.

Pregnancy and Lactation

The risk benefit discussion for continuing treatment in pregnant/breastfeeding patients or those considering pregnancy/breastfeeding will be undertaken by secondary care

The manufacturer advises that azathioprine is contra-indicated in pregnancy, although many specialists consider it to be a low risk.⁵ Women of child bearing potential should be advised to use effective contraception. In most cases Azathioprine/MP should not be prescribed if there is a risk of pregnancy

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although there may be some circumstances where continuing treatment for the safety of the individual outweighs the possible risks related to the unborn child. Dose reduction at 32 weeks of gestation may prevent neonatal leucopenia. Women treated with Azathioprine/MP should not breast feed, contact Specialist for advice

Monitoring Standards for Azathioprine and Mercaptopurine based on BSR BHPR Standards 2017

The following standards have been agreed for the monitoring of Azathioprine and Mercaptopurine in all patients at Princess Alexandra Hospital NHS Trust.

| | | |
|---|---|--|
| Pre-treatment by Specialist | Height, weight, blood pressure, FBC, U&Es, LFTs, TPMT phenotype, creatinine, varicella status, hepatitis B&C status | |
| Initial monitoring by Specialist | FBC Creatinine / calculated GFR ALT +/- AST Albumin | Every 2 weeks until on stable dose for 6 weeks. |
| Ongoing monitoring by GP | FBC Creatinine / calculated GFR ALT +/- AST Albumin | Then once on stable dose monitor monthly for 3 months. |
| | FBC Creatinine / calculated GFR ALT +/- AST Albumin | At least every 12 weeks |
| Dose increase | FBC Creatinine / calculated GFR ALT +/- AST Albumin | Every 2 weeks until on stable dose for 6 weeks, then revert to previous schedule |
| | Heterozygotes for TPMT | Continue monitoring FBC and LFTs monthly. GP will be informed of this by secondary care when shared care is initiated. |

Action and Advice

If a GP has taken blood tests for the general medical management of a patient and blood test results fall into the categories below or the patient reports one of the adverse events below, these are recommendations for considering the withdrawal of Azathioprine / MP therapy:

| Blood Test Results | |
|--|--|
| • WBC < 3.5 x 10 ⁹ /l | Withhold until discussed with specialist team |
| • Neutrophils < 2.0 x 10 ⁹ /l | Withhold until discussed with specialist team |
| • Platelets < 150 x 10 ⁹ /l | Withhold until discussed with specialist team |
| • > 2-fold rise in AST, ALT (from upper limit of reference range) | Withhold until discussed with specialist team |
| • MCV > 105fl | Check B12, serum folate and TSH. Treat any underlying abnormality. If results normal, discuss with specialist team |
| • U&Es | Abnormal result discuss with specialist team |
| Unexplained reduction in albumin <30 g/l | Discuss with specialist team |
| Creatinine increase >30% over 12 months and/or calculated GFR <60 ml/min | Withhold until discussed with specialist team |
| Symptoms | |
| • Abnormal bruising or bleeding | Withhold until FBC results available & discuss with specialist team |
| • Severe sore throat | Withhold until FBC results available & discuss with specialist team |


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Clinically relevant Drug interactions – see SPC for complete listing

- **Allopurinol:** Dose of Azathioprine/MP should be reduced to 25% of original dose.
- **Warfarin:** Azathioprine/MP inhibits the anti-coagulant effect of warfarin
- **Carbamazepine, Phenytoin, Sodium Valproate:** Azathioprine/MP reduces the absorption of these drugs
- **Angiotensin-converting enzyme (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.
- **Co-trimoxazole and trimethoprim** can cause life threatening haematotoxicity

References

- 1) [BAD guidelines for prescribing Azathioprine in Dermatology:](#)
- 2) [BSG guidelines for management of inflammatory bowel disease in adults:](#)
- 3) BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs 2017 <https://academic.oup.com/rheumatology/article/3053478/BSR-and-BHPR-guideline-for-the-prescription-and?searchresult=1>
- 4) Azathioprine prescribing in neurology J Neurol (2008) 255:791–795

Azathioprine in Neurology.pdf
- 5). The Second European Evidenced-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease Journal of Crohn's and Colitis, Volume 9, Issue 2, 1 February 2015, Pages 107–124, <https://doi.org/10.1093/ecco-icc/jju006>

Useful information

This document does not replace the SPC and BNF and should be read in conjunction with it.

West Essex CCG webpage for Shared Cared Guidelines –

<https://westessexccg.nhs.uk/your-health/medicines-optimisation-and-pharmacy/shared-care-medicines/255-shared-care-letter/file>

Arthritis Research UK Patient Information Leaflet - Azathioprine

<http://www.arthritisresearchuk.org/arthritis-information/drugs/azathioprine.aspx>

Patient.co.uk Patient Information Leaflet - Mercaptopurine

<http://www.patient.co.uk/medicine/mercaptopurine-xaluprine>

CKS DMARDs

<http://cks.nice.org.uk/dmards#!scenario:1>

GMC Prescribing Guidance: Shared Care

<https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/shared-care>

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GP response to Shared Care Agreement

(only complete & send if NOT participating in shared care)

This shared care agreement has been approved by the Medicines Management Optimisation Programme Board June 2016

| | |
|---------------|---|
| Patient Name: | NHS No: |
| Consultant: | Medicine requested for shared care: Azathioprine / Mercaptopurine delete as appropriate |

I will **NOT** be undertaking the GP responsibilities as described in the agreed shared care agreement. My clinical reasons for declining shared care for this patient are listed in the box below:

Yours sincerely

{GP name}

{Surgery}

Please send a copy of this response to:


1. The specialist/consultant requesting shared care
2. **ANONYMISED COPY OF THIS FORM ONLY** to the E-MAIL: tpa-tr.ClinicalPharmacy@nhs.net

(sending a copy of this form to the PAH pharmacy will help to identify any inappropriate requests for shared care e.g. indication not covered, hospital monitoring requirements not fulfilled. It will also help to inform the CCG Medicines Optimisation Team of the reasons shared care is not being undertaken by GPs allowing for changes to be made in future updates to improve patient safety)

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P14064

The Princess Alexandra Hospital 
NHS Trust

Information for patients:

SHARED CARE:

Agreement information and confirmation

Hamstel Road
Harlow, Essex
CM20 1QX

Tel: 01279 444455

Patient name:

Medicine:

We would be grateful if you would take time to read this information as it will help us work with you to manage your condition and ensure safe prescribing of the specific medicine listed above.

What is a Shared Care Agreement?

A Shared Care Agreement (SCA) enables the care you have for a specific condition to be shared between the hospital and your GP.

The agreement means that the medicine the hospital has started, can be continued by your GP, so you won't have to visit the hospital to collect your medicine.

The SCA gives information on your medicine, guidance on the prescribing and monitoring responsibilities for your consultant (in the hospital), your GP and you. For an SCA to work everyone involved must understand it and communicate effectively.

Your consultant and your GP will need to sign the agreement and if you agree to this approach we would ask you to sign this letter, to indicate your agreement to have your care managed in this way.

How does Shared Care work?

Your consultant and GP share responsibility for your care.

The consultant is a specialist in your condition and will start prescribing your medicine, making sure it is suitable for you. There will come a point in your treatment when you may not need to be monitored by the consultant as often and this monitoring can be done by your GP.

Once your GP has agreed to the SCA, they will be able to prescribe the same medicine for you at the dose recommended by the consultant.

The organisation which regulates GPs, the General Medical Council, says that 'when a GP prescribes a medicine, the GP needs to satisfy themselves that the prescription is needed, appropriate for the patient and within the limits of their competence'.

So, your GP can only issue a prescription if the consultant and you keep to the responsibilities you have agreed (see below). If responsibilities are not kept or if the GP no longer feels it is safe to prescribe the medicine he/she will explain the reasons to you and your consultant, then prescribing responsibilities will be transferred back to the hospital.

What do I need to do to ensure the SCA can continue?

- ▶ **Attend hospital outpatients**
You must still attend the hospital for regular reviews as directed by your consultant (these maybe less frequent than before). If you do not attend your hospital appointments your GP will not be able to continue issuing prescriptions for this medication.
- ▶ **Attend GP appointments**
You must attend any appointments you have with your GP in relation to this medicine, so they can look after you effectively.

continued overleaf

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- ▶ Have blood tests as you have been advised to
Your consultant should have informed you if and how often you need to have blood monitoring tests. You can usually have your blood taken at an appropriate clinic and not need to go to the hospital.

If you do not have the blood monitoring tests as advised by your consultant, your GP will no longer be able to issue you with prescriptions as it would not be safe to do so.

What do I do if I am having side effects to the medicine?

Your consultant should have informed you of the common side effects to expect and what to do if you experience them. If you think you may be having side effects from a medicine discuss these with your pharmacist and GP. Your GP may need to seek advice from your consultant before issuing you with another prescription; this is to ensure it is safe for you to continue on the medication.

What if my disease symptoms change or get worse?

Report any changes in disease symptoms or circumstances that could affect management of your disease to your GP.

What about the other medicines I take?

Inform your GP and the consultant of all other medicines you are taking, including those you may have bought yourself. Do not take new medicines (including those you could buy) until you have discussed this with your pharmacist, GP or consultant.

If you would like to go ahead with a shared care agreement for the specific medication identified on page 1, please sign below to confirm that you:

- ▶ Understand the shared care agreement
- ▶ Are happy to have your care for this aspect of your health managed by a shared care agreement
- ▶ You agree to attend regular review appointments as requested
- ▶ You agree to have blood tests as required

Patient's signature

Date

Print name

If at any point in time you would like this shared care agreement to stop, please talk to your GP.