

Effective Shared Care Agreement for Azathioprine for non-rheumatological indications

This local safety monitoring schedule supports clinicians providing shared care under the Local Enhanced Service for High Risk Drug Monitoring (formerly Near Patient Testing)

This shared care agreement outlines suggested ways in which the prescribing responsibilities can be shared between the specialist and GP. GPs are invited to participate. If the GP feels that undertaking the roles outlined in the shared care agreement is outside their area of expertise or have clinical concerns about the safe management of the drug in primary care, then he or she is under no obligation to do so. In such an event, clinical responsibility for the patient's health remains with the specialist. If a specialist asks the GP to prescribe, the GP should reply to this request as soon as practicable. Sharing of care assumes communication between specialist, GP and patient.

| Consultant details | GP details | Patient details |
|--------------------|-----------------|-----------------|
| Name: | Name: | Name: |
| Address: | Address: | NHS Number: |
| Email: | Email: | Date of birth: |
| Contact number: | Contact number: | Contact: |

Signing indicates agreement with the responsibilities suggested in this document, and that the patient has been informed of the need to report any issues with their treatment to their doctor.

| | |
|------------------------------|--|
| Specialist signature: | General Practitioner signature: |
| Date: | Date: |

Introduction

Azathioprine is an immunosuppressant antimetabolite drug that interferes with nucleic acid synthesis. Azathioprine is extensively metabolised to mercaptopurine *in vivo*.

Licensed indications: inflammatory bowel diseaseⁱ

Unlicensed indications: Psoriatic arthritis; severe refractory eczema; atopic dermatitis; psoriasis

For rheumatological indications for azathioprine, please consult the separate rheumatology ESCA.

Adult dosage and administration

Dosage regimens may vary between 1 - 3 mg/kg daily orally specific to the patient and the condition.

Dosage may need to be reduced in renal or hepatic impairment, and in the elderly.

Preparations available:

- Azathioprine 25mg, 50mg tablets

Specialist responsibilities

- Discuss with the patient the different options for treatment and the suitability of azathioprine, including the potential benefits and side-effects of treatment with the patient.
- Provide the patient/carer with relevant (written) information on use, side-effects and need for monitoring for infection.
- **Advise on need for adequate contraception.**
- Provide shared care monitoring record booklet if required
- Arrange pre-treatment baseline investigations

- Baseline tests:
 - **FBC**
 - **LFT**
 - **U&Es + creatinine**
 - **TPMT** result prior to treatment (1 in 300 individuals have complete deficiency of this enzyme and must not receive any dose of azathioprine. Note that TPMT only predicts haematological toxicity)
- Review results of safety monitoring and request additional tests as required
- Titrate azathioprine to an effective dose and stabilise the patient on an appropriate maintenance dose before seeking to initiate shared care
- Monitor disease response to treatment and need to continue therapy
- Once patient stabilised, transfer prescribing and monitoring to GP when agreed
- Provide GP with clear written advice on required dosage and frequency of azathioprine, written monitoring guidelines and drug information. Check for interactions with other medicines.
- Continue to review the patient at agreed specified intervals (at least annually), sending a written summary to the GP whenever the patient is reviewed
- Advise GP on dosage adjustment and when and how to stop treatment
- Have mechanisms in place to allow rapid referral of patients from GP in the event of deteriorating clinical condition
- Provide any other advice or information for the GP if required
- Report adverse events to the MHRA via Yellow Card Scheme
- Varicella Zoster- consider immunisation of non-immune patients before starting immunosuppression (after discussion with appropriate specialist)

Primary Care responsibilities

- Prescribe azathioprine at the dose recommended if patient is having appropriate regular blood monitoring and monitoring results are within acceptable range
- **Repeat prescriptions should be removed from the surgery repeat pile and retained separately for prescribers to review prior to signing. Maximum of 28 days' supply recommended.**
- Arrange and record ongoing monitoring as agreed with specialist:
 - **FBC & LFT:** weekly for at least 6 weeks, continue every 2 weeks until dose is stable for 6 weeks. When stable, monthly thereafter. When the disease, dose and blood monitoring is stable for 6 months, the FBC and LFT can be reduced to 3 monthly. After dose increase, repeat FBC and LFTs after 2 weeks and then monthly. When patient dose and test results are stable for 6 months, consider discussing with patient reducing monitoring frequency for FBC and LFTs to 3 monthly.ⁱⁱ
 - **U&Es and creatinine:** every 6 months
- Report any adverse drug reactions to the initiating specialist and the usual bodies (e.g. MHRA)
- Ensure no drug interactions with other medicines
- Administer influenza vaccine annually unless otherwise advised by the initiating specialist
- Check patient is using adequate contraception
- Check patient has had ONE DOSE of pneumococcal vaccine (revaccination is not recommended except every five years in patients whose antibody levels are likely to have declined more rapidly e.g. asplenia.) - see BNF or Green Book
- Varicella zoster
 - *Non-immune patients* should avoid contact with people with chicken pox or shingles; consider passive immunisation using Varicella immunoglobulin (VZIG) if exposure if suspected (contact Public Health England/ Blood Transfusion Service for advice)
 - Varicella infection can be severe in immunocompromised patients, and early systemic anti-viral and supportive therapy may be required. Suspend azathioprine if possible until recovered (consult specialist).
- Ask about oral ulceration/sore throat, unexplained rash or unusual bruising at every consultation
- Ensure a clinician updates the patient's record following specialist review

Withhold azathioprine and contact specialist if:ⁱⁱ

- WCC <math>< 3.5 \times 10^9/L</math>
- Neutrophils <math>< 2 \times 10^9/L</math>
- Platelets <math>< 150 \times 10^9/L</math>
- AST/ALT/ALP/GGT >2 times the upper limit of normal
- MCV >105 fL (check serum folate, B12 and TSH. Treat any underlying abnormality. If results normal, discuss with specialist team)
- Oral ulceration/sore throat
- Unexplained rash or unusual bruising
- Treatment for acute infections

Please note: a rapid increasing or decreasing trend in any values should prompt caution and extra vigilance. Some patients may have abnormal baseline values, specialist will advise. Results should be recorded in the patient's monitoring booklet.

Adverse effects, Precautions and Contra-indications

General signs of malaise such as headaches, dizziness, diarrhoea, rash, myalgia and arthralgia occur infrequently. If severe or persistent refer to initiating specialist. **Note: drug hypersensitivity may manifest as severe nausea, vomiting, rash or fever, and precipitous leucopenia, requiring immediate drug withdrawal and supportive therapy as necessary.**

Nausea can occur initially but can be reduced by taking the tablets after food.

Leucopenia, anaemia and thrombocytopenia: GPs should be alert to any oral ulceration/ sore throat, unexplained rash or abnormal bruising or bleeding.

Abnormal liver function can occur early in treatment.

Pancreatitis has been reported in a small percentage of patients.

Pregnancy / Contraception: women of childbearing potential and men receiving azathioprine should be advised to use effective contraception. Patients discovered or planning to become pregnant should be referred to the initiating specialist at the earliest opportunity without discontinuing azathioprine.

Breastfeeding: Women being treated with azathioprine should not breastfeed

Cancer risk: Patients receiving azathioprine are at increased risk of lymphomas and malignancies of the skin: avoiding excessive exposure to the sun and use of high factor sunscreens are advised.

Contraindications

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

TPMT deficiency - avoid if deficient or reduce dose if low levels.

Azathioprine therapy should not be initiated in patients who may be pregnant, or who are likely to become pregnant without careful assessment of risk versus benefit. If breast-feeding, consult with specialist.

Live Vaccines should be avoided (see Green Book re varicella zoster shingle vaccine).

Common Drug Interactions

The following drugs should not be initiated by a GP unless discussed with the initiating specialist:ⁱⁱⁱ

Warfarin: effect may be reduced requiring an increased dose of warfarin

Aminosalicylates: e.g. sulfasalazine: contribute to bone marrow toxicity – increased monitoring may be required

Febuxostat – avoid as per SPC

Trimethoprim or **Co-trimoxazole:** potential risk of haematological abnormalities

Phenytoin, sodium valproate, carbamazepine: absorption may be reduced

ACE inhibitors: rarely co-prescription may cause anaemia- if significant consider alternative to ACEI or different DMARD

Do **not** prescribe concomitant **Allopurinol** due to risk of severe myelosuppression, unless expressly requested by the specialist. **Azathioprine should be reduced to one quarter (25%) of the original dose.**

Communication

For any queries relating to this patient's treatment with azathioprine, please contact the consultant named at the top of this document.

**This information is not inclusive of all prescribing information, potential adverse effects and drug interactions
Please refer to full prescribing data in the Summary of Product Characteristics (www.medicines.org.uk) or the
British National Formulary (www.bnf.org)**

Adapted with kind permission from work by MG, NHS Telford and Wrekin CCG Medicines Management

ⁱ British National Formulary, Edition 68, Sections 1.5.3 and 13.5.3. Azathioprine

ⁱⁱ Suggestions for Drug Monitoring in Adults in Primary Care. NHS UKMi, February 2014. Available at www.evidence.nhs.uk

ⁱⁱⁱ Imuran Tablets 25mg – Summary of Product Characteristics. Available at www.medicines.org.uk/emc/medicine/2881