Azathioprine for rheumatoid arthritis and other rheumatological diseases (Adults)

It is vital for safe and appropriate patient care that there is a clear understanding of where clinical and prescribing responsibility rests between Consultants and General Practitioners (GPs). This guideline reinforces the basic premise that:

When clinical and/or prescribing responsibility for a patient is transferred from hospital to GP, the GP should have full confidence to prescribe the necessary medicines. Therefore, it is essential that a transfer of care involving medicines that a GP would not normally be familiar with, should not take place without the “sharing of information with the individual GP and their mutual agreement to the transfer of care.”

These are not rigid guidelines. On occasions, Consultants and GPs may agree to work outside of this guidance. As always, the doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

**Indications:**
Azathioprine is used in the management of severe rheumatoid arthritis, psoriatic arthritis, and other rheumatological conditions.

**Dosage and administration:**
Usual starting dose is 1mg/kg/day, increased after 4-6 weeks to 2-3mg/kg/day.

N.B. Please see p3 for strengths of preparations available.

When the therapeutic response is evident, this dose can be maintained, although consideration should be given to reducing the maintenance dose to the lowest level that maintains the response.

Patients with renal or hepatic insufficiency should be given the lowest effective dose.

**Additional Information**
- Mercaptopurine is the active metabolite of azathioprine.

**Monitoring requirements:**

**Before treatment:**
- Full blood count (FBC) including platelets, urea and electrolyes (U&Es), creatinine and liver function tests (LFTs)
- Test for thiopurine methyl transferase (TPMT), as a deficiency increases the risk of myelosuppression

**During treatment:**
- FBC, LFTs, U/Es and creatinine weekly for the first month then monthly thereafter if stable
- If dose is increased, repeat FBC and LFTs after 2 weeks, and then return to monthly.
- Annual fasting lipids (HDL, Cholesterol, HDL/Cholesterol ratio)
- ESR monthly for disease monitoring purposes

**Responsibility for monitoring rests with the GP**

**Action to be taken if abnormal results/adverse effects:**
- WBC < 3.5 x 10^9/l Check neutrophil count
- Neutrophils < 2.0 x 10^9/l Monitor weekly. If it falls below 1.5 x 10^9/l STOP DRUG and contact helpline.
- Platelets < 150 x 10^9/l Monitor weekly. If drop below 100 x 10^9/l contact helpline
- 3 fold rise in ALT/AST Monitor weekly. If ALT continues to rise, contact helpline.
- Rash Mild: drug can be continued at reduced dose if necessary. Severe: STOP DRUG and contact helpline
- Oral ulceration Repeat FBC and act on results as above
### Contraindications:
- TPMT deficiency (homozygous state). Avoid, can be fatal.
- Azathioprine should not be given to women who are pregnant, or likely to become pregnant without a careful assessment of risk versus benefit.
- Breastfeeding
- Hypersensitivity to azathioprine or mercaptopurine
- Live vaccines are contra-indicated in patients receiving azathioprine on theoretical grounds.

### Drug interactions:
- Azathioprine activity is inhibited by allopurinol - avoid co-prescription where possible. If essential, contact helpline for advice on azathioprine dose reduction
- Azathioprine can inhibit the anticoagulant effect of warfarin.
- Avoid co-prescription of co-trimoxazole (sulfamethoxazole + trimethoprim) as increased risk of haematological toxicity.
- For patients with a deficiency (heterozygous state) of the TPMT enzyme, lower doses of azathioprine should be used and it should also be administered with caution in patients receiving aminosalicylate derivatives eg olsalazine, mesalazine or sulfasalazine as these drugs inhibit TPMT.
- A diminished response to killed vaccines is likely.

### Cautions:
- TPMT deficiency (heterozygous state). May be associated with delayed haematotoxicity including bone marrow toxicity.
- Renal or hepatic insufficiency may enhance the toxicity of azathioprine. The haematological response should be carefully monitored and doses at the lower end of the range should be used.
- Increased risk of skin cancers; avoid exposure to sunlight and UV light by using sunscreen and protective clothing.

### Adverse Effects:
Hypersensitivity reactions (incl. malaise, dizziness, vomiting, diarrhoea, fever, myalgia, arthralgia, rash, hypotension & interstitial nephritis) - requires immediate withdrawal
Depression of bone marrow function, leucopenia, thrombocytopenia, anaemia and other blood disorders.
Alopecia and increased risk of infections and colitis for patients also receiving corticosteroids.
Neoplasms, including non-Hodgkin’s Lymphomas, skin cancers, sarcomas and uterine cervical cancer.
Nausea, hepatic impairment
**Specialist responsibilities:**
- Confirm the rheumatological diagnosis or indication for azathioprine.
- Discuss with the patient the benefits and side effects of treatment with azathioprine.
- If the patient is a woman of child bearing potential – ensure that they are aware of the importance of effective contraception and the need to discuss with their consultant if they wish to become pregnant.
- Ensure that the patient understands and accepts their responsibilities (see section below).
- Seek consent for treatment and document in the patient’s notes.
- Ensure baseline monitoring of full blood count and biochemical profile.
- Discuss how the patient / carer can be aware of possible signs of azathioprine toxicity or intolerance.
- Provide written instruction to the GP for initiation and escalation of azathioprine.
- Provide the patient with a shared care booklet and enter the blood results into the booklet.
- Review the patient at the intervals specified below to monitor the patient’s disease activity, the efficacy of the treatment and the ability to tolerate it, and consider whether continuation of treatment is appropriate.
- Discontinue if no response or patient has a significant adverse effect.
- Promptly communicate with the GP via a clinic letter any changes in treatment, results of monitoring undertaken, and assessment of adverse events. The clinic letter should clearly state if the dose has remained the same or if a dose adjustment had been made – specifically highlighting the new dose in comparison with the preceding one.
- Advise GPs when to stop treatment.
- Provide clear arrangements for back-up, advice and support.
- Report serious adverse events to the Committee on Safety of Medicines (CSM).

**GP's responsibilities:**
- Initial referral to Consultant Rheumatologist raising the possibility of rheumatological disease.
- Provide the patient with monthly repeat prescriptions of medication following written instructions for initiation and escalation by the specialist. The patient should allow at least 48 hours for the prescription from the GP to be generated.
- Continue monitoring as outlined on the first page and document the results in the shared care booklet.
- Ensure patient’s shared care booklet and practice computer system are updated with any dose changes.
- Refer promptly to the specialist if there is a change in the patient’s status or concerns regarding compliance. In most cases, do not stop treatment without discussion with the Rheumatology Helpline.
- If patient fails to attend more than 2 monitoring visits it is not safe to continue treatment – contact the Rheumatology Helpline for advice.
- Report serious adverse events to the specialist and CSM.
- Administer Pneumococcal Vaccine/ Pneumovax® II and annual influenza vaccines.
- Consider passive immunisation with Varicella zoster immunoglobulin in non-immune patients exposed to chicken pox or shingles.

**Patient responsibilities:**
- Read the written information provided about the drug and have a clear understanding of the risks / benefits of oral azathioprine treatment.
- Attend for blood tests.
- Report any adverse effects to their GP and/or specialist whilst treated with azathioprine.
- Limit alcohol to national safe weekly limits.
- Take monitoring booklet every time the patient sees the GP, has a hospital appointment or visits the pharmacist.
**Secondary care review:** During initiation: 4 – 6 weekly until controlled

**Once disease controlled:** Annual review by consultant

**Availability:**
- 25mg tablet: 28 = £4.81 100 = £10.59
- 50mg tablet: 56 = £3.99 100 = £6.72

*Prices from November 2011 Drug Tariff*

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<th>Back up advice and support:</th>
<th>Telephone: 0151 604 7505</th>
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<td>Rheumatology Helpline</td>
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