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:	**Dosage and administration:**
Azathioprine is used in the management of severe rheumatoid arthritis, psoriatic arthritis, and other rheumatological conditions	Usual starting dose is 1mg/kg/day, increased after 4-6 weeks to 2-3mg/kg/day. N.B. Please see p4 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. Lower doses should be used in frail elderly patients and those with significant renal or hepatic disease

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)
- Thiopurine methyl transferase (TPMT) enzyme activity, deficiency increases the risk of myelosuppression

During treatment:

- FBC, LFTs, U/Es and creatinine weekly for the first month then monthly for 3 months, then every 2 months 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 (discretionary) 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. Mild: salt water mouth wash. Moderate: Hydrocortisone (Corlan) pellets (1 applied to affected area qds). Severe: Hydrocortisone (Corlan) pellets and contact helpline
- MCV > 100fl — Check B12, Folate and TSH and, if low, start appropriate supplements
- Significant deterioration in renal function. Contact Helpline for advice on dose reduction
- Abnormal bruising — Repeat FBC and act on results as above
- Sore throat — Repeat FBC and act on results as above
- Acute abdominal symptoms of pancreatitis STOP drug
- Fever, arthralgia, myalgia on starting STOP drug
- Nausea — Usually self-limiting, take after meal

Please note that in addition to absolute values for haematological indices, a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.

Contraindications:

- TPMT deficiency (homozygous state). Avoid, can be fatal.
- Seriously impaired hepatic or bone marrow function
- Azathioprine should not be given to women who are pregnant, or likely to become pregnant without a careful assessment of risk versus benefit.
- Breastfeeding
- Pancreatitis
- Severe infections
- Hypersensitivity to azathioprine or mercaptopurine
- Live vaccines are contra-indicated in patients receiving azathioprinedue to impaired immune response. .

Drug interactions: check current BNF Appendix 1 before co-prescribing any other drugs

- Allopurinol: azathioprine activity is inhibited,-avoid co-prescription where possible. If essential, reduce azathioprine dose by a quarter
- Warfarin (coumarins): azathioprine can inhibit the anticoagulant effect ofcoumarins.
- Greater risk of excessive immunosuppression if azathioprine is combined with other immunosuppressants, such as cyclosporin or tacrolimus.
- Co-trimoxazole (sulfamethoxazole + trimethoprim): avoid co-prescription of increased risk of haematological toxicity.
- Aminosalicylates, such as mesalazine, olsalazine and sulphasalazine, may increase the risk of leucopenia with azathioprine/mercaptopurine as they inhibit the effects of thiopurine
- methyltransferase (TPMT).
- A diminished response to killed vaccines is likely.
- Concomitant therapy with azathioprine and ACE-inhibitors, trimethoprim/ sulpfamethoxazole, cimetidine or indomethacin increases the risk of myelosuppression

Cautions:

- **TPMT deficiency** (heterozygous state). May be associated with delayed haematotoxicity including bone marrow toxicity, **lower doses of azathioprine should be used**
- 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.

- Note for handling: Azathioprine is mutagenic and potentially carcinogenic. When handling this substance appropriate precautions must be taken. This should be especially considered in pregnant Healthcare Professionals
- Withdrawal of azathioprine should always be a gradual process performed under close monitoring
- Patients receiving immunosuppressive therapy are at slightly increased risk of developing lymphomas and other malignancies, notably skin cancers – exposure to sunlight and UV light should be limited and patients should be advised to wear protective clothing and use a sunscreen with a high protection factor.

Adverse Effects:

Hypersensitivity reactions (incl. malaise, dizziness, vomiting, diarrhoea, fever, myalgia, arthralgia, Pancreatitis, 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, 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 monitoring 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 at https://yellowcard.mhra.gov.uk/

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 monitoring 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 at https://yellowcard.mhra.gov.uk/
- 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 = £2.63
50mg tablet: 56 = £2.79
Prices from Online Electronic Drug Tariff February 2016

Back up advice and support: Rheumatology Helpline		**Telephone:** 0151 604 7505
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