

Azathioprine

Rheumatology Local Safety Monitoring Schedule

This local safety monitoring schedule supports clinicians under the Local Enhanced Service for High Risk Drug Monitoring (formerly Near Patient Testing). Aligning clinical and prescribing responsibility enhances patient safety because the individual signing the prescription will also be responsible for ensuring that any necessary monitoring has been undertaken and will have access to the results of this.

The prescriber and specialist assume joint clinical responsibility for the drug and the consequences of its use.

Specialist details	GP details	Patient details
Name:	Name:	Name:
Address:	Address:	Contact number:
Email:	Email:	
Contact number:	Contact number:	

Introduction

Azathioprine is an immunosuppressant antimetabolite drug that interferes with nucleic acid synthesis.

Azathioprine is a pro-drug extensively metabolised to the active mercaptopurine in vivo.

Licensed indications: Severe rheumatoid arthritis; systemic lupus erythematosus, dermatomyositis and polymyositis

Unlicensed indications: Psoriatic arthritis, steroid sparing agent in miscellaneous situations such as giant cell arteritis, maintenance therapy in systemic vasculitis

Adult dosage and administration

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.

Preparations available:

- Azathioprine 25mg, 50mg, 100mg tablets. Due to the variation in bioavailability between different generic preparations please prescribe as Imuran tablets.

It may take up to 3 months for significant response to be achieved.

Specialist responsibilities

- 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.
- Provide the patient/carer with relevant (written) information on use side effects and need for monitoring for infection.
- Advise on need for adequate contraception, although azathioprine can be used during pregnancy if the benefits outweigh the risks.
- Provide shared care monitoring record booklet if required.
- Arrange pre-treatment baseline investigations.
- Baseline tests:
 - **FBC**
 - **LFT**
 - **U&Es + creatinine**

- **TPMT** result must be known 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.
 - **ESR & CRP**
 - **Varicella zoster IgG in suspected non-immune patients** and notify general practitioner as appropriate
- Review results of safety monitoring and request additional tests as required.
 - Monitor disease response to treatment and need to continue therapy.
 - Continue to review the patient at agreed specified intervals, sending a written summary to the GP whenever the patient is reviewed.
 - Provide any other advice or information for the GP if required.
- Identify and report adverse events to the GP and the MHRA (via yellow card).

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 repeats pile and retained separately for prescribers to review prior to signing. Maximum 28 days supply.
- 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, and if stable monthly thereafter. After a dose increase, repeat FBC and LFTs after 2 weeks and then monthly. Selected patients* may be reduced to 3 monthly testing if disease, dose and blood monitoring are stable for 6 months, if recommended by the specialist. (* except TPMT heterozygotes)
 - **U&Es and creatinine:** every 6 months
 - **CRP & / or ESR** may be done every 3 months.
- Patients on combination DMARD therapy may need more frequent monitoring. Please check the Local Safety Monitoring Schedule for each drug.
- 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 is suspected (contact Public Health England/Blood Transfusion Service for advice). Consider active immunisation of non-immune subjects before starting immunosuppression (if recommended by specialist)
- Varicella infection can be severe in immunosuppressed patients, and early systemic anti-viral and supportive therapy may be required. Suspend azathioprine if possible until recovered.
- Ask about oral ulceration/sore throat, unexplained rash or unusual bruising at every consultation.
- If patient develops symptoms/signs of systemic infection, this should be treated promptly and azathioprine withheld until the infection has cleared.
- Ensure a clinician updates the patient's record following specialist review.

Withhold azathioprine and contact specialist if:

- WCC < 3.5 x 10⁹ /L
- Neutrophils < 2 x 10⁹ /L
- Platelets < 150 x 10⁹ /L
- AST/ALT > 2 times the upper limit of normal
- MCV >105 fl check serum folate and B12 & TSH. Treat any underlying abnormality. If results normal discuss with specialist team.
- eGFR <30 ml/min
- Oral ulceration/sore throat
- Unexplained rash or unusual bruising

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 and Precautions

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 if 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. Selected patients will be advised to continue with azathioprine during pregnancy, if benefits exceed risks, BUT DOSE MAY BE REDUCED AT 32 WEEKS to reduce risk of neonatal bone marrow suppression.

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: excessive sun exposure should be avoided, and use of high-factor sunscreens are advised.

Contra-indications

Contraindications include:

Hypersensitivity to azathioprine or 6-mercaptopurine (see above)

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

Live Vaccines should be avoided during treatment, and consider live vaccines prior to commencing methotrexate (see Green Book re zoster vaccine)

Common Drug Interactions

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

Aminosalicylates: e.g. sulfasalazine, mesalazine: contribute to bone marrow toxicity – increased monitoring may be required and reduced dosage of azathioprine

Methotrexate: avoid concomitant usage due to increased risk of bone marrow toxicity

Febuxostat – avoid as per SPC

Trimethoprim or Co-trimoxazole: potential risk of life-threatening haematotoxicity

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. If used **azathioprine dosage should be reduced to one quarter 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 SPC or the BNF

References

GMC: Prescribing guidance: Shared care www.gmc-uk.org/guidance/ethical_guidance/14321.asp(accessed 20/10/2014)

NMC : Standards of proficiency for nurse and midwife prescribers <http://www.nmc-uk.org/Documents/NMC-Publications/NMC-Standards-proficiency-nurse-and-midwife-prescribers.pdf> (accessed 3/11/2014)

SPC Azathioprine : <http://www.medicines.org.uk/emc/medicine/26877>

Chakravarty, K., McDonald, H., Pullar, T. et al. (2008) BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology* **47**(6), 924-925.