

Azathioprine

Traffic light classification- Amber 1
Information sheet for Primary Care Prescribers

Management of Inflammatory Bowel Disease in children over 12 years old with AZATHIOPRINE

Indications

Maintenance of remission of acute ulcerative colitis and Crohn's disease in children – off-label but in line with national guidelines

Any patient groups to be excluded from shared care

Patients receiving azathioprine for an indication classified as **RED** on the Nottinghamshire traffic light list, e.g. for suppression of organ transplant rejection.

Patients under the age of 12 years

Therapeutic Summary

In Inflammatory Bowel Disease the imidazole purine analogue, Azathioprine is used in patients with steroid dependent, frequently relapsing disease. Azathioprine is generally the immunosuppressant of choice.

The exact mode of action is unknown.

Products available

Azathioprine 25mg and 50 mg tablets (off-label)

Dosage and route of administration

Azathioprine is given orally. Patients with a low TPMT will be started on a low dose of 1mg/kg/day. The maintenance dose for patients with normal TPMT levels is 2mg/kg/per day. This can be taken as a once daily dose, or divided into 2 doses per day.

Duration of treatment

Azathioprine has a cumulative action and a clinical improvement can take up to 3 months. Once stabilised on treatment it can be continued for a number of years.

Monitoring Requirements and Responsibilities

Pre-treatment assessment to be performed by the specialist and will include:

- FBC, U&Es, LFTs, CRP, ESR and thiopurine methyltransferase (TPMT) assay, chickenpox and measles immunity screening.
- Care should only be transferred to the GP when the patient is stable, established on treatment and arrangements for taking blood samples in primary care has been confirmed.

Ongoing monitoring:

Time period in treatment	Frequency of monitoring	FBC	LFTs	U&Es	ESR and CRP
0 - 4 weeks	Weekly	✓	✓	✓	
4 weeks – 8 weeks	Fortnightly	✓	✓	✓	✓
8 weeks – 4 months	Monthly	✓	✓	✓	✓
Dose and monitoring stable for >4 months*	2 monthly*	✓	✓	✓	✓
Any dose change	Weekly for 2 weeks then monthly followed by reducing frequency as per this table.	✓	✓		

*** The Gastroenterology Specialist team may advise more frequent monitoring for patients heterozygote for TPMT (increased risk of toxicity).**

- Monitoring results should be accessible to all clinicians involved in the patients' care.
- Patients should report any rash, oral ulceration, sore throat, abnormal bruising or bleeding
- Each patient will be seen at least annually by a gastroenterologist/ IBD specialist
- No additional monitoring requirements are required in primary care for patients receiving additional biological therapy including anti- TNF therapy.
- Routine influenza and pneumococcal vaccinations are highly recommended.

There is variation in children and young people's community phlebotomy services in Nottinghamshire. Practitioners are advised to consult their local service provider.

Explicit criteria for review and discontinuation of the medicine - Other benchmark values may be set by secondary care in specific clinical circumstances. This will be communicated by secondary care.

Adverse Event	Action
Nausea, vomiting or diarrhoea	Ensure patient is taking tablets with food. Withhold until discussed possible dose reduction with gastroenterology specialist team.
Severe general malaise	This maybe part of a hypersensitivity reaction. Withhold until discussed with gastroenterology specialist team.
WBC <3	Notify patient and repeat blood count in one week
Neutrophils <1.5	Repeat blood test in 1 week
Neutrophils <1	Withhold until discussed with gastroenterology specialist team.
Platelets – if halved from previous value	Withhold until discussed with gastroenterology specialist team.
AST, ALT > twice upper limit of reference range	Withhold until discussed with gastroenterology specialist team.
Rash or oral ulceration	Withhold until discussed with gastroenterology specialist team.
Abnormal bruising/ fever/ severe sore throat	Withhold until FBC results available and discuss with gastroenterology specialist team.
Severe abdominal pain	Withhold and consider pancreatitis, measure amylase and discuss with gastroenterology specialist team

In addition to absolute values for haematological indices a rapid fall or consistent downward trend in any values should prompt caution and extra vigilance

For a full list of side effects refer to the BNF or Summary of Product Characteristics

IF YOU ARE IN ANY DOUBT ABOUT ANY POTENTIAL ADVERSE REACTION, PLEASE CONTACT THE GASTROENTEROLOGY SPECIALIST TEAM:

Amy-Jo Hooley - Specialist Clinical Pharmacist NUH

Lucy Davies – Specialist Nurse NUH

David Devadason – Consultant NUH

Relevant contraindications

- Known hypersensitivity to azathioprine and/or 6-mercaptopurine.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at <https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book> - **chapter 6**: Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. N.B. Routine influenza and pneumococcal vaccinations are highly recommended.
- Pregnancy. Azathioprine has been safely used in pregnancy; however men and women wishing to start a family should be discussed with the specialist team.
- Breast feeding.
- Severe hepatic impairment.

Relevant precautions

- Localised or systemic infection including hepatitis B or C and history of tuberculosis.
- Renal impairment. Dose reduction may be required in moderate or severe renal impairment. Please discuss with the gastroenterology specialist team.
- Patients who have no history of exposure to varicella zoster virus (VZV) i.e. chickenpox or herpes zoster (shingles), should avoid contact with individuals with chickenpox or herpes zoster. Varicella-zoster immunoglobulin (VZIG) is recommended for individuals who are at increased risk of severe varicella (including patients taking immunosuppressant medicines e.g. azathioprine, ciclosporin, methotrexate, leflunomide) and who have no antibodies to varicella-zoster virus and who have significant exposure to chickenpox or herpes zoster. Contact the on-call microbiologist via the hospital switchboard for advice if required.
See <https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book> – chapter 34 for detailed guidance. If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.
- Patients should be advised to limit exposure to sunlight and UV light and sunscreens and protective covering should be encouraged to reduce sunlight exposure.
- Patients heterozygote for TPMT – use with caution due to increased risk of toxicity. The Gastroenterology Specialist Team will recommend increased monitoring if necessary.

Clinically relevant medicine interactions and their management

- Co-trimoxazole and trimethoprim should be avoided – can cause life threatening haematotoxicity.
- Allopurinol: enhanced effects and increased toxicity of azathioprine when given with allopurinol (reduce dose of azathioprine to one quarter of usual dose)
- Warfarin: Azathioprine inhibits the anticoagulant effects of warfarin. Consider increasing the dose of warfarin and monitor closely.
- Phenytoin, sodium valproate, carbamazepine absorption may be reduced by azathioprine.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at <https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book> - chapter 6): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. Inactivated polio is available although a suboptimal response may be seen.
- ACE inhibitors – increased risk of leucopenia.

For a full list of contraindications, precautions and drug interactions refer to the Summary of Product Characteristics

Information given to patient

- Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. inexplicable bruising or bleeding, infection.
- Patients should be advised to limit exposure to sunlight and UV light and sunscreens and protective covering should be encouraged to reduce sunlight exposure.
- Patients should be advised to avoid contact between themselves and individuals with chickenpox or shingles if they have no prior history of exposure. Any exposure of patients with no varicella–zoster virus antibodies to chickenpox and shingles sufferers, should be reported to the GP for assessment and possible treatment.
- The patient will be given details of their treatment, follow up appointments, monitoring requirements and nurse specialist contact details.

Patient's roles and responsibilities

- To attend for regular blood tests.
- The patient will report any suspected adverse reactions (as above) to the GP for assessment.

References

1. Imuran tablets 25mg Summary of Product Characteristics. Last updated on www.emc.medicines.uk 22/05/2012. [accessed 8/7/14]
2. 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.
3. [BNF Online](#).
4. NICE Guidance CG152 Oct 2012. Crohns Disease: Management in adults, children and young people. [accessed 08/08/14]
5. Baxter K (ed), *Stockley's Drug Interactions*. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com
6. Ashley C, and Currie A [Eds]. *The Renal Drug Handbook* [3rd edition] Oxford: Radcliffe Publishing Ltd [2009].

There are no current NICE guidelines on the use of azathioprine for Inflammatory Bowel Disease.