Azathioprine

Traffic light classification- Amber 1
Information sheet for Primary Care Prescribers
Part of the Shared Care Protocol: Management of Inflammatory Bowel Disease in ADULTS with AZATHIOPRINE, 6-MERCAPTOPURINE or METHOTREXATE

Indications:
Maintenance of remission of acute ulcerative colitis and Crohn's disease in adults – unlicensed but in line with national guidelines[4].

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.
Children (under 18 years of age).

Therapeutic summary:
In Inflammatory Bowel Disease the imidazole purine analogues, Azathioprine and Mercaptopurine, are used in patients with steroid dependent, frequently relapsing disease. Azathioprine is generally the immunosuppressant of choice, but if azathioprine treatment fails, its active metabolite mercaptopurine may be tolerated.
Azathioprine and mercaptopurine appear identical in their pharmacologic and biologic effects, but their exact mode of action is unknown.

Products available[1]
Azathioprine 25mg and 50 mg tablets (off-label).

Dosage and route of administration:
Azathioprine is given orally as a single daily dose. The usual maintenance dose is in the range of 100mg-200mg/day (2-2.5mg/kg daily) [4].

Azathioprine should not be taken with dairy products
(At least 1 hour before or 2 hours after any dairy containing food and drink)

Duration of treatment: [1]
Treatment is usually continued for a minimum of 12 months if there is a good clinical response. Azathioprine has a cumulative action and a clinical improvement can take up to 3 to 4 months.

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

- FBC, U&Es, LFTs, and thiopurine methyltransferase (TPMT) assay.

Ongoing monitoring[2, 4]**:**

Time period in treatment	Frequency of monitoring	Tests to be done		
		FBC	LFTs	U&Es
0 - 6 weeks	Fortnightly	✓	✓	✓
6 weeks - 3 months	Monthly	✓	✓	✓
>3 months and stable dose for 6 weeks	3 monthly*	✓	✓	✓
Any dose increase	2 weeks post dose increase then revert to above protocol	✓	✓	✓
* The Gastroenterology Specialist team may advise more frequent monitoring for patients heterozygote for TPMT (increased risk of toxicity).				

- Patients should report immediately any evidence of infection, rash, oral ulceration, sore throat, abnormal bruising or bleeding, or other manifestations of bone marrow depression.
- 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.

Explicit criteria for review and/or discontinuation of the medicine[2, 4]:
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 or continue drug with split dosing. In some individual, nausea will normally resolve after a few days. If troublesome prescribe antiemetic. If recurs then withhold until discussed possible dose reduction with gastroenterology specialist team.
Severe general malaise and flu-like symptoms	This may be an early hypersensitivity reaction. Withhold until discussed with gastroenterology specialist team.
WBC 3.5 - 4 $x10^9$/l	Notify patient and repeat blood count in one week
WBC <3.5 $x10^9$/l	Withhold until discussed with gastroenterology specialist team.
Neutrophils <1.6 $x10^9$/l	Withhold until discussed with gastroenterology specialist team.
Platelets <140 $x10^9$/l	Withhold until discussed with gastroenterology specialist team.
AST, ALT > twice upper limit of reference range and/or unexplained reduction in albumin <30 g/l	Withhold until discussed with gastroenterology specialist team.
Rash or oral ulceration	Withhold until discussed with gastroenterology specialist team.
Macrocytosis (MCV > 105 fL)	This does not usually signify a medical problem. Check serum folate and B12 & TSH. Treat any underlying abnormality. If result is normal, interrupt treatment until discussed with gastroenterology specialist team. (If macrocytosis is non-progressive, no action is required. If worse, contact the specialist team).
Unexplained eosinophilia >0.5 x 10^9/l	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.

Relevant contraindications[1, 2, 4]**:**

- Known hypersensitivity to azathioprine and/or 6-mercaptopurine.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' - chapter 6, page 43: Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. N.B. Routine influenza and pneumococcal vaccinations are highly recommended with a single pneumococcal booster after 5 years.[4]
- 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[2].
- Severe hepatic impairment.

Relevant precautions[1, 2]**:**

- Localised or systemic infection including hepatitis B or C and history of tuberculosis.
- Concurrent use with allopurinol or febuxostat should be avoided.
- Renal impairment. Dose reduction may be required in moderate or severe renal impairment (CrCl<20ml/min).[6, 7] 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 'The Green Book' – chapter 34, page 429 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[1, 2,3,5,7]**:**

- Prolonged courses (>4 weeks) of Co-trimoxazole and trimethoprim should be used with caution – can cause life threatening haematotoxicity. (Note: occasionally, some patients are on co-trimoxazole for special circumstances. E.g. PCP prophylaxis)
- Concomitant use of allopurinol (haematological effects greatly increased) or febuxostat (may increase azathioprine levels) should be avoided.
- Warfarin and acenocoumarol: Azathioprine inhibits the anticoagulant effects of warfarin. Consider increasing the dose of the anticoagulant and monitor closely.
- Phenytoin, sodium valproate, carbamazepine absorption may be reduced by azathioprine.
- Aminosalicylate derivatives (eg. Olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme and increased haematological toxicity of azathioprine, administer with caution.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' - chapter 6, page 43: 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. N.B. Routine influenza and pneumococcal vaccinations are highly recommended with a single pneumococcal booster after 5 years.[4]
  ACE inhibitors – increased risk of anaemia and/or leucopoenia.

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

Information given to patient:

- Azathioprine should not be taken with dairy products (at least 1 hour before or 2 hours after milk or dairy products).
- 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, routine influenza and pneumococcal vaccinations.
- The patient will report any suspected adverse reactions (as above) to the GP for assessment.
- Request supply of maintenance therapy in a timely manner, and store medication securely away from children.

References:

1. Imuran tablets 25mg Summary of Product Characteristics. Last updated 07 November 2019. [accessed 27/08/2020] – www.medicines.org.uk
2. Ledingham, J., Gullick, N. et al. (2017) BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology **56**(6), 865-868.
3. BNF. Available from www.bnf.org [accessed 27/08/2020]
4. Lamb, CA., Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut2019;68:s1-s106. Baxter K (ed), *Stockley's Drug Interactions*. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com (accessed 27/08/2020)
5. Ashley C, and Currie A [Eds]. The Renal Drug Handbook [3rd edition] Oxford: Radcliffe Publishing Ltd [2009].
6. The Renal Drug Database. Last reviewed 30/10/2017. Available from www.renaldrugdatabase.com [accessed 27/08/2020].
7. NICE UC
8. NICE CROHNS

There are no current NICE guidelines on the use of azathioprine, mercaptopurine or methotrexate for Inflammatory Bowel Disease further than reference in Crohn's and UC guidelines.

Version Control- **Azathioprine: Inflammatory Bowel Disease in Adults**			
Version	Author(s)	Date	Changes
2.1	Shary Walker	19/11/2020	- Dairy products warning - CrCl specified for U&E's and linked to CrCl calculator - Explicit criteria for review updated - Routine influenza and pneumococcal vaccinations updated to include a single pneumococcal booster after 5 years - Note added: "occasionally, some patients are on co-trimoxazole for special circumstances. E.g. PCP prophylaxis" - Added information to information given to patient and patient roles and responsibilities