# 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 or 6-MERCAPTOPURINE**

**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.

**Duration of treatment:**
Treatment is usually continued for a minimum of two years if there is a good clinical response. Azathioprine has a cumulative action and a clinical improvement can take up to 3 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:**

| **Time period in treatment** | **Frequency of monitoring** | **Tests to be done** | | |
|---|---|---|---|---|
| | | **FBC** | **LFTs** | **U&Es** |
| 0 - 6 weeks | Weekly | ✓ | ✓ | |
| 6 weeks - 3 months | Fortnightly | ✓ | ✓ | |
| >3 months and stable dose for 6 weeks | Monthly | ✓ | ✓ | |
| Dose & monitoring stable for >6 months* | 3 monthly* | ✓ | ✓ | |
| Any dose change | 2 weeks post dose change then monthly followed by reducing frequency as per this table. | ✓ | ✓ | |
| **All patients** | **6 monthly** | | | ✓ |
| * The Rheumatology Specialist team may advise more frequent monitoring for patients heterozygote for TPMT (increased risk of toxicity). | | | | |

- 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.

**Explicit criteria for review and/or 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 3.5 - 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 <2 $x10^9$/l | Withhold until discussed with gastroenterology specialist team. |
| Platelets <150 $x10^9$/l | 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. |
| Macrocytosis (MCV > upper limit of reference range) | This does not usually signify a medical problem. Check serum folate and B12 & TSH. Treat any underlying abnormality. If results normal discuss 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]:**

- 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, 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.
- 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 (GFR<20ml/min).[6] 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, 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]:**
- Co-trimoxazole and trimethoprim should be avoided – can cause life threatening haematotoxicity.
- Concomitant use of allopurinol (haematological effects greatly increased) or febuxostat (may increase azathioprine levels) should be avoided.
- 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, 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.
- 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. BNFJuly 2014. Available from www.bnf.org [accessed 8/7/14]
4. Mowat C et al. Guidelines for the management of inflammatory bowel disease in adults. British Society of Gastroenterology. 2010 www.bsg.org.uk
5. Baxter K (ed), *Stockley's Drug Interactions*. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com (accessed 8/7/14)
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 or mercaptopurine for Inflammatory Bowel Disease**.

Pergolide Traffic light classification- Amber 2 Information sheet for Primary Care Prescribers CLINICAL INFORMATION Key points/interactions â€¢ Use of pergolide is no longer recommended unless already established on it and attempts to change to alternative therapy have failed â€¢ Ergot based agonists can cause pleural, pericardial and retroperitoneal fibrosis and cardiac valve damage and should not be used unless patients cannot tolerate a nonergot.Â  The dosage may then be increased by 250 micrograms/day every third day until an optimal therapeutic dosage is achieved but not to exceed 3 mg/day. The daily dose is usually administered in 3 divided doses Page 1 of 4 Date approved by Notts APC Prescriptions written for NHS patients in primary care are done so on set prescription forms â€“ either as part of a handwritten prescription pad or prescription forms which can be printed on using GP practice computer software. The legal prescription requirements are the same across these forms, but it is important to understand the differences so the correct one is used.Â  The BNF is the go-to resource for drugs information in the UK. It is available as a printed book, mobile app or website. The BNF is organised into 16 main chapters which are subdivided by condition, the drugs are then organised under the conditions by class.Â  Legal classifications and controlled drugs. Medicines licensed for use in the UK can be broken down into four basic categories. General sales list (GSL). 1 Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK. 2 Research in Real-Life Ltd, Cambridge, UK. 3 Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium ; Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands ; Department of Respiratory Medicine, Erasmus Medical Center, Rotterdam, the Netherlands. 4 Box Surgery, Wiltshire, UK.Â  Conclusion: COPD is not treated according to GOLD and National Institute for Health and Care Excellence recommendations in the UK primary-care setting. Some patients receive no treatment despite experiencing symptoms. Among those on treatment, most receive ICS irrespective of severity of airflow limitation, asthma diagnosis, and exacerbation history. Leflunomide Traffic light classification- Amber 1 Information sheet for Primary Care Prescribers Part of the Shared Care Protocol: Management of Rheumatological Conditions with Disease-Modifying Anti Rheumatic Drugs in Adults Indications1 Rheumatoid Arthritis (RA) and psoriatic arthritis â€“ licensed. Therapeutic Summary Leflunomide can be used to reduce disease activity in patients with rheumatological disease. A factsheet on antibiotic resistance in primary care provides primary care prescribers with EU and national data on the latest trends.Â  factsheet information material toolkit material. 18 Nov 2009. Twitter Facebook Linked In Mail. A factsheet on antibiotic resistance in primary care provides primary care prescribers with EU and national data on the latest trends. Download. Factsheet for primary care prescribers - EN - [PDF-525.91 KB].