Leeds NHS

Azathioprine: Amber Drug Guidance for the use in Adult Rheumatology, Gastroenterology, Respiratory, Dermatology, Ophthalmology and Neurology Patients

Amber Drug Level 3 (amber drug with monitoring requirements)

Amber Level 3 'Medicines that should be initiated by a specialist, and which require significant monitoring on an ongoing basis. These medicines are considered suitable for GP prescribing (which may include titration of dose). After a successful initiation period and assessment of efficacy, a transition to GP care can take place. Full agreement to share the care of each specific patient must be reached under the amber drug agreement, and amber drug guidance must be provided to the GP (available on LHP).

We have started your patient on azathioprine*. We will continue to see the patient and prescribe* azathioprine *until the patient (and their condition) is stable (minimum period of* two months*). After this period the GP will be asked to take over prescribing, titration of dose (if required) and monitoring responsibilities within this amber drug protocol.* ***This drug requires ongoing monitoring which does include blood tests.***

This guideline outlines the specific responsibilities of the Specialist, GP, and patient when azathioprine *is prescribed.*

The link to azathioprine *on the Leeds formulary can be found here.*

Prescribing Information

Indication for therapy:

Azathioprine is an immunosuppressant anti-metabolite with steroid sparing effects.

Also indicated in the management of organ transplant and auto immune hepatitis. Please refer to separate guidance:

- Azathioprine: Amber Drug Guidance for the Prophylaxis of Adult Liver Transplant Rejection
- Azathioprine: Amber Drug Guidance for the Prophylaxis of Adult Kidney Transplant Rejection
- Azathioprine: Amber Drug Guidance for the Treatment of Adult Patients with Autoimmune Hepatitis.

Licensed indications:

Rheumatology: severe rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis and polymyositis, auto-immune chronic active hepatitis, pemphigus vulgaris, polyarteritis nodosa, auto-immune haemolytic anaemia, chronic refractory idiopathic thrombocytopenic purpura and Behcet's syndrome.

Gastroenterology: inflammatory bowel disease.

Unlicensed indications:

Dermatological conditions, including bullous pemphigoid, eczema and vasculitis

Fibrotic non-specific interstitial pneumonia (NSIP), sarcoidosis, hypersensitivity pneumonitis, connective tissue disease (CTD)-associated ILD and vasculitis.

For the management of a variety of autoimmune and inflammatory neurological conditions, such as; myasthenia gravis, inflammatory neuropathies, inflammatory myopathies, vasculitis, multiple sclerosis and neuromyelitis-optica spectrum disorders.

Ophthalmology: ocular inflammatory disease including uveitis

Classification: Amber Level 3

Monitoring: Required

Baseline Tests:

- FBC
- U&Es
- LFTs
- Thiopurine methyltransferase (TPMT) to assess potential risk of myelotoxicity as per Yorkshire Regional Guidelines for the monitoring of adult patients on DMARDs, 6th edition 2014)

Routine Tests/Monitoring:

- FBC and LFTs: 2 weekly for 2 months (0-2 months)
  Monthly for 4 months (2-6 months)
  Then 3 monthly (once a stable dose is reached)

Following a dose change of a patient already established on azathioprine we recommend 2-weekly blood test for 4 weeks and the recommencement of the usual monitoring schedule.

If patients present with symptoms of potential adverse effects (see below) the GP must request urgent FBCs and LFTs:

  - Unexplained infection, mouth or throat ulceration, unexplained bruising, bleeding, diffuse alopecia, fever, nausea, diarrhoea and vomiting.

- If any of the following occur, **stop azathioprine** and contact the hospital specialist:
  - WCC < 3.5×10^9/L
  - Neutrophils < 1.6×10^9/L
  - Platelets < 150×10^9/L
  - AST or ALT > 3 times normal range

Note that cytopenias (especially lymphopaenia) and liver function abnormalities may also be due to autoimmune diseases being treated rather than the azathioprine. Lymphopaenia occurs frequently and is generally of no clinical consequence.

Specialists may therefore advise different blood monitoring guidelines in certain cases and will advise GPs by clinic letter if so.

Disease Monitoring:

Respond to any side effects of treatment (as listed above) and assess the need to continue therapy. The specialist will continue to review and assess the patient's therapeutic response to treatment. The specialist will communicate the follow-up plan from the specialist perspective.

The following is a summary of prescribing information only.
Consult the BNF and SPC for full and current prescribing information.

Dose: Depending on the indication, treatment may begin with a dose of 50mg daily with or after breakfast and increased by 50mg every week up to 150mg daily if tolerated. This is usually the stable dose, but it may be increased up to 3mg/kg or occasionally more.

Gastroenterology initiate full dose therapy at a weight based dose of 2-2.5mg/kg bodyweight daily. Please refer to the letter from the specialist.

See clinic referral letter for recommended dose for your patient.

Ophthalmology initiate full dose therapy at a weight based dose of 1-3mg/kg bodyweight daily. Please refer to the letter from the specialist.

Patients with an intolerance or loss of response, azathioprine metabolites may be measured to guide dosing. This may result in the deliberate co-prescribing of a low dose allopurinol with a low dose of azathioprine. Should allopurinol be co-prescribed, the specialist will take over prescribing and monitoring until a stable dose is reached, at which point the specialist will write to the GP to request they take over prescribing.

The following information has been added only if it differs from the BNF and SPC;

Formulation: Azathioprine 25mg Tablets
Azathioprine 50mg Tablets

Adverse drug reactions:
Mucocutaneous: Skin rashes and alopecia occur rarely. Excessive exposure to sunlight and UV light should be avoided, patients should wear protective clothing and use a sunscreen with a high protection factor to minimise the risk of skin cancer and photosensitivity.

Haematological: Leucopenia, thrombocytopenia, and anaemia. Rarely agranulocytosis and erythroid hypoplasia.

Gastro-intestinal: Nausea, vomiting, loss of appetite, diarrhoea, pancreatitis and colitis.

Hepatic: Cholestasis and alterations in LFTs. Rare, but life-threatening hepatic damage associated with chronic administration.

Immune disorders: Hypersensitivity reactions and very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis.

Infection: Opportunistic infections may occur in patients treated with azathioprine in combination with other immunosuppressants, such as biologics.

Varicella zoster virus - patients with no immunity to varicella zoster should avoid contact with individuals with chicken pox or herpes zoster. If the patient is exposed passive immunisation with varicella-zoster immunoglobulin should be considered.

Other: Other rare side effects include myalgia, arthralgia, drug fevers (allergic), reversible pneumonitis, arrhythmias, hypotension and interstitial nephritis.

Cautions/Contra-indications:

- Known hypersensitivity to azathioprine and 6-merpatopurine.
- Patients with Hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome).
- Patients deficient in thiopurine methyltransferase (TPMT) enzyme are at increased risk of haematological toxicity.
- Renal and hepatic dysfunction, dosage reduction may be warranted to reduce the risk of haematological toxicity. See the manufacturer's information for further details or contact the specialist or Medicines Information
- Patients without a previous history of exposure to Varicella Zoster Virus infection (refer to adverse drug reaction section)

Interactions:

- Allopurinol, oxypurinol and thiopurinol - if co-prescribed a reduced dose of azathioprine will be used. Clinic letter will indicate when intentionally co-prescribed and relevant doses. This is due to reduced elimination of azathioprine and 6-mercaptopurine.
- Neuromuscular blocking agents - increased blockade with depolarising agents and reduced blockade with non-depolarising agents.
- Warfarin - reduced anticoagulant effect.
- Captopril and possibly other ACE inhibitors - increased risk of myelosuppression.
- Co-trimoxazole and trimethoprim - increased risk of myelosuppression.
- Clozapine - increased risk of agranulocytosis.
- Sulfasalazine and olsalazine - possible increased risk of leucopenia due to inhibition of TPMT enzyme.
- ***Live*** vaccines - for guidance on the use of live vaccines in individuals taking immunosuppressants (including biologics) please see: The Green Book - Special Considerations. Please contact the Specialist Physician if further guidance is needed.

Influenza and Pneumoccocal Vaccinations
All patients should be advised to have the yearly influenza vaccine and pneumococcal vaccinations every 5 years unless contra-indicated.

Pregnancy/breast-feeding:
_ Please discuss with the specialist, should your patient wish to or become pregnant. Do

not make any changes to medication without discussing with the specialist.

Contact Names and Details

Leeds Teaching Hospitals NHS Trust
Medicines Information phone number and e-mail: 0113 2064344
medicines.information@nhs.net

Medicines Information Patient Helpline phone number: 0113 2064376

Specialist who makes request via switchboard: LGI: 0113 2432799
SJUH: 0113 2433144

Communication

Prepared by:
Toby Capstick, Advanced Clinical Pharmacist – Respiratory
Dan Greer, Advanced Clinical Pharmacist – Gastroenterology
Jeremy Robson, Advanced Clinical Pharmacist – Neurology/Stroke
Sumrah Shaffiq, Advanced Clinical Pharmacist – Neurology/Stroke
Joanne Sanderson, Advanced Clinical Pharmacist – Rheumatology/Dermatology

Reviewed by:
Dr Paul Beirne, Respiratory Consultant
Dr Christian Sellinger, Consultant Gastroenterologist
Dr Oliver Lily, Consultant Neurologist
Dr Philip Laws, Consultant Dermatologist
Professor Edward Vital, Consultant Rheumatologist
Professor Maya Buch, Consultant Rheumatologist
Nicola Carey, IBD clinical nurse specialist

Declarations of Interest

Declarations of Interest by authors

All (or any) declarations of interest were declared and considered, through the appropriate process.

Contributors are to declare any changes to their declaration of interest submission within 28 days.

Responsibilities of Specialist

Specialist clinician responsibilities:

Responsibilities Specific to Azathioprine in Adults

- Ensure current diagnosis of condition and the treatment options have been discussed and understood by the patient and their carers where appropriate.
- Ensure that the ongoing treatment has been agreed with and by the patient and carer where appropriate.
- To assess the suitability of the patient for this treatment.
- To discuss the benefits and side effects of treatment with the patient/carer and where applicable the need for long term monitoring.
- Checking for allergies, interactions and contra-indications.

- To perform baseline tests.
- To initiate treatment in agreement with the patient.
- To assess and monitor the patients response to treatment until stable before prescribing transferred to General Practitioner (GP).
- To ask the GP whether they are willing to take over the prescribing and monitoring responsibilities under this amber drug guidance.
- To advise the GP on dose to be prescribed and any titration schedule if appropriate.
- To advise GP what routine monitoring will be completed by the specialist and what monitoring the GP will be responsible for.
- To forward results of monitoring to GP.
- Outlining to the GP when therapy may be reduced and stopped assuming no relapse in patient's condition. Review periods to be agreed.
- Ensure this is also known understood and agreed with the patient (and where appropriate their carers).
- Responding to issues raised by GP and informing the patient (and carers) of any material changes to any advice shared or agreements made at the outset.
- To monitor the patient for adverse events/side effects and report to the GP and where appropriate Commission on Human Medicines/MHRA (Yellow card scheme).
- Discuss with the patient their responsibilities outlined below, confirm understanding and confirm that the patient is happy to adhere to them.

Responsibilities of GP

GP responsibilities:

- Checking for allergies, interactions and contra-indications when taking over prescribing and when changing treatment.
- To ensure all required monitoring is up to date before prescribing.
- To prescribe azathioprine and adjust the dose as recommended by the specialist following initiation and stabilisation by the specialist.
- Monitoring the patient's overall health and wellbeing, observing patient for evidence of ADRs and liaising with specialist clinician if necessary. Routine disease monitoring should continue.
- When patient attends for review of treatment confirm, in line with the information already provided by the specialist, (or other specialist acting on their behalf) the circumstances under which the medicines should be immediately stopped and what action the patient is to take.
- To ensure that there is an agreed process in place for accessing the ongoing supply of the medicines that is not placing any unnecessary burden or workload on the patient or their carers.
- Ensuring advice is sought from the responsible specialist clinician if there is any significant change in the patient's physical health status that may affect prescribing or appropriateness of the amber medicine, or any information relevant to their care that becomes available that was not made available at the time of the specialist diagnosis and treatment option agreement.
- Reducing/stopping treatment in line with specialist clinician's original request.
- Take reasonable steps to ensure that the patient is using their medicines as prescribed and intended, i.e. include amber medication as part of medication review.
- Encourage the patient at medication review appointments to ask questions and raise any concerns they have about their treatment, particularly anything that may be affecting their adherence to treatment. Use the Me & My Medicines Charter - https://meandmymedicines.org.uk/the-charter/.
- To report adverse events to the specialist and where appropriate the Commission on

Responsibilities of Patient/Carer	Human Medicines/MHRA (Yellow card scheme). • To ensure patients have yearly influenza vaccine and pneumococcal vaccinations every 5 years unless contra-indicated. **Patient/carer responsibilities:** • To be responsible for taking azathioprine as prescribed. • To understand how to take this medicine safely. • To understand contents of written information provided by the Specialist and in the patient information leaflet supplied with the medicines and to seek clarification if required. • The duration of treatment prescribed initially by the hospital specialist should be understood. • To attend for blood tests/disease monitoring on time (if appropriate). • To understand potential for adverse events/side effects and report these to the Specialist and/or GP. • To understand the circumstances under which the medicines should be immediately stopped and what action to take. • To check with the community pharmacist that there are no interactions with azathioprine, when buying any over the counter medicines or herbal/homoeopathic products. • To check with dentists or other specialists who may prescribe medicines that there are no interactions with azathioprine. • To contact the GP, Specialist or Medicines Information patient helpline if further information or advice is needed about this medication or if there is anything they do not understand. More information on asking about medication can be found in the Me & My Medicines Charter https://meandmymedicines.org.uk/the-charter/.