Indications:  
Auto-immune Hepatitis

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:
Azathioprine is of proven benefit as a steroid sparing agent in the treatment of auto-immune hepatitis. Clinical efficacy may take up to 3 months. Therefore, majority of the patients start azathioprine while still on steroid therapy. Patient reported adverse effects usually occur early in therapy, but please see explicit criteria for review below.

Any modifications of the therapy including changes in the dose of immunosuppressive therapy shall be determined by the treating specialist.

Products available:
Azathioprine 25mg and 50 mg tablets.

Dosage and route of administration:
Azathioprine is given orally as a single daily dose; but, this can be individualised in those who tolerate divided daily doses. The usual maintenance dose is 1 to 2 mg/ kg/ day (50-150mg/day).

Duration of treatment:
Azathioprine has a cumulative action and a clinical improvement can take up to 3 months. It is standard practice to continue azathioprine therapy if tolerated for at least 2 years.

Decision regarding dosage modification and withdrawal shall be taken with discussion between patient and the treating specialist.

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.

<table>
<thead>
<tr>
<th>Time Period in treatment</th>
<th>Frequency of monitoring</th>
<th>Tests to be done</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FBC</td>
</tr>
<tr>
<td>0-4 weeks</td>
<td>Weekly</td>
<td>✓</td>
</tr>
<tr>
<td>4 weeks – 3 months</td>
<td>Monthly</td>
<td>✓</td>
</tr>
<tr>
<td>&gt;3 months and stable dose</td>
<td>3 monthly</td>
<td>✓</td>
</tr>
<tr>
<td>Any dose change</td>
<td>2 weeks post dose change then monthly followed by reducing frequency as per this table.</td>
<td>✓</td>
</tr>
<tr>
<td>All patients</td>
<td>6 monthly</td>
<td>✓</td>
</tr>
</tbody>
</table>

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

Routine influenza and pneumococcal vaccinations are highly recommended.
Monitoring associated with long term corticosteroid use:
Most patients with AIH are treated with long term corticosteroids and should be monitored accordingly.

**Baseline:**
Blood pressure, body weight, ophthalmic examination (can be done by optician), HbA$_{1c}$, triglycerides and potassium.$^6$

**Regular monitoring:**
Blood pressure (every visit), body weight, triglycerides & potassium (1 month post initiation, then 6-12 monthly), HbA$_{1c}$ (1 month post initiation then 3 monthly). Monitor people with confirmed diabetes mellitus regularly, depending on clinical judgement.$^6$

**Osteoporosis risk management:**
Patients should receive calcium and vitamin D supplementation. Bone DEXA scanning should be performed at commencement of prednisolone treatment and at 1-2 yearly intervals while on steroids, with osteopenia/ osteoporosis actively treated.$^2$

**Glaucoma & cataract monitoring:**
Annual examination by an ophthalmologist is recommended. An earlier examination is required in patients with symptoms of cataracts (namely blurred vision).$^7$
Early referral for monitoring of intra-ocular pressure (glaucoma) is recommended in patients at higher risk of developing steroid-induced glaucoma, such as those with a personal or family history of open angle glaucoma, diabetes mellitus, high myopia, or connective tissue disease (especially rheumatoid arthritis).$^7$

For more detail (including monitoring for adrenal suppression) please see NICE CKS Corticosteroids – oral.

**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.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Ensure patient is taking tablets with food. If troublesome prescribe antiemetic.</td>
</tr>
<tr>
<td>Severe general malaise</td>
<td>This may be part of a hypersensitivity reaction. Withhold and discuss with specialist team.</td>
</tr>
<tr>
<td>WBC &lt;3.5x10$^9$/l</td>
<td>Withhold until discussed with specialist team.</td>
</tr>
<tr>
<td>Neutrophils &lt;2x10$^9$/l</td>
<td>Withhold until discussed with specialist team.</td>
</tr>
<tr>
<td>Platelets &lt;150x10$^9$/l</td>
<td>Withhold until discussed with specialist team.</td>
</tr>
<tr>
<td>Rash or oral ulceration</td>
<td>Withhold until discussed with specialist team.</td>
</tr>
<tr>
<td>Macrocytosis (MCV &gt; upper limit of reference range)</td>
<td>This does not usually signify a medical problem. Check serum folate and B12 &amp; TSH. Treat any underlying abnormality. If results normal discuss with specialist team.</td>
</tr>
<tr>
<td>Abnormal bruising / fever / severe sore throat</td>
<td>Withhold until FBC results available and discuss with specialist team.</td>
</tr>
</tbody>
</table>

In addition to absolute values for haematological or biochemical indices a rapid fall or rise or consistent downward or upward trend in any value 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
Relevant contraindications:¹
- Known hypersensitivity to azathioprine and/or 6-mercaptopurine.
- Pregnancy. Azathioprine has been safely used in pregnancy; however women wishing to become pregnant should be discussed with the specialist team.
- Breast feeding.

Relevant precautions:¹
- 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) ⁴. Please discuss with the 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 specialist team will recommend increased monitoring if necessary.

Clinically relevant medicine interactions and their management: ¹, ³, ⁵
- Co-trimoxazole and trimethoprim should be avoided – can cause life threatening bone marrow suppression.
- 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.
- Aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, administer with caution.
- 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