6-Mercaptopurine

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

Any patient groups to be excluded from shared care:
Patients receiving mercaptopurine 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:
Mercaptopurine 50mg tablets – off label (10mg tablets are unlicensed – rarely used for difficult to titrate patients).

Dosage and route of administration:
Mercaptopurine is given orally as a single daily dose. Maximum dose: 100mg daily. Smaller doses are often effective.
A conversion factor of approximately 0.5 can be used when equating azathioprine doses to 6-mercaptopurine, i.e. 1-1.5mg/kg/day or tolerated dose.

Duration of treatment:
Treatment is usually continued for a minimum of two years if there is a good clinical response. Mercaptopurine 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:
- 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.

Monitoring table is on page 2
Monitoring:

<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>0 - 6 weeks</td>
<td>Weekly</td>
<td>✅</td>
</tr>
<tr>
<td>6 weeks - 3 months</td>
<td>Fortnightly</td>
<td>✅</td>
</tr>
<tr>
<td>&gt;3 months and stable dose for 6 weeks</td>
<td>Monthly</td>
<td>✅</td>
</tr>
<tr>
<td>Dose and monitoring stable for &gt;6 months*</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 Gastroenterology Specialist team may advise more frequent monitoring for patients heterozygote for TPMT (increased risk of toxicity).

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.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting or diarrhoea</td>
<td>Ensure patient is taking tablets with food. Withhold until discussed possible dose reduction with gastroenterology specialist team.</td>
</tr>
<tr>
<td>Severe general malaise</td>
<td>This may be part of a hypersensitivity reaction. Withhold until discussed with gastroenterology specialist team.</td>
</tr>
<tr>
<td>WBC 3.5 - 4 x10^9/l</td>
<td>Notify patient and repeat blood count in one week</td>
</tr>
<tr>
<td>WBC &lt;3.5 x10^9/l</td>
<td>Withhold until discussed with gastroenterology specialist team.</td>
</tr>
<tr>
<td>Neutrophils &lt;2 x10^9/l</td>
<td>Withhold until discussed with gastroenterology specialist team.</td>
</tr>
<tr>
<td>Platelets &lt;150 x10^9/l</td>
<td>Withhold until discussed with gastroenterology specialist team.</td>
</tr>
<tr>
<td>AST, ALT &gt; twice upper limit of reference range</td>
<td>Withhold until discussed with gastroenterology specialist team.</td>
</tr>
<tr>
<td>Rash or oral ulceration</td>
<td>Withhold until discussed with gastroenterology 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 gastroenterology specialist team.</td>
</tr>
<tr>
<td>Abnormal bruising/ fever/ severe sore throat</td>
<td>Withhold until FBC results available and discuss with gastroenterology specialist team.</td>
</tr>
<tr>
<td>Severe abdominal pain</td>
<td>Withhold and consider pancreatitis, measure amylase and discuss with gastroenterology specialist team.</td>
</tr>
</tbody>
</table>

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\textsuperscript{1,2}:
- Known hypersensitivity to azathioprine and/or 6-mercaptopurine.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at \url{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. 6-Mercaptopurine has been safely used in pregnancy; however men and women wishing to start a family should be discussed with the specialist team.
- Breast feeding\textsuperscript{2}.
- Severe hepatic impairment.

Relevant precautions\textsuperscript{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 renal impairment (GFR<50ml/min).\textsuperscript{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.
- 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\textsuperscript{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: Mercaptopurine possibly inhibits the anticoagulant effects of warfarin. Consider increasing the dose of warfarin and monitor closely.
- Phenytoin, sodium valproate, carbamazepine absorption may be reduced by mercaptopurine.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at \url{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.

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.
- To report any suspected adverse reactions (as above) to the GP for assessment.

References


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