6-Mercaptopurine Therapy – Brief Summary

6-mercaptopurine is not licensed for the treatment of inflammatory bowel disease however its use in inflammatory bowel disease is widely established and is supported by national guidelines (BSG 2011 and NICE Crohn’s disease CG 152).

As the use of 6-mercaptopurine is unlicensed for the treatment of inflammatory bowel disease and the drug is a metabolite of azathioprine, the information in this Brief Summary for the purpose of treating inflammatory bowel disease has been adapted from the azathioprine shared care Brief Summary, the azathioprine SPC (Sandoz), the BNF and the 6-mercaptopurine SPC (manufactured by Aspen).

Clinicians should consult the full Shared Care Guideline, current BNF and SPC’s for full information

To ensure the safe use of 6-mercaptopurine it is crucial that there is a good, robust 2-way communication of prescribing information and blood test results between the Specialist and the GP. It is also important that the patient communicates with both the Specialist and the GP.

Under this shared care agreement, the GP accepts responsibility for the prescribing AND monitoring of the required on-going blood tests once the patient is on a stable maintenance dose of 6-mercaptopurine. The GP as the prescribing clinician is therefore responsible for ensuring that the relevant blood test monitoring is carried out at the required frequency and the results are checked PRIOR to issuing a prescription for the medication.

NB: Although the Specialist will not routinely check blood test results, they may wish to access blood test results at some point (i.e. when patient attends out-patients, when contacted by GP for advice in the event of an abnormal blood test). If the blood tests are processed at Bedford hospital, then the Specialist can access the results electronically. If the blood tests are processed in a different hospital laboratory, the GP should routinely send a paper copy of the blood test results to the Specialist for information.
| **Patient’s Name:** |  |
| **Date of Birth:** |  |
| **NHS Number:** |  |
| **Patient’s Address:** |  |

| **Consultant’s Name:** |  |
| **Consultant’s Contact Details:** |  |
| **GP’s Name:** |  |
| **GP’s Contact Details:** |  |

| **Patient’s diagnosis:** | Severe or moderately severe inflammatory bowel disease (Crohn’s or Ulcerative Colitis) in patients who are intolerant to steroids or who are dependent on steroids and in whom the therapeutic response is inadequate despite treatment with high doses of steroids |
| **Drug dose, formulation and frequency:** | Usually started at 50mg and increased to a maximum of 0.75-1.5mg/kg/day by mouth. (exact maintenance dose will depend on patient’s TPMT level, clinical response, side effect profile and haematological tolerance). Available as 50mg tablets. (NB Patients should be advised on correct handling of cytotoxic agents. |

<table>
<thead>
<tr>
<th><strong>Contra-indications</strong></th>
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<tr>
<td>• TPMT deficiency (exact level will vary depending on hospital laboratory)</td>
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<tr>
<td>• Haemotological impairment (see blood test monitoring section)</td>
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<tr>
<td>• Hypersensitivity to 6-mercaptopurine, azathioprine (pro-drug of 6-mercaptopurine) or to any of the excipients.</td>
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<tr>
<td>• Severe infections.</td>
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<td>• Severely impaired hepatic or bone-marrow function.</td>
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<tr>
<td>• Severe hepatic impairment</td>
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<td>• Pancreatitis.</td>
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<td>• Any live vaccine e.g. oral polio, MMR, BCG, yellow fever.</td>
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<td>• Pregnancy unless the benefits outweigh the risks (see SpC)</td>
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<tr>
<td>• Lactation (see SpC).</td>
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<tr>
<td>• Patients with hereditary hypoxanthine-guanine-phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome).</td>
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<tr>
<td>• Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption (as tablets contain lactose).</td>
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### Cautions

- Blood test monitoring is essential when prescribing 6-mercaptopurine.
- Renal impairment – Both a reduction in dose and increased frequency of blood test monitoring may be required.
- Mild to moderate hepatic impairment - Both a reduction in dose and increased frequency of blood test monitoring may be required.
- Patients must inform GP / Specialist immediately about oral ulcerations, ulcerations of the throat, recurrent sore throats, fever, infections, bruising, bleeding or other signs of myelosuppression.
- Caution if co-prescribe with certain medications- see drug interaction section below.
- Patients who have not had exposure to Varicella zoster (patient should report any exposure to chickenpox or shingles urgently to clinician.
- Advice patient to use sunscreens and protective clothing to reduce risk of skin cancer
- Caution in withdrawal of 6-mercaptopurine as may result in a severe worsening of disease. Withdrawal should be a gradual process under close monitoring. (If immediate withdrawal needed due to abnormal blood results / side effects , discuss with Specialist)

### Pregnancy & Lactation

The SPC states that 6-mercaptopurine is contraindicated in pregnancy unless the benefits outweigh the risks. The SPC also states 6-mercaptopurine is contraindicated in breastfeeding.

The British Society of Gastroenterologists (BSG) follows different recommendations. **GP’s should refer any pregnant patients/breastfeeding patients or patients considering pregnancy to the Specialist.**

### Side effects:

**Refer to BNF /SPC for further side effects.**

- Hypersensitivity reactions - (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis – calls for immediate withdrawal)
- Bone marrow suppression (leucopenia, anaemia, thrombocytopenia)
- Increased risk of opportunistic infections
- Liver impairment
- Cholestatic jaundice
- Hepatotoxicity (hepatic necrosis, biliary stasis)
- Anorexia, nausea, vomiting
- Oral ulceration, rarely gastrointestinal ulceration
- Increase risk of certain types of skin cancer / lymphoma (see SpC for more details)
- Pancreatitis, interstitial nephritis, pneumonitis, hepatic veno-occlusive disease, lymphoma, red cell aplasia
- Alopecia
Drug interactions
Refer to BNF / SpC for further Drug interactions

Serious Interactions
- Allopurinol, (oxipurinol or thiopurinol*)
  NB: Due to severity of interaction, GPs should contact the Specialist for advice before starting a patient on allopurinol, (oxipurinol or thiopurinol*).
  (* oxipurinol and thiopurinol are not licensed in the UK but could possibly be obtained on a named patient basis)
- Trimethoprim / co-trimoxazole – Close monitoring of FBC is required (increased risk of haematological toxicity).
- Warfarin – anticoagulant effects of warfarin and other coumarins possible reduced. The dose of warfarin may need to be adjusted when starting or stopping 6-mercaptopurine.
- Febuxostat – AVOID concomitant use with 6-mercaptopurine.
- Clozapine – AVOID concomitant use with 6-mercaptopurine.
  Increased risk of agranulocytosis.
- Ribavarin – myelosuppressive effects of 6-mercaptopurine are possible enhanced. (NB This interaction is not specifically listed for 6-mercaptopurine however it is listed as a serious interaction under the azathioprine entry in the BNF).

Other interactions
Close monitoring of blood counts is required with concomitant use:
- Allopurinol, (oxipurinol, thiopurinol*) (see above)
- Aminosalicylates e.g. mesalazine, olsalazine or sulfasalazine
- ACE inhibitors
- Cimetidine
- Indomethacin (NB Patients with IBD should not be prescribed Indomethacin)
- Agents with cytotoxic/myelosuppressive properties

GP TO ARRANGE BLOOD TESTS AT THE REQUIRED FREQUENCY AND CHECK THE RESULTS PRIOR TO ISSUING A PRESCRIPTION ONCE PATIENT IS ON A STABLE MAINTENANCE DOSE

Blood Test Monitoring requirements and frequency
TO BE ARRANGED BY GP

GP should only take over both the prescribing and blood test monitoring of 6-mercaptopurine once the patient is on a stable maintenance dose.

- Monitor FBC, U&E, LFT, every 3 months
- Monitor TFT every 6 months

After a dose change:
Revised frequency of blood test monitoring required – discuss with Specialist

Situations where more frequent blood monitoring may be required
- continuing downward trend in WBC or neutrophil count
<table>
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<tr>
<th>Action to be taken by GP in event of abnormal blood test results or if patient experiences certain symptoms / adverse events</th>
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</table>
| ○ After a dose change  
○ Renal impairment  
○ Mild to moderate hepatic impairment  
○ Elderly patients  
○ Concomitant drug therapy with certain drugs (see drug interactions above) |
| Frequency of blood tests in the above situations should be agreed between the Specialist and the GP. |
| **NB:** Urgent FBC should be processed if the patient complains of intercurrent illness. |
| Although the Specialist will not routinely check blood test results, they may wish to access blood test results at some point (i.e. when patient attends out-patients, when contacted by GP for advice in the event of an abnormal blood test). If the blood tests are processed at Bedford hospital, then the Specialist can access the results electronically. **NB:** If the blood tests are processed in a different hospital laboratory, the GP should routinely send a paper copy of the blood test results to the Specialist for information. |
| **Refer to tables 1) and 2) at end of this document for action to be taken by GP** |

<table>
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<th>Prescribing</th>
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| ▪ A prescription should only be issued if recent blood tests have been done and the results are within acceptable limits.  
▪ GP should ensure that a robust system is in place to deal with repeat prescriptions as 6-mercaptopurine is a high risk drug that requires regular blood test monitoring.  
▪ Ensure that an “appropriate quantity” of tablets are issued (usually only sufficient to last until the next blood test will be reported and the next prescription issued). |

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<tr>
<th>When to refer back to Specialist:</th>
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| ▪ Report to and seek advice on any abnormal blood test results (see table 1 below).  
▪ Report to and seek advice if patient experiences any of the symptoms / adverse events listed in table 2 below.  
▪ Seek advice if considering starting a patient on allopurinol, (oxipurinol or thiopurinol*) therapy (due to severity of interaction).  
▪ Report to and seek advice on any aspect of patient care that is of concern to the GP and may affect treatment.  
▪ Refer all pregnant patients/ patients who wish to breastfeed and patients considering pregnancy. |
* Refer any patient who does not comply with blood test monitoring.

How often will the patient be reviewed by the specialist?

- Frequency will vary between individual patients. Regardless of disease severity, ALL patients should be reviewed at least annually by the Specialist.

Communication

- The dosage regimen and the required frequency of blood test monitoring should be clearly explained to the patient.
- Results of blood tests arranged by the GP should be recorded in the GP medical records and the GP should ensure that the Specialist can access the results (either electronically or paper copy depending on availability of electronic access to blood test results. Although the Specialist will not routinely check blood test results, they may wish to access blood test results at some point (i.e. when patient attends out-patients, when contacted by GP for advice in the event of an abnormal blood test). (If the blood tests are processed at Bedford hospital, then the Specialist can access the results electronically. If the blood tests are processed in a different hospital laboratory, the GP should routinely send a paper copy of the blood test results to the Specialist for information.)
- Results of blood tests if arranged by the Specialist and any dose adjustments made by the Specialist should be recorded in the hospital records and full details sent to the GP (either electronically or paper copy depending on availability of electronic access to blood test results)
- GP’s should contact the Specialist for advice if any dose adjustments are required or if the need to stop the drug arises.
- GP to seek advice from Specialist in the event of an abnormal blood test (see table1) or if patient experiences any of the symptoms / adverse events as highlighted in table 2.
- Patient should be told to inform the prescribing clinician immediately if any oral ulcerations, ulcerations of the throat, recurrent sore throats, fever, bruising, bleeding or other signs of myelosuppression occur.
- Patient should be advised to report any other side effects to the prescribing clinician.
- Patient should be advised to report any suspected pregnancy to the GP and / or Specialist.
- Patient should be advised to avoid excessive sun exposure and to use sunscreens and protective clothing.
- Patients who have not had exposure to Varicella-zoster, should be advised to avoid contact with people who have active chickenpox or shingles and report any such contact urgently to their GP or Specialist.

Table 1)

**ACTION TO BE TAKEN BY GP if the following occurs:**
- White Blood Cells < 3.5 x 10^9/l Discuss with Specialist
- White Blood Cells < 2.5 x 10^9/l Stop 6-mercaptopurine and discuss with Specialist
- Neutrophils 1.5 – 2 x 10^9/l Discuss with Specialist
- Neutrophils < 1.5 x 10^9/l Stop 6-mercaptopurine and discuss with Specialist
- Platelets < 150 x 10^9/l Stop 6-mercaptopurine and discuss with Specialist
- Hb If haemoglobin is low, haematinics should be checked and discuss results with the Specialist
- ALP > 250 IU/l ALT >100 IU/l Stop 6-mercaptopurine and discuss with Specialist
- Significant reduction in renal function Stop 6-mercaptopurine and discuss with Specialist.
- MCV > 105 fl Check TSH , B12, Folate If B12, folate low, start appropriate supplementation

PLEASE NOTE THAT IN ADDITION TO ABSOLUTE VALUES FOR HAEMATOLOGICAL INDICES, A RAPID FALL OR RISE, OR A CONSISTENT UPWARD OR DOWNWARD TREND IN ANY VALUE SHOULD PROMPT CAUTION AND EXTRA VIGILANCE.

Table 2
Symptoms / Adverse events

<table>
<thead>
<tr>
<th>Symptom / Adverse event</th>
<th>Action</th>
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<tbody>
<tr>
<td>Rash (significant and new)</td>
<td>Contact Specialist for advice. If concerned, stop 6-mercaptopurine and check FBC</td>
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<tr>
<td>Abnormal bruising or bleeding</td>
<td>Check FBC and contact Specialist for advice</td>
</tr>
<tr>
<td>Oral ulcerations, ulceration of the throat, recurrent sore throats, infections , fever, chills</td>
<td>Check FBC and contact Specialist for advice If severe, stop 6-mercaptopurine and discuss with Specialist.</td>
</tr>
<tr>
<td>Any other signs of myelosuppression</td>
<td>Check FBC and contact Specialist for advice</td>
</tr>
<tr>
<td>Severe abdominal pain</td>
<td>Stop treatment and consider pancreatitis. Check amylase and contact Specialist for</td>
</tr>
<tr>
<td>Symptom</td>
<td>Advice</td>
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<tr>
<td>Nausea and/or vomiting</td>
<td>Advice to take drug at night. If persists, advise patient to divide dose and take with food. If no improvement, discuss a possible dose reduction with Specialist.</td>
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<tr>
<td>Persistent/worsening diarrhoea</td>
<td>Contact specialist for advice.</td>
</tr>
<tr>
<td>Hair loss</td>
<td>Mild – consider dose reduction on advice of Specialist. If severe, <strong>stop</strong> 6-mercaptopurine and discuss with Specialist.</td>
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**IF IN ANY DOUBT ABOUT ANY ASPECT OF PRESCRIBING 6-MERCAPTOPURINE and/or BLOOD TEST MONITORING ETC, PLEASE CONTACT THE GASTROENTEROLOGY TEAM:**

**Bedford Hospital:**
- Dr R Harvey: 01234 795754
- Dr J Harvey: 01234 792300
- Dr S Musa: 01234 792271
- Dr Y-Al Naeeb: 01234 792271
- Colorectal Nurse Specialists: 01234 792887