

6-Mercaptopurine- Summary Fact Sheet

Information for GPs

- This document provides general prescribing information and blood test monitoring requirements for 6-mercaptopurine when used for the **maintenance of remission** of Crohn's disease and Ulcerative colitis.
- Any patients requiring **induction of remission** should be referred to the Speciality team.
- Clinicians should refer to the '*Shared Care Guideline for the Use of Thiopurines (azathioprine and 6-mercaptopurine) for the treatment of Inflammatory bowel disease* for full details of GP and Specialist individual responsibilities under shared care with regards prescribing and monitoring requirements, **NB** Due to slight differences in practise, there are two versions of the shared care guideline, one applicable for patients under the care of the L&D hospital and the other for patients under the care of Bedford Hospital Bowel disease'.

[Click here for L&D specific guidelines.](#)

[Click here for Bedford Hospital specific guidelines.](#)

- GPs are advised to contact the Specialist team If in any doubt about any aspect of prescribing 6-mercaptopruine and /or blood test monitoring.

General Information

- Thiopurines (azathioprine and 6-mercaptopurine) are used as a disease-modifying agents to maintain remission in Ulcerative Colitis (UC) and Crohn's Disease (CD).
- 6-mercaptopruine is used in patients who are intolerant to azathioprine.
- 6-mercaptopurine* use has been widely established in the maintenance of remission of Inflammatory Bowel Disease and is supported by national guidelines (BSG Guidelines Consensus guidelines 2019, NICE Crohn's disease Management, NG 129 , NICE Ulcerative Colitis Management, NG 132)
- As the use of 6-mercaptopurine is 'off label' for the treatment of inflammatory bowel disease and the drug is a metabolite of azathioprine, the information in this information sheet for the purpose of treating inflammatory bowel disease has been adapted from the azathioprine SmPC (Abbots brand), the electronic BNF and the 6-mercaptopurine SmPC (manufactured by Aspen).
- 6-mercaptopurine may be used to augment anti-TNF therapy, in-part by reducing immunogenicity of biologic agents. (Ref ECCO guidelines)
- Regular blood test are required for monitoring for signs of myelosuppression due to the potential hematological and biochemical toxicity associated with 6-mercaptopurine use. (See Blood Test monitoring section)
- **Patients must be advised to inform their doctor immediately about ulcerations of the throat, fever, infections, bruising, bleeding or other signs of myelosuppression.**

* **NB:** Although use is common in UK clinical practice, at the time of publication of NICE guidance NG 129 (May

2019) 6-mercaptopurine did **not** have a UK marketing authorisation for this indication.(Use is therefore classed as 'off label').

NICE NG 129 states 'The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

TPMT testing

- 6-mercaptopurine is metabolised by the enzyme thiopurine methyltransferase (TPMT). Approximately 0.3% of the population lack thiopurine 6-methyltransferase (TPMT), an enzyme which helps remove thiopurine drugs such as 6-mercaptopurine from the body. In addition approximately 11% of the population have measurable but reduced levels of TPMT (so called intermediate group). (Ref labtestonline)
- Patients with deficient or no detectable TPMT activity are at risk of suffering life-threatening complications even when treated with low doses of 6-mercaptopurine. The predominant toxic effect is myelosuppression, although hepatotoxicity is also well recognised.
- A patient's TPMT level should be checked before commencing therapy with 6-mercaptopurine (NB: The TPMT level range may vary depending on the hospital laboratory).
- The Specialist will be responsible for reviewing the TPMT level and deciding if therapy should / should not be commenced and at what dosage.

Immunity Status and Vaccinations

- All patients with Inflammatory Bowel disease should have an immunity screen prior to starting any immunosuppressive therapy.
- The specialist team will ensure that the patient undergoes necessary screening tests prior to starting immunosuppressant therapy. (BSG Consensus Guideline for Inflammatory Bowel Disease, Gut 10th June 19, *Statement 79 recommends screening for HBV, HCV and HIV, (and VZV if no history of chicken pox, shingles or varicella vaccination).*
- The Specialist team should provide any vaccinations that are required prior to the initiation of 6-mercaptopurine, with the exception of the pneumococcal vaccine and the yearly flu vaccine as these vaccines can be given in primary care.
- Female Patients should be advised to attend for regular cervical smear tests and the need for a HPV vaccine should be considered on a case by case basis by the Specialist team.

Prescribing Information

- As the use of 6-mercaptopurine is 'off label' for the treatment of inflammatory bowel disease and the drug is a metabolite of azathioprine, the information in this information sheet for the purpose of treating inflammatory bowel disease has been adapted from the azathioprine SmPC (Abbots brand), the electronic BNF and the 6-mercaptopurine SmPC (manufactured by Aspen).
- For the most up to date, full prescribing information, please consult the electronic BNF and Summary of Product Characteristics (SmPC); available at www.bnf.org and www.medicines.org.uk.

Treatment Indication	<p>6-mercaptopurine is used for the treatment of the following:</p> <ul style="list-style-type: none"> • severe acute Crohn's disease • Maintenance of remission of Crohn's disease • Maintenance of remission of acute Ulcerative colitis <p>NB: 6-mercaptopurine does not have a licensed for the treatment of inflammatory bowel disease; therefore use is classed as 'off-label use'.</p>
Drug Dose	<p>Adult patients:-</p> <p>On initiation of therapy (started by the Specialist team)</p> <ul style="list-style-type: none"> • The exact starting dose is dependent on factors such as the patients TPMT level and their body weight and will be determined by the Specialist team. • Thioguanine levels are checked after 2-3 months <p>Maintenance dose</p> <ul style="list-style-type: none"> • Typical maintenance dose is 0.75-1.5mg/kg/day • Exact maintenance dose will depend on patient's TPMT level, clinical response, side effect profile and haematological tolerance. • Shared care with GP should only commence once the patient is on a stable maintenance dose. <p>NB:</p> <ul style="list-style-type: none"> ○ The Specialists team may consider prescribing a lower dose of 6-mercaptopurine (approx. 25% of the usual dose) in combination with allopurinol ○ The addition of allopurinol allows a significant reduction in the dose of 6-mercaptopurine required due to the <u>significant interaction</u> that occurs between the two drugs. This combination approach allows the dose of 6-mercaptopurine to be reduced to a quarter of its original dose. <p>NB: Due to the severity of the interaction between these two drugs, allopurinol should only be started by the Specialist team</p>
Dose modifications in Special Populations	<p>Renal Impairment</p> <ul style="list-style-type: none"> • In patients with renal dysfunction, dosages should be given at the lower end of the normal range. • More frequent blood test monitoring may be required. (Seek Specialist advice) <p>Hepatic Impairment</p> <ul style="list-style-type: none"> • In patients mild to moderate hepatic dysfunction, dosages should be given at the lower end of the normal range. • More frequent blood test monitoring may be required. (Seek Specialist advice) • Contra-indicated in severe hepatic impairment.
Duration of Treatment / Clinical Review	<ul style="list-style-type: none"> • Clinical response may take several weeks (12-16 weeks) • Once a maintenance dose is reached, blood test monitoring should be performed every 3 months (see blood test monitoring section) • Consideration should be given to stopping 6-mercaptopurine after 3-6 months if no improvement on optimum dose • Specialist team should review all patients annually.

	<ul style="list-style-type: none"> • Specialist team should review on-going treatment in patients in sustained remission after 4 years.
Formulations	<ul style="list-style-type: none"> • Available as a 50mg tablet • (A liquid preparation is available – contact pharmacy / Specialist team if a liquid preparation is required as the tablets and liquid preparation are not bioequivalent and haematological monitoring is required if switching formulation). • Contain lactose - See manufacturer specific individual SmPC for full list of excipients.
Administration details	<ul style="list-style-type: none"> • 6-mercaptopurine may be taken with food or on an empty stomach, but patients should standardise the method of administration. • The dose should not be taken with milk or dairy products • 6-mercaptopurine should be taken at least 1 hour before or 2 hours after milk or dairy products.
Contra-indications	<p>Clinicians should refer to the <u>Summary of Product Characteristics</u> (SmPC's) for full list of contraindications and cautions details:-</p> <p>The 6-mercaptopurine SmPC only states the following (as it only covers cancer indications)</p> <ul style="list-style-type: none"> • Hypersensitivity to mercaptopurine or to any of the excipients listed in section 6.1. • In view of the seriousness of the indications there are no other absolute contraindications. <p>As 6-mercaptopurine is a metabolite of azathioprine, it has been agreed by local specialists that the information from the azathioprine SmPC will be include here :-</p> <p>The following information is taken from the azathioprine SmPC</p> <ul style="list-style-type: none"> • Hypersensitivity to azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any of the excipients (See individual SmPCs for list of excipients) • TPMT deficiency • Severe infections • Seriously impaired hepatic or bone marrow function • Pancreatitis • Hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome). • Any live vaccine, especially BCG, smallpox, yellow fever. • Pregnancy unless the benefits outweigh the risks (refer to Specialist) • Lactation (refer to specialist) • Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD), and there could potentially be an increased susceptibility for developing the condition with the use of azathioprine. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with azathioprine should be discontinued. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Precautions	<p>Clinicians should refer to the <u>Summary of Product Characteristics</u> (SmPC's) for full details of contraindication and cautions:-</p> <p>The information below has been extrapolated from the Bedfordshire and Luton Joint Prescribing committee approved 'azathioprine summary fact sheet':-</p> <ul style="list-style-type: none"> • 6-mercaptopurine should only be prescribed if the patient can be adequately monitored for toxic effects throughout duration of treatment. (See blood test monitoring section below for full details.) • Patients must be advised to inform their doctor immediately about oral ulcerations, ulcerations of the throat, recurrent sore throats, fever, infections, bruising, bleeding or other signs of myelosuppression. • Avoid concomitant use with certain medications (See Drug interaction section for full details.) • Need to reduce dose of 6-mercaptopurine if co-prescribed with allopurinol, (oxipurinol or thiopurinol*) (see drug interaction section for full details) (* oxipurinol and thiopurinol are not licensed in the UK but could possibly be obtained on a named patient basis) • Close monitoring of blood counts is required if 6-mercaptopurine is given together with certain drugs (see Drug interaction section for full details.) • Patients who have not had exposure to Varicella-zoster should avoid contact with people who have active chickenpox or shingles and should report any such contact urgently to their GP or Specialist • Careful assessment of risk versus benefit should be carried out before use during pregnancy. • Sunscreens and protective covering should be encouraged to reduce sunlight exposure and the skin should be examined at regular intervals. (This is because an increased number of skin tumours (mainly on areas exposed to the sun) have occurred in patients during treatment with azathioprine.) • Withdrawal of 6-mercaptopurine can result in a severe worsening of the condition, e. g. in SLE with nephritis, Crohn's disease, ulcerative colitis or autoimmune hepatitis. • Withdrawal of 6-mercaptopurine should always be a gradual process performed under close monitoring unless immediate withdrawal is needed due to abnormal results / side effects. If withdrawal of therapy is required, seek immediate advice from Specialist team.
Side effects	<p>This is a summarised list – for a comprehensive list of side effects, refer to electronic BNF and individual SmPC's.</p> <p>Extract from BNF</p> <p>Common or very common Anaemia; appetite decreased; bone marrow depression; diarrhoea; hepatic disorders; hepatotoxicity (more common at high doses); leucopenia; nausea; oral disorders; thrombocytopenia; vomiting</p> <p>Uncommon Arthralgia; fever; increased risk of infection; neutropenia; pancreatitis; rash</p> <p>Rare or very rare Alopecia; face oedema; intestinal ulcer; neoplasms; oligozoospermia</p> <p>Frequency not known Photosensitivity reaction</p> <p>The information below has been extrapolated from the Bedfordshire and Luton Joint Prescribing committee approved azathioprine summary fact sheet:-</p>


- 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

See table 1 below for advice on the management of symptoms and adverse effects

Symptoms / Adverse events

<ul style="list-style-type: none"> • Rash (significant and new) 	<p>Contact Specialist for advice. If concerned, stop 6-mercaptopurine and check FBC and seek immediate specialist advice.</p>
<ul style="list-style-type: none"> • Abnormal bruising or bleeding 	<p>Check FBC and contact Specialist for advice</p>
<ul style="list-style-type: none"> • Oral ulcerations, ulceration of the throat, recurrent sore throats, infections, fever, chills 	<p>Check FBC and contact Specialist for advice If severe, stop 6-mercaptopurine and seek immediate specialist advice.</p>
<ul style="list-style-type: none"> • Any other signs of myelosuppression 	<p>Check FBC and contact Specialist for advice</p>
<ul style="list-style-type: none"> • Severe abdominal pain 	<p>Stop treatment and consider pancreatitis. Check amylase and seek immediate Specialist advice.</p>
<ul style="list-style-type: none"> • Nausea and /or vomiting 	<p>Nausea is common early in the course of treatment and usually resolves after a few weeks.</p> <p>Advise patient to divide dose and take after food. If no improvement, discuss a possible dose reduction with Specialist.</p>

	<ul style="list-style-type: none"> • Persistent /worsening diarrhoea 	Contact specialist for advice.
	<ul style="list-style-type: none"> • Hair loss 	Mild – consider dose reduction on advice of Specialist. If severe, stop 6-mercaptopurine and seek immediate specialist advice.
Drug Interactions	<p>Clinicians are advised to check the drug interaction list in the electronic BNF and the Summary of Product of Characteristics (SmPC) for full drug interaction details and prescribing advice before starting patients on 6-mercaptopurine or when adding any new medication or stopping any existing medication in patients already receiving 6-mercaptopurine.</p> <p>Click here for information relating to drug interactions (Ref electronic BNF)</p> <p>https://bnf.nice.org.uk/interaction/mercaptopurine-2.html</p> <p><u>Examples of Serious interactions</u> NB this list is not exhaustive</p> <p>Allopurinol, (oxipurinol or thiopurinol*)- manufacturer advises to reduce the dose of 6-mercaptopurine to one-quarter of the usual dose with concurrent use of allopurinol.</p> <p>NB: Due to severity of interaction, GPs should contact the Specialist for advice before starting a patient on allopurinol, (oxipurinol or thiopurinol*).</p> <p>(* oxipurinol and thiopurinol are not licensed in the UK but could possibly be obtained on a named patient basis)</p> <p>ACE inhibitors –predicated to increase risk of anaemia and/ or leucopenia</p> <p>Trimethoprim / co-trimoxazole –close monitoring of FBC is required due to increased risk of haematological toxicity.</p> <p>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.</p> <p>Ribavarin – myelosuppressive effects of 6-mercaptopurine are possibly enhanced.</p> <p>Febuxostat – AVOID concomitant use with 6-mercaptopurine.</p> <p>Live vaccines – AVOID due to increased risk of generalised infection (possibly life threatening)</p> <p>Clozapine – AVOID concomitant use with 6-mercaptopurine as increased risk of agranulocytosis.</p> <p><u>Examples of Other interactions</u> (NB This list is not exhaustive)</p> <p>Close monitoring of blood counts is required if 6-mercaptopurine is given together with the following drugs due to increased risk of myelosuppression:</p> <ul style="list-style-type: none"> • Any drug that has cytotoxic /myelosuppressive properties (see BNF Interaction table 15) 	

	<ul style="list-style-type: none"> • Aminosalicylates e.g. mesalazine, olsalazine or sulfasalazine - possible increase risk of leucopenia • Cimetidine • Indomethacin (NB: Patients with IBD should not be prescribed indomethacin)
Pregnancy and Breastfeeding	<ul style="list-style-type: none"> • GPs should contact the Specialist team for advice if a patient who is taking 6-mercaptopurine becomes pregnant or wishes to breastfeed. • GPs should contact the Specialist team for advice if a patient wishes to become pregnant
Practical advice to Patients	<ul style="list-style-type: none"> • Patients must be advised to inform their doctor immediately about oral ulcerations, ulcerations of the throat, recurrent sore throats, fever, infections, bruising, bleeding or other signs of myelosuppression. • Patients should be informed of the importance of attending for blood test monitoring and advised that further supplies of medication will only be issued if blood test monitoring is up to date. • Patients who have not had exposure to Varicella-zoster should avoid contact with people who have active chickenpox or shingles and should report any such contact urgently to their GP or Specialist • Patients who are considering pregnancy or who become pregnant should be advised to contact the GP and Specialist team as soon as possible to discuss treatment options. • Patients should be given advice regarding a pneumococcal vaccination and an annual flu vaccination. • Female patients should be advised to attend for regular cervical smear tests. • Sunscreens and protective covering should be encouraged to reduce sunlight exposure and the skin should be examined at regular intervals. (This is because an increased number of skin tumours (mainly on areas exposed to the sun) have occurred in patients during treatment with azathioprine.) • Patients should be advised that the tablets are cytotoxic and should be handled and disposed of as per cytotoxic guidelines. • Patients should be provided with written information regarding their medication. • Click here for link to the patient information leaflet published by Crohn's & Colitis UK or open the embedded document. <p>http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/Azathioprine.pdf</p>  <p>Azathioprine & Mercaptopurine pat</p>

Blood Test Monitoring Requirements

- The Specialist initiating therapy is responsible for checking a patient's TPMT level and pre-treatment blood test monitoring. The Specialist is responsible for arranging blood tests and checking blood test results during the initial period of treatment until the patient is stabilised on a maintenance dose.

- Once the patient is stabilised on a maintenance dose, the Specialist and GP can agree who will take over arranging routine blood test monitoring. Regardless of whether the routine blood tests are ordered by the Specialist or the GP, **the GP as the prescribing clinician, is responsible for checking the blood test results PRIOR to the issue of a prescription for 6-mercaptopurine.** If the decision is made that the Specialist will retain the responsibility for arranging the blood tests, the results of any blood tests arranged by the Specialist should be made available to the GP in a timely manner (This can be electronically if the GP is able to access the hospital blood test system. A paper copy should be sent to the GP if electronic access is not possible.)

NB: The exact type of tests and the frequency of testing will depend on individual patient factors and may vary between different hospitals. The regimen below is that followed by the Luton & Dunstable Gastroenterology Department.

- Pre-treatment Baseline Blood tests**
 - CRP, FBC, U&E, LFT, TPMT level, Amylase, TFT (or as per local hospital guidelines) & Full Immunity Screening (HIV, Hep B, Hep C, VSV, EBV, T Spot, CMV, HSVS).
- Blood Test Frequency during initiation of therapy until a stable maintenance dose is achieved**

Test	Frequency
FBC , U&E , LFT, Amylase, TFT, ESR	At week 2, 4, 6, 10 & 12
6TGN & 6MMPN	At week 6 & 12 Initially every week or fortnightly for 1 month (frequency will depend on individual patient factors and individual hospital practices) then monthly for 2 months, then every 3 months once dose is stable
Amylase testing at the same frequency as FBC, U&E , LFT is also recommended by some local hospitals.	
TFT	After 3 months, then every 6 months once dose is stable
After any dose change: Revised frequency of blood test monitoring required.	

- Blood/ Tests Frequency once stable maintenance dose is achieved**

Test	Frequency
FBC, U&E, LFT ESR, Amylase, TFT	Every 3 months
Amylase testing at the same frequency as FBC, U&E , LFT is also recommended by some local hospitals.	
6TGN & 6MMPN & Faecal Calprotectin	Every 6 months

Situations where more frequent blood monitoring may be required

- continuing downward trend in WBC or neutrophil count
- After a dose change
- Renal impairment
- Mild to moderate hepatic impairment
- Elderly patients
- Concomitant drug therapy with certain drugs (see drug interactions above)

The required 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.

Other monitoring:

Monitoring of metabolites maybe required to optimise dose. Such monitoring should be advised by the Specialist.

Abnormal Blood Test - Action and Advice

In the event of an abnormal blood test result or if the patient reports one of the symptoms / adverse events below, the GP should follow the recommendations given below and discuss with the Specialist.

Table 2

• 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 seek immediate specialist advice.
• Neutrophils 1.5 – 2 x 10 ⁹ /l	Discuss with Specialist
• Neutrophils < 1.5 x 10 ⁹ /l	Stop 6-mercaptopurine and seek immediate specialist advice.
• Platelets < 150 x 10 ⁹ /l	Stop 6-mercaptopurine seek immediate specialist advice.
• 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 seek immediate specialist advice.
• Significant reduction in renal function	Stop 6-mercaptopurine and seek immediate specialist advice.

<ul style="list-style-type: none"> • MCV > 105 fl 	<p>Check TSH , B12, Folate</p> <p>If B12, folate low, start appropriate supplementation</p>

NB: 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

References:-

This list is currently being prepared and is available upon request from the Medicine Management Team

Dec 2019

Update Sept 2020 – amendment of blood test schedules due to covid 19 pandemic

Update April 2022 – Revert back to original blood test schedules as per BSG