BNSSG Shared Care Guidance
Please complete all sections

Section 1: Heading

Drug	Mercaptopurine
Amber *three months*	
Indication	Autoimmune hepatitis

Section 2: Treatment Schedule

Usual dose and frequency of administration *(Please indicate if this is licensed or unlicensed and any relevant dosing information)*	Prior to initiation it may be appropriate to check TPMT (thiopurine methyltransferase) level. Individuals with an inherited deficiency of TPMT may be more sensitive to the myelosuppressive effects of mercaptopurine. The gastroenterology team will consider whether a lower dose should be used in patients with intermediate or low TPMT activity. Target dose: 1mg/kg once daily (if TPMT activity is normal). Mercaptopurine for autoimmune hepatitis is an unlicensed indication. In patients with renal or hepatic impairment, or in elderly patients, it is recommended to use doses at the lower end of the normal range. Clinical response may take up to 2-3 months.
Route and formulation	Oral 50mg tablets
Duration of treatment	Ongoing

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist.

Baseline tests - where appropriate
1. TPMT level or phenotype (if appropriate) 2. Full blood count (FBC) 3. Urea and Electrolytes (U&Es) 4. Liver function tests (LFTs) Infection screening (if appropriate). Varicella status, history of MMR/DTaP vaccination, Hep B and Hep C status, history of HPV vaccination (women only), CMV status, HIV status (high risk patients).

Subsequent tests - where appropriate *(Please indicate who takes responsibility for taking bloods and interpreting results)*

Test	Frequency	Who by	Action/management
FBC	Weekly for 4 weeks then monthly for 2 months, then if stable 3 monthly thereafter.	Primary care	If the following occur, stop mercaptopurine, recheck level in one week and refer to specialist. - WBC < 3.0 x 10^9/L - Lymphocytes <0.5 x 10^9/L - Neutrophils <1.5 x 10^9/L - Platelets <100 x 10^9/L
LFTs	Weekly for 4 weeks then monthly for 2 months, then if stable 3 monthly thereafter.	Primary care	If ALT/AST/ALP > 3 x upper limit of normal – stop mercaptopurine and contact hospital clinician immediately. Recheck level in one week.
U&Es	Every 6 months and more frequently if there is any reason to suspect deteriorating renal function.	Primary care	Check for other causes of deteriorating renal function before referring to specialist. If patient develops AKI hold drug and refer back to specialist urgently. If patient develops a steady deterioration (>30% rise in creatinine in 12 months), continue drug but refer back to specialist.

Section 4: Side Effects

Please list only the most pertinent side effects and management. Please provide guidance on when the GP should refer back to the specialist. For everything else, please see BNF or SPC.

Side effects and management

Side effect	Frequency	Action/management
Diarrhoea, nausea/vomiting, loss of appetite, mild aches and pains	Common	May occur initially and should settle within 2 to 3 weeks. If patients are reporting nausea they can divide the dose and take with food (although preferred on an empty stomach- see below) or take at night so that nausea is experienced during sleep.
Rash, dizziness, fever, rigors, myalgia, arthralgia, hypotension and renal dysfunction	Uncommon	Treatment should be stopped as this indicates hypersensitivity.
Persistent sore throat/infection	Common	Mercaptopurine should be stopped until the result of the FBC and any other investigations are known and the treatment for infection has been started.
Signs of bone marrow suppression (thrombocytopaenia, ulcers, neutropaenia, leucopaenia, anaemia) i.e. infection, fever, unexplained bruising or bleeding.	Common	Treatment should be stopped and FBC checked. Dose-dependent, generally reversible.

<table>
<tr><td></td><td>
<table>
<tr><td>Hair loss</td><td>Uncommon</td><td>Many instances the symptom resolved spontaneously despite continuing therapy.</td></tr>
<tr><td>Inflammation of the pancreas or lung</td><td>Rare</td><td>Reversible on stopping treatment but mercaptopurine should not be restarted on recovery.</td></tr>
<tr><td>Hepatotoxicity (cholestasis, destructive cholangitis, peliosis hepatitis, perisinusoidal fibrosis, and nodular regenerative hyperplasia)</td><td>Uncommon</td><td>Hold if ALT >3 x upper limit of normal, re-check in 1 week and refer to specialist for advice. Cholestasis and deterioration of liver function are usually reversible on withdrawal of therapy</td></tr>
</table>
Patients will be at increased susceptibility to viral, fungal and bacterial infections. Patients should be advised to report any signs of bone marrow suppression (thrombocytopaenia, neutropaenia, leucopaenia) i.e. infection, fever, unexplained bruising or bleeding. Treatment should be stopped and FBC checked.

Chicken pox/shingles infection - stop and commence aciclovir</td></tr>
<tr><td>Referral back to specialist</td><td>As above in side effects and management.
If ALT worsens whilst on treatment.</td></tr>
</table>

Section 5: Other Issues

(e.g. Drug Interactions, Contra-indications, Cautions, Special Recommendations)

Please list only the most pertinent action for GP to take (For full list please see BNF or SPC)

Issues	**Drug interactions** Allopurinol - due to inhibition of xanthine oxidase activity by allopurinol the combination should be avoided or reduce mercaptopurine dose to one-quarter the original dose. Febuxostat – may increase exposure to mercaptopurine, combination should be avoided. Neuromuscular blocking agents - mercaptopurine may antagonise the effect of non-depolarizing muscle relaxants and potentiate the effect of depolarizing agents - patients should advise their anaesthetist that they are taking mercaptopurine. Warfarin - mercaptopurine may significantly decrease the anticoagulant effect of warfarin - higher warfarin doses may be needed. Cytostatic/myelosuppressive agents - avoid cytostatic drugs or drugs which may have a myelosuppressive effect, such as penicillamine. Cimetidine and indomethacin - very rarely cause leucopaenia so use with care. Trimethoprim - There is evidence of an increased risk of haematological toxicity in renal transplant patients taking co-trimoxazole or trimethoprim with mercaptopurine, however the interaction was not demonstrated in all studies and the combination is often used safely, e.g. co-trimoxazole prophylaxis against P. jirovecii infection.

ACE inhibitors - may increase the risk of leucopaenia or anaemia with mercaptopurine.

Mesalazine, olsalazine and sulfasalazine - inhibits the activity of TPMT and may increase the risk of leucopaenia. More regular monitoring of FBC may be advisable when initiating a 5-ASA in a patient stabilised on mercaptopurine.

Clozapine - concomitant use increases the risk of agranulocytosis.

Live vaccines - Atypical and potentially harmful responses could occur to live vaccines such as polio, oral typhoid, MMR, BCG and yellow fever. Live vaccines are contraindicated during mercaptopurine therapy, within 3 weeks of initiation and for 3 months after stopping. A diminished response to killed live vaccines is likely, e.g. Hepatitis B vaccine.

The AstraZeneca COVID-19 vaccine contains a live adenovirus vector. However, this vaccine is non-replicating and considered safe in immunosuppressed people. More information on COVID-19 vaccines can be found in 'The Green Book' here.

Administer all appropriate vaccines as recommended by secondary care.

Contraindications

Hypersensitivity to azathioprine, mercaptopurine or excipients

Severe infections

Lesch-Nyhan syndrome

Pancreatitis caused by azathioprine/mercaptopurine.

Absent TPMT activity

Cautions and Special Recommendations

Caution in moderate/severe renal impairment, liver impairment and significant haematological impairment.

Caution in patients with low TPMT/TPMT deficiency.

Reduce dose in the elderly.

Cease therapy in all but minor infections as the body defences may be reduced and delay recovery or worsen the condition.

Patients may be at an increased risk of lymphoproliferative disorders. The risk appears to be related to the degree and duration of immunosuppression and absolute risk very small (<1% risk after 10 years of thiopurine use). The benefits of therapy are thought to outweigh the risks.

Thiopurines increase the risk of non-melanoma skin cancers. Patients should avoid excessive sun exposure and wear protective clothing and a high factor sun screen.

Patients should avoid unpasteurised milk or cheese, uncooked meat and raw vegetables to prevent Listeria Monocytogenes infection.

	Patients with inherited mutated NUDT15 gene are at increased risk for severe azathioprine toxicity, such as leucopenia and alopecia, from conventional doses of thiopurine therapy. Dose reductions are recommended and close monitoring of blood counts. Patients should avoid contact with people who have active chickenpox or shingles and report any contact to their GP and hospital specialist. If immunosuppressed patients are exposed to chickenpox or shingles, they will need to be assessed for susceptibility and the need for aciclovir post exposure prophylaxis, see: UKHSA guidance: Guidelines on post-exposure prophylaxis (PEP) for varicella/shingles and the Green Book Chapter 34. **Pregnancy**: Assess risk versus benefit before initiation in women of child-bearing age. There have been some reports of increased rates of pre-term birth, low birth weight and congenital defects following maternal exposure, particularly in combination with corticosteroids. There have also been reports of spontaneous abortion following either maternal or paternal exposure. As with all cytotoxic drugs, adequate contraceptive measures are recommended when either partner is receiving mercaptopurine therapy. If they, or their partners, become pregnant they must tell their GP or gastroenterologist The FDA pregnancy rating of D is due to a high incidence of miscarriage in animal studies. Human studies suggest thiopurines are safe and well tolerated during pregnancy. As the risk of active disease usually outweighs the risk of exposure to mercaptopurine it should usually be continued if the mother is in remission. **Lactation**: Mercaptopurine and its metabolites are undetectable or have been detected in tiny amounts in breast milk. It is acceptable to breast feed whilst taking mercaptopurine. **Overdose**: There is no specific antidote. FBC and LFTs should be monitored very closely after an overdose. Bone marrow suppression is the principle complication, peaking after 9-14 days. Other symptoms include nausea, vomiting and diarrhoea.
Reminder to ask patient about specific problems	Any evidence of infections, unexpected bruising or bleeding or other manifestations of bone marrow suppression.

Section 6: Advice to the patient

Advice for prescribing clinician to inform patient

1. Inform the patient of the side effects, particularly infection/leucopaenia and the need for regular blood tests. Where patients do not comply with the monitoring programme the medication should be ceased as it is unsafe.
2. Instruct patients to report immediately any signs or symptoms of bone marrow suppression, for example any bruising or bleeding, infection or any side effects from the drug.
3. Where patients are not immune to chicken pox/shingles and are in contact with individuals with chicken pox/shingles they should report this to their GP.
4. Advise patients on what vaccinations they should receive from their GP.
5. Take either with food or on an empty stomach (patients must maintain standard of administration). Advice on taking with food may alter depending on the brand of mercaptopurine- see patient information leaflet. Take at least 1 hour before or 2 hours after milk or dairy products.
6. Patients (and their partners) should be advised to use adequate contraception whilst taking mercaptopurine. If they, or their partners, become pregnant they must tell their GP or gastroenterologist.
7. Thiopurines increase the risk of non-melanoma skin cancers. Patients should avoid excessive sun exposure; wear protective clothing and a high factor sun screen.
8. Patients should avoid unpasteurised milk or cheese, uncooked meat and raw vegetables to prevent Listeria Monocytogenes infection.
9. Give the patient a thiopurine monitoring schedule letter if available.

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Section 7: Generic principles of shared care for SECONDARY CARE

Please do not amend.

Core responsibilities

1. Initiating treatment and prescribing for the length of time specified in **section 1.**
2. Undertaking the clinical assessment and monitoring for the length of time specified in **section 1** and thereafter undertaking any ongoing monitoring as detailed in **section 3.**
3. Communicate details of the above in 1 and 2 to GP within the first month of treatment. This information should be transferred in a timely manner.
4. Refer patients to GP and provide information of further action where appropriate e.g. if blood test is due.
5. To provide advice to primary care when appropriate.
6. Review concurrent medications for potential interaction prior to initiation of drug specified in **section 1.**
7. Stopping treatment where appropriate or providing advice on when to stop.
8. Reporting adverse events to the MHRA.
9. Reminder to ask patients about particular problems see **section 5.**

Section 8: Generic principles of shared care for PRIMARY CARE

Please do not amend.

Core responsibilities

1. Responsible for taking over prescribing after the length of time specified in **section 1.**
2. Responsible for any clinical assessment and monitoring if detailed in **section 3** after the length of time specified in **section 1.**
3. Review of any new concurrent medications for potential interactions.
4. Reporting adverse events to the MHRA.
5. Refer for advice to specialist where appropriate.
6. Reminder to ask patients about particular problems see **section 5.**

Section 10: Contact Details

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Section 11: Document Details

Date prepared	June 2020

Prepared by	Cara Leung/Jade Chan Specialist Pharmacists – Gastroenterology and Hepatology Change to information about PEP for varicella/shingles February 2023 added by BNSSG Formulary Team.
Date approved by JFG	16th March 2021
Date of review	March 2023
Document Identification: Version	2.1

Section 12: Collaboration

All shared care protocols should be BNSSG wide where possible. Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

1. This document has been sent to the hepatologists at NBT

Section 13: References

Please list references

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