BNSSG Shared Care Guidance
Please complete all sections

Section 1: Heading

Drug	Azathioprine
Amber *one month*	
Indication	Maintenance therapy in Ulcerative Colitis or Crohn's Disease

Section 2: Treatment Schedule

Usual dose and frequency of administration	Prior to initiation it is recommended that TPMT (thiopurine methyltransferase) level is checked. Individuals with an inherited deficiency of TPMT may be more sensitive to the myelosuppressive effects of azathioprine. The gastroenterology team will consider whether a lower dose should be used in patients with intermediate or low TPMT activity. There are 2 approaches to dosing which are selected on consultant preference: 1. Initial oral dose 25-50mg once daily, gradually increased over 2-3 weeks to target dose, OR 2. Initiate at the target dose. This is commonplace and achieves therapeutic effect faster but may be accompanied by more initial side-effects. Target dose: 2-2.5mg/kg once daily (if TPMT activity is normal). Azathioprine should be avoided in patients with no TPMT. If TPMT activity is high then a higher target dose (2.5-3mg/kg) may be chosen by the consultant. If activity is low, a lower target dose (1mg/kg) may be chosen. Dose may change depending on the metabolite levels. Based on the results of the TGN the dose may be changed aiming for a therapeutic response (235-450 pmol). 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. As clinical response may take 2-3 months, oral steroids are often started to bridge symptoms and tapered during a course of up to 12 weeks.
Route and formulation	Oral 25mg tablets 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. Full blood count (FBC)
2. Liver function tests (LFTs)
3. Urea and Electrolytes (U&Es)
4. Thiopurine methyltransferase (TPMT)
5. Infection screening will preferably occur at diagnosis of IBD. Varicella status, history of MMR/DTaP vaccination, Hep B and Hep C status, history of HPV vaccination (women only), CMV status, EBV status (in men taking concomitant anti-TNFs), 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
U&Es	Every 6 months	Primary care	Can be taken more frequently if there is any reason to suspect deteriorating renal function. 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. Secondary Care to monitor every week for the first 4 weeks then primary care is responsible for monitoring after the first month.
FBC	Weekly for 4 weeks then monthly for 2 months, then if stable 3 monthly thereafter	Primary care	Secondary Care to monitor every week for the first 4 weeks then primary care is responsible for monitoring after the first month. Blood results and associated actions: WBC < 3.0 x 10^9/L – stop drug and recheck weekly until stable. Discuss with hospital clinician. Lymphocytes <0.5 x 10^9/L – stop and discuss with hospital clinician. Neutrophils <1.5 x 10^9/L – stop and discuss with hospital clinician. Platelets <100 x 10^9/L –discuss with hospital clinician.
LFTs	Weekly for 4 weeks then	Primary care	LFTs >3x increase in AST/ALT/ALP – stop and contact hospital clinician

	monthly for 2 months, then if stable 3 monthly thereafter		immediately. Secondary Care to monitor every week for the first 4 weeks then primary care is responsible for monitoring after the first month.
Thiopurine metabolite levels	1-2 months after starting treatment and when considering dose escalation	Primary or secondary care	To determine if taking a therapeutic dose and, to ensure not at risk of hepatotoxicity. Secondary care will either take this test in clinic or will request test on ICE for patient to go to the GP who will take the bloods. Results will be checked and interpreted by secondary care who will advise GP accordingly.

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/severity	Action/management
Bone marrow depression i.e. leucopenia, thrombocytopenia or anaemia	Very common (≥1/10) - Leucopenia Common (≥1/100 to<1/10) – thrombocytopenia and anaemia	Treatment should be stopped and FBC checked. Dose-dependent, generally reversible.
Nausea and with isolated reports of vomiting Loss of appetite	Very common (≥1/10)	May occur initially but 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; avoid milk or dairy products (this is brand specific) or take at night so that nausea is experienced during sleep.
Pancreatitis or inflammation of the lung	Common (≥1/100 to<1/10)	This is reversible on stopping treatment but azathioprine should not be restarted on recovery and patients should not be switched to mercaptopurine as an alternative.
Hepatotoxicity (cholestasis, destructive cholangitis, peliosis hepatitis, perisinusoidal	Common (≥1/100 to<1/10)	Hold if ALT >3 x ULN and re-check in 1 week and refer to specialist for advice. Cholestasis and deterioration of liver function are usually

	fibrosis, and nodular regenerative hyperplasia)		reversible on withdrawal of therapy
	Persistent sore throat/infection	Common (≥1/100 to<1/10)	Azathioprine should be stopped until the result of the FBC and any other investigations are known and the treatment for infection has been started
	Mild aches/pains	Uncommon (≥1/1,000 to <1/100)	May occur initially but should settle within 2 to 3 weeks.
	'Flu-like' symptoms	Uncommon (≥1/1,000 to <1/100)	Where 'flu-like symptoms do not resolve within 3 weeks a switch to mercaptopurine may be beneficial.
	Rash	Uncommon (≥1/1,000 to <1/100)	Treatment should be stopped as this indicates hypersensitivity.
	Diarrhoea	Uncommon (≥1/1,000 to <1/100)	May occur initially but should settle within 2 to 3 weeks.
	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. Other side effects are rarer these include oral ulceration, rarely gastrointestinal ulceration, purple discolouration of the skin and jaundice. Hair loss has been described on a number of occasions and often resolves spontaneously despite continued therapy.		
Referral back to specialist	As above in side effects and management. Low dose allopurinol (25-300mg/day; usually 100mg) may be used in addition to a reduced dose of azathioprine to alter the TGN:MMPN ratio or to normalise LFTs (on specialist recommendation only).		

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 azathioprine dose to one-quarter the original dose (unless given on specialist advice as in section 4 above). Neuromuscular blocking agents Azathioprine 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 azathioprine. Warfarin Azathioprine may significantly decrease the anticoagulant effect of warfarin - higher warfarin doses may be needed and increased monitoring. Cytostatic/myelosuppressive agents Avoid cytostatic drugs or drugs which may have a myelosuppressive effect, such as penicillamine. Cimetidine and indometacin very rarely cause leucopaenia so use with care. There is evidence of an increased risk of haematological toxicity in renal transplant patients taking co-trimoxazole or trimethoprim with azathioprine, 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 plus azathioprine may increase the risk of leucopaenia or anaemia. Mesalazine, olsalazine and sulfasalazine inhibit 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 stabilized on azathioprine. Concomitant use of clozapine increases the risk of agranulocytosis. **Contraindications, cautions and special recommendations:** 1. Contraindications: Hypersensitivity to azathioprine, pancreatitis, severe infections, moderate/severe renal impairment, liver impairment, significant haematological impairment. 2. Cease therapy in all but minor infections as the body defences may be reduced and delay recovery or worsen the condition. 3. 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. 4. 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. 5. 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 azathioprine 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. 6. Patients should avoid unpasteurised milk or cheese, uncooked meat and raw vegetables to prevent Listeria Monocytogenes infection. 7. 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. 8. Avoid azathioprine in patients with Lesch-Nyhan syndrome. 9. 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 but there is mounting evidence from case-control studies that there is no overall increase in congenital defects when thiopurines are taken during pregnancy. 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 azathioprine it should usually be continued if the mother is in remission. 10. Lactation: Azathioprine and its metabolites are undetectable or have been detected in tiny amounts in breast milk. It is acceptable to breast feed whilst taking azathioprine. 11. 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 9-19 days. 12. Administer all appropriate vaccines as recommended by secondary care
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 azathioprine- see patient information leaflet. Take at least 1 hour before or 3 hours after milk or dairy products
6. Seek advice from IBD team if planning on pregnancy or you become pregnant so that a management plan is in place or advice can be given on continuing treatment (please do not stop treatment without discussion with IBD team)
7. Exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.
8. Use of combination therapy in female patients planning pregnancy needs to be discussed as allopurinol contraindicated in 1st trimester.

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 9: Contact Details

Name	Organisation	Telephone Number	E mail address
Aileen Fraser IBD Advanced clinical practitioner	UHBW NHS Trust Bristol Royal Infirmary	0117 342 1100	ibdnurses@uhbw.nhs.uk
Theresa Tindall Trainee Advanced Clinical practioner	UHBW NHS Trust Weston General	01934 881254	theresatindall@nhs.net
Debbie Corris/Rebecca Antliff, IBD Specialist Nurses	North Bristol NHS Trust	0117 4146354	ibdnurses@nbt.nhs.uk
Cara Leung/Jade Chan, Specialist Pharmacists	North Bristol NHS Trust	0117 4142255	gastropharmacists@nbt.nhs.uk
Gastroenterology consultants	North Bristol NHS Trust	0117 4146349	GastroenterologyandHepatologySecretaries@nbt.nhs.uk

Section 10: Document Details

Date prepared	May 2020 Change to information about PEP for varicella/shingles February 2023 added by BNSSG Formulary Team.
Prepared by	Cara Leung/Jade Chan Specialist Pharmacists – Gastroenterology and Hepatology
Date approved by JFG	July 2020

Date of review	July 2022
Document Identification: Version	V2.1

Section 11: 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. Adapted from document written by Aileen Fraser, Inflammatory Bowel Disease Clinical Nurse Specialist and Kevin Gibbs. Clinical Pharmacy Manager (UHB).

Section 12: References

Please list references

1. Azathioprine SpC, Accord, last updated 13/10/2017accessed at https://www.medicines.org.uk/emc/product/3301/smpc on 29/11/2019
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3. North Bristol NHS Trust. Thiopurine metabolites. 2020. Accessed at https://www.nbt.nhs.uk/severn-pathology/requesting/test-information/thiopurine-metabolites.
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5. The third European evidence based consensus on the diagnosis and management of Crohn's Disease 2016. Part 1: Diagnosis and Medical management, ECCO (2016), accessed at https://academic.oup.com/ecco-jcc/article/11/1/3/2456546
6. Guidelines for the management of inflammatory bowel disease in adults, BSG (2019), accessed at https://www.bsg.org.uk/resource/bsg-consensus-guidelines-ibd-in-adults.html on 29/11/2019