The Pennine Acute Hospitals NHS Trust

Greater Manchester Interface Prescribing Group Shared Care Template

Shared Care Guideline for Azathioprine and 6-Mercaptopurine for Chronic Inflammatory Bowel Disease		**Reference Number**
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Date approved by Commissioners: *31/August/2012*	**Review Date:** *31/August/2014*	

Please complete all sections

1. Licensed Indications	Both Azathioprine and 6-Mercaptopurine are unlicensed for use in the management of inflammatory bowel disease.
2. Therapeutic use & background	• The idiopathic inflammatory bowel diseases comprise mainly two types of intestinal disorder, Crohn's disease and ulcerative colitis. The clinical course is marked by exacerbations and remissions that occur spontaneously in response to treatment or intercurrent illness. The disease affects approximately 240,000 patients in the UK. • Azathioprine and 6-Mercaptopurine are immunosuppressant drugs that are used to induce or maintain remission in those patients whose disease is not controlled by aminosalicylates and/or those requiring repeated or high dose corticosteroids. • Azathioprine is a pro-drug metabolised by the liver to 6-Mercaptopurine and then to 6-thioguaninenucleotide which is the active metabolite. • Azathioprine and 6-Mercaptopurine are both drugs that work by suppressing cell-mediated immunity. • Corticosteroids when taken on a long-term basis can cause many adverse effects including – diabetes, weight gain, adrenal suppression. • NICE guidance is currently being produced for Crohn's disease and ulcerative colitis. • The guidance in this protocol should be used in conjunction with the SPCs for azathioprine and 6-Mercaptopurine, current BNF and patient information leaflets.

3. Contraindications (please note this does not replace the SPC or BNF and should be read in conjunction with it).	***Azathioprine and 6-Mercaptopurine*** *– patients known to be hypersensitive to the ingredients. It should not routinely be initiated in patients who may be pregnant without careful risk assessment by the Specialist.*	
4. Prescribing in pregnancy and lactation	***Azathioprine and 6-Mercaptopurine*** *can be prescribed in the pregnant/breastfeeding patient. Under these circumstances prescribing should be the responsibility of the Specialist and a full risk vs. benefit assessment should be undertaken. There have been reports of premature birth and low birth weight following maternal exposure to Azathioprine, particularly in combination with corticosteroids, however, it is difficult to ascertain if this is due to the medication or disease activity.* *6 Mercaptopurine has been found in breast milk of women receiving Azathioprine.* *For full information about the use of Azathioprine/6-6 Mercaptopurine in pregnancy/breastfeeding, please see the UKMi Q&A 97.3.* *http://www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Q—A/Can-mothers-breast-feed-while-taking-azathioprine/* or contact the UK Teratology Information Service online: www.toxbase.com or 0844 892 0909 (where you can speak to a teratology specialist to discuss individual cases).	
5. Dosage regimen for continuing care	Route of administration	Oral
	Preparations available (include in this section any necessary information relating to availability of special preparations for children or those with swallowing difficulties). □ **Azathioprine 2-2.5 mg/kg/day** □ **6-Mercaptopurine 1-1.5 mg/kg/day** If the patient's thiopurine methyltransferase enzyme (TPMT) is normal dose as above. If the patient's TPMT is reduced a lower dosing regimen may be commenced. Specialists will advise.	
	Is titration required	**Yes**
	The maintenance dose will differ between individuals and effectively confers to the level at which leucopenia develops. Titration dosage may vary dependent upon TPMT levels. Slower frequency of dosing increments is not recommended as this may reduce the time taken to achieve response (and achieve appropriate 6-thioguanine-nucleotide levels).	
	Adjunctive treatment regime: May include 6-aminosalicylates, corticosteroids, antibiotics, dietary supplements or anti-TNF agents (eg Infliximab or Adalimumab) at the direction of the specialist service.	
	Conditions requiring dose reduction e.g. impaired renal/ liver function For patients prescribed higher doses or if severe hepatic or renal impairment is present, monitoring should be undertaken more frequently.	

	Elderly patients may require dose reduction. In patients taking Allopurinol, Azathioprine therapy must only be given under the expert supervision of an IBD specialist and the dose of Azathioprine must be reduced to a quarter of the normal expected dose in patients with normal TPMT levels and with weekly monitoring of blood counts for 3 months followed by monthly monitoring for the entire duration of intended concurrent therapy. In these patients prescribing responsibility will remain with the Consultant initiating therapy
	Usual response time Clinical response can usually be expected in 6-12 weeks. Response to both drugs can take between 6 weeks to up to 6 months.
	Duration of treatment: Treatment should be reviewed after 12 weeks to assess response. Patients not responding should have their treatment reviewed. Discuss with the Specialist – 6-thioguanine-nucleotide levels (6TGN) may be appropriate for testing. To potentially continue indefinitely but may be withdrawn after a prolonged period of disease remission in selected cases (at the Gastroenterologists discretion) typically at 5 years.
	Termination of treatment If the patient experiences adverse effects (eg blood dyscrasias), the GP should discuss with the Specialist. In the event of lack of effectiveness the Specialist should review. In all circumstances the GP should liaise with the Specialist if there are any concerns.
	NB. All dose adjustments will be the responsibility of the initiating specialist care unless directions have been specified in the medical letter to the GP.
6.Drug Interactions ***For a comprehensive list consult the BNF or Summary of Product Characteristics***	The following drugs must <u>not</u> be prescribed without consultation with the specialist: • Immunisation using a live organism vaccine (eg: oral polio, oral typhoid, MMR, BCG, yellow fever) has the potential to cause infection in immunocompromised patients. • Allopurinol has the potential to cause mercaptopurine toxicity; please see Section 5 under *"conditions requiring dose reduction".* • Coumarins – Azathioprine/6-Mercaptopurine possibly reduced anticoagulant effects of anticoagulant. • Febuxostat – avoid in combination with Azathioprine/6-6 Mercaptopurine. • Sulfamethoxazole – increased risk of haematological toxicity when Azathioprine/6-Mercaptopurine given concurrently. • Trimethoprim or Co-Trimoxazole – as for Sulfamethoxazole.
	The following drugs may be prescribed with caution: Aminosalicylates, Captopril, Enalapril, possible interactions with Digoxin and Phenytoin (cytotoxics reduce absorption).

7. Adverse drug reactions

For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult Summary of Product Characteristics or BNF

Specialist to detail below the action to be taken upon occurrence of a particular adverse event as appropriate. Most serious toxicity is seen with long-term use and may therefore present first to GPs.

Adverse event System – symptom/sign	**Action to be taken** Include whether drug should be stopped prior to contacting secondary care specialist	**By whom**
Gastrointestinal symptoms (eg: nausea, diarrhoea, vomiting, abdominal discomfort)	Advise patient to divide dosage and take with food. If no improvement, reduce dose and contact secondary care specialist	General practitioner
Jaundice / liver dysfunction	Stop and contact secondary care specialist for advice	General practitioner
Bone marrow suppression (leucopenia, thrombocytopenia)	Contact secondary care specialist for advice	General practitioner
Rash, ulceration	If rash is significant and new, stop drug until rash settles, consider dermatological referral and inform gastroenterologist immediately Consider re-treating at reduced dose (providing no blood dyscrasias).	

The patient should be advised to report any of the following signs or symptoms to their GP without delay:

Signs or symptoms indicating blood dyscrasias eg sore throat, infection, unexplained or abnormal bruising or bleeding.

- Any signs of bone marrow suppression (ie infection, fever, unexplained bruising or bleeding)
- Jaundice

	Other important co-morbidities (e.g. Chickenpox exposure). Include advice on management and prevention and who will be responsible for this in each case: • History of TB – treatment with these drugs should be avoided and infectious diseases specialist advice sought if treatment with Azathioprine deemed necessary. • History of active hepatitis B or C – treatment with these drugs should be avoided (consider vaccination where appropriate). • Live vaccines should not be given concurrently with these treatments. • Pneumococcal and annual influenza vaccines should be given (due to suppressed immune system with these drugs). • Human-Papilloma Virus (HPV) vaccination should be considered. • In non-immune patients exposed to chickenpox or shingles, passive immunization should be carried out using varicella zoster immunoglobulin (VZIG). Patients should try to avoid contact with people who have active chickenpox or shingles and should report any such contact urgently to their GP or specialist.
	Any adverse reaction to a black triangle drug or serious reaction to an established drug should be reported to the MHRA via the "Yellow Card" scheme.
8.Baseline investigations	Baseline monitoring FBC, U&Es, LFTs and creatinine. Pre screening for TPMT may be considered. Full Blood Count (FBC) and Liver function tests (LFTs). *See appendix 1 for summary of monitoring* Weight (kg) – for initial dosing of drugs. TPMT – patients who are deficient or lacking in the enzyme thiopurine methyltransferase (TPMT) are at higher risk of myelosuppression. Patients with reduced TPMT activity can still have treatment but should be monitored monthly and should remain under the care of the Specialist, unless the GP is willing and able to take on this responsibility. The specialist team will undertake initial monitoring of patients including FBC, U+Es and LFTs until therapeutic dose is established, typically weekly for the first month, monthly for 3 months. If dose changes during course of treatment, the specialist service will be responsible for monitoring until patient is stabilised on new regime. Once patient stabilised on medication, shared care will be initiated with the GP.

9. Ongoing monitoring requirements to be undertaken by GP	**Is monitoring required?**		**Yes**		
	Monitoring	**Frequency**	**Results**	**Action**	**By whom**
	FBC	3 monthly	***Neutrophils*** < 0.5x 10^9/l >0.5 < 2x10^9/l **Platelets** <100x10^9/l **White cell count** <3 x10_9/l	**Withhold and contact on call Haematologist** **Withhold until discussed with Specialist (gastroenterologist)** **Investigate VitB12 or Folate and commence supplementation if low**	**GP**
	LFT	3 monthly	**>2-fold increase from upper limit of reference range in AST, ALT, ALP**	**Dose reduction may be required – Discuss with Specialist**	**GP**
	U&E	6 monthly	**Creatinine eGFR**	**If concern discuss with Specialist**	**GP**
10. Pharmaceutical aspects	*e.g. special storage requirements, washout periods Or where there are "no special considerations"* Azathioprine – providing the film coating of the tablets remains intact, there is no risk and no additional precautions are required when handling them. These tablets should not be divided/split/crushed. 6-Mercaptopurine – should be handled following the local recommendations and regulations for the handling and disposal of cytotoxic drugs.				
11. Secondary care contact information	**If stopping medication or needing advice please contact:**				
	Dr *[insert text here]*_____				
	Contact number: *[insert text here]*_____				
	Hospital: *[insert text here]*_____ **E mail contact:** *[insert text here]*_____				
12. Criteria for shared care	Prescribing responsibility will only be transferred when • Treatment is for a specified indication • Treatment has been initiated and established by the secondary care specialist. • The patient's initial reaction to and progress on the drug is satisfactory. • The GP has agreed in writing in each individual case that shared care is appropriate. • The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements.				

13. Responsibilities of initiating specialist	Initiate treatment and prescribe until dose is stable Undertake baseline monitoring. Dose adjustments. Monitor patient's initial reaction to and progress on the drug. Ensure that the patient has an adequate supply of medication until shared care protocol in place Continue to monitor and supervise the patient according to this protocol, while the patient remains on this drug, and agree to review the patient promptly if contacted by the GP. Provide GP with diagnosis, relevant clinical information and baseline results, treatment to date and treatment plan, duration of treatment before consultant review. Provide GP with details of outpatient consultations, ideally within 14 days of seeing the patient *or* inform GP if the patient does not attend appointment. Provide GP with advice on when to stop this drug. Provide patient with relevant drug information to enable Informed consent to therapy. Provide patient with relevant drug information to enable understanding of potential side effects and appropriate action. Provide patient with relevant drug information to enable understanding of the role of monitoring. Provide patient with monitoring booklet where appropriate.
14. Responsibilities of the GP	Continue treatment as directed by the specialist. Ensure no drug interactions with concomitant medicines. To monitor and prescribe in collaboration with the specialist according to this protocol. To ensure that the monitoring and dosage record is kept up to date. To undertake vaccination as directed by the initiating consultant, the BNF or Green Book. Symptoms or results are appropriately actioned, recorded and communicated to secondary care when necessary.
15. Responsibilities of the patient	To take medication as directed by the prescriber, or to contact the GP if not taking medication. To attend hospital and GP clinic appointments, bring monitoring booklet (if issued). Failure to attend will result in medication being stopped (on specialist advice). To report adverse effects to their Specialist or GP.

16.Additional Responsibilities	**List any special considerations**	**Action required**	**By whom**	**Date**
	[insert]	***[insert]***	***[insert]***	***[insert]***
	[insert]	***[insert]***	***[insert]***	***[insert]***
17. Supporting documentation	The SCG must be accompanied by a patient information leaflet.			
18. Patient monitoring booklet	The patient must receive a monitoring booklet from the specialist upon initiation of treatment. The patient must bring this booklet to all specialist and GP appointments where it will be updated by the health professional conducting the appointment. The patient must also produce the booklet to any health professional involved in other aspects of their care e.g. pharmacists and dentists.			
19. Shared care agreement form	Attached below			

Shared Care Agreement Form

Specialist request

***IMPORTANT: ACTION NEEDED**

Dear Dr *[insert Doctors name here]*

Patient name: *[insert Patients name here]*
Date of birth: *[insert date of birth]*
Diagnosis: *[insert diagnosis here]*

This patient is suitable for treatment with *[insert drug name]* for the treatment of
[insert indication]

This drug has been accepted for Shared Care according to the enclosed protocol (as agreed by PAT / NESDAT*). I am therefore requesting your agreement to share the care of this patient.

Treatment was started on *[insert date started]* *[insert dose].*

If you are in agreement, please undertake monitoring and treatment from *[insert date]*

NB: date must be at least 3-4 months from initiation of treatment.

Next review with this department: *[insert date]*
You will be sent a written summary within 14 days. The medical staff of the department are available at all times to give you advice. The patient will not be discharged from out-patient follow-up while taking *[insert text here]*.

Please use the reply slip overleaf and return it as soon as possible.

Thank you.

Yours

[insert Specialist name]

* Approved by NESDAT (North East Sector Drugs and Therapeutics Committee) which includes CCG representation

Shared Care Agreement Form

GP Response

Dear Dr *[insert Doctors name]*

Patient *[insert Patients name]*

Identifier *[insert patient date of birth/address]*

I have received your request for shared care of this patient who has been advised to start *[insert text here]*

A I am willing to undertake shared care for this patient as set out in the protocol

B I wish to discuss this request with you

C I am unable to undertake shared care of this patient.

GP signature Date

GP address/practice stamp

Appendix 1 – Summary Table Specialist Care

IMMUNOSUPPRESSANT MONITORING – Inflammatory bowel disease		**SPECIALIST CARE** (usually transferred from specialist after – 4 months but only when dose and monitoring are stable)				**Additional notes**
Drug	**Typical dose (unlicensed) – see BNF**	**Screening/monitoring**		**Pre-treatment**	**Frequency summary**	
Azathioprine Preparations available: 25 mg and 50 mg tablets	2-2.5 mg/kg daily Can take 12 weeks to exert any effect	Exam	Weight	√		Weight for initial dosing calculation (dose mg/kg basis)
		Phlebotomy	Hep B and C screen	√		If the patient is vaccinated or previously exposed – no action required. If the patient is a chronic carrier they are reviewed in gastroenterology clinic. If the patient is negative – offer vaccination.
			TB screen	√		Complete a TB risk assessment.
			TPMT assay	√		Identifies patients at risk of developing rapid bone marrow suppression, therefore testing before commencing treatment is recommended.
6-Mercaptopurine Preparations available 50 mg tablets	1-1.5 mg/kg daily Can take 12 weeks to exert any effect		FBC (including WCC)	√	Weekly for the first 4 weeks, monthly for 3 months then 3 monthly until dose change / shared care agreement in place	Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. inexplicable bruising or bleeding, infection monitor more frequently if higher doses used or severe hepatic/renal impairment present or if patient has been identified as having reduced TPMT – suggest monthly
			U+Es	√	Baseline monitoring then six monthly until shared care agreement in place	
			LFTs	√	Weekly for the first 4 weeks, monthly for 3 months then 3 monthly until dose change / shared care agreement in place	

Appendix 2 – Summary Table General Practitioner

IMMUNOSUPPRESSANT MONITORING – Inflammatory bowel disease		**General Practitioner** (Care usually transferred from specialist after – 4 months but only when dose and monitoring are stable)				
Drug	**Typical dose (unlicensed) – see BNF**	**monitoring**		**Frequency**	**Results**	**Action**
Azathioprine Preparations available: 25 mg and 50 mg tablets	2-2.5 mg/kg daily	Phlebotomy	FBC (including WCC)	3 monthly	Neutrophils < 0.5 x 10^9/l >0.5 < 2x 10^9/l Platelets < 100 x 10^9/l White Cell Count < 3 x 10g/l	Withhold and contact on call haematologist at PAT With hold and discuss with specialist gastroenterologist With hold and discuss with specialist gastroenterologist With hold and discuss with specialist gastroenterologist
6-Mercaptopurine			Vitamin B12 and folate levels	3 monthly	Low	Consider supplementation
Preparations available 50 mg tablets	1-1.5 mg/kg daily		LFT	3 monthly	> 2 fold increase from upper limit of reference range in AST, ALT and ALP	Discuss with specialist as dose reduction may be required
			U&Es	6 Monthly	If significant electrolyte abnormalities (e.g. 30% rise in creatinine or any concerns)	Discuss with specialist