Azathioprine or Mercaptopurine for Inflammatory Bowel Disease

ESCA: For the treatment of inflammatory bowel disease refractory to 5ASA treatment and/or steroid dependent

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of azathioprine or mercaptopurine for inflammatory bowel disease refractory to 5ASA treatment and/or steroid dependent can be shared between the specialist and general practitioner (GP). You are **invited** to participate; however, if you do not feel confident to undertake this role, then you are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care will be explained to the patient by the specialist initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with inflammatory bowel disease refractory to 5ASA treatment and/or steroid dependent are usually under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

RESPONSIBILITIES and ROLES

Specialist responsibilities
1. Confirm the diagnosis of inflammatory bowel disease.
2. Discuss the potential benefits, treatment side effects, and possible drug interactions with the patient
3. Ask the GP whether he or she is willing to participate in shared care before initiating therapy so that appropriate follow on prescribing arrangements can be made.
4. Do baseline monitoring prior to initiation of azathioprine or mercaptopurine.
5. Initiate treatment and stabilise dose of azathioprine or mercaptopurine.
6. Review the patient's condition and monitor response to treatment regularly.
7. A written summary to be sent promptly to the GP i.e. within 10 working days of a hospital outpatient review or inpatient stay.
8. Report serious adverse events to the MHRA.
9. Ensure clear backup arrangements exist for GPs, for advice and support (please complete details below).

General Practitioner responsibilities						
1. Reply to the request for shared care as soon as practicable i.e. within 10 working days.						
2. Prescribe azathioprine or mercaptopurine at the dose recommended.						
3. In the patient's notes, using the appropriate Read Code listed below, denote that the patient is receiving treatment under a shared care agreement.						
GP Prescribing System	**Read Code**	**Description**		**GP Prescribing System**	**Read Code**	**Description**
EMIS and Vision	8BM5.00	Shared care prescribing		SystmOne	XaB58	Shared care
4. Monitor patient's response to treatment; make dosage adjustments if agreed with specialist						
5. Report to and seek advice from the specialist or clinical nurse specialist on any aspect of patient care that is of concern to the GP, patient or carer and may affect treatment.						
6. Refer back to specialist if condition deteriorates.						
7. Report serious adverse events to specialist and MHRA.						
8. Stop treatment on advice of specialist.						

Patient's role
1. Report to the specialist, clinical nurse specialist or GP if he or she does not have a clear understanding of the treatment
2. Share any concerns in relation to treatment with azathioprine or mercaptopurine with the specialist, clinical nurse specialist or GP
3. Report any adverse effects to the specialist or GP whilst taking azathioprine or mercaptopurine
4. Attend regular outpatient appointments with the specialist

BACK-UP ADVICE AND SUPPORT

Trust	Contact details	Telephone No.	Email address:
	Consultant:-		
	Specialist Nurse		

SUPPORTING INFORMATION

	Azathioprine	Mercaptopurine
Indication	Inflammatory bowel disease	
Dosage and Administration	2-2.5 mg/kg per day in 1 or 2 doses (BSG recommendation)	1.5 mg/kg/day in 1 or 2 doses (BSG recommendation)
Renal Impairment	In patients with renal insufficiency, dosages should be given at the lower end of the normal range.	Consideration should be given to reducing the dosage in patients with impaired renal function.
Hepatic impairment	In patients with hepatic insufficiency, dosages should be given at the lower end of the normal range.	Consideration should be given to reducing the dosage in patients with impaired hepatic function.
Contra-indications / Special precautions	**Contraindications:-** In patients known to be hypersensitive to azathioprine. Hypersensitivity to mercaptopurine In patients who may be pregnant, or who are likely to become pregnant without careful assessment of risk versus benefit **Caution** • Patients receiving azathioprine should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or other manifestations of bone marrow depression. • There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with azathioprine. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Also it has been reported that decreased TPMT activity increases the risk of secondary leukaemias and myelodysplasia in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics • It has been suggested that the toxicity of azathioprine may be enhanced in the presence of renal insufficiency, but controlled studies have not supported this suggestion. Nevertheless, it is recommended that the dosages used should be at the lower end of the normal range and that haematological response should be carefully monitored. Dosage should be further reduced if haematological toxicity occurs.	**Contraindication** Hypersensitivity to any component of the preparation. In view of the seriousness of the indications there are no other absolute contra-indications. **Caution** • Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended. • Treatment with mercaptopurine causes bone marrow suppression leading to leucopenia and thrombocytopenia and, less frequently, to anaemia. Full blood counts must be taken daily during remission induction and careful monitoring of haematological parameters should be conducted during maintenance therapy. • There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppresive effect of 6-mercaptopurine and prone to developing rapid bone marrow depression following the initiation of treatment with mercaptopurine. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfazalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6–mercaptopurine in combination with other cytotoxics. Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore close monitoring of blood counts is still necessary.

	• Caution is necessary during the administration of azathioprine to patients with hepatic dysfunction, and regular complete blood counts and liver function tests should be undertaken. In such patients the metabolism of azathioprine may be impaired, and the dosage of azathioprine should therefore be reduced if hepatic or haematological toxicity occurs. • Patients receiving immunosuppressive therapy are at an increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*. Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor to minimize the risk of skin cancer and photosensitivity, • Infection with varicella zoster virus (VZV; chickenpox and herpes zoster) may become severe during the administration of immunosuppressants. Caution should be exercised especially with respect to the following: • Before starting the administration of immunosuppressants, the prescriber should check to see if the patient has a history of VZV. Serologic testing may be useful in determining previous exposure. Patients who have no history of exposure should avoid contact with individuals with chickenpox or herpes zoster. If the patient is exposed to VZV, special care must be taken to avoid patients developing chickenpox or herpes zoster, and passive immunisation with varicella-zoster immunoglobulin (VZIG) may be considered. • If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.	• Mercaptopurine is hepatotoxic and liver function tests should be monitored weekly during treatment. More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. The patient should be instructed to discontinue mercaptopurine immediately if jaundice becomes apparent • In view of its action on cellular deoxyribonucleic acid (DNA) mercaptopurine is potentially carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment.
Side Effects		
Very common	Depression of bone marrow function; leucopenia.	Bone marrow suppression; leucopenia and thrombocytopenia.
Common	Thrombocytopenia.	Nausea; vomiting; pancreatitis in the IBD population (an unlicensed indication), biliary stasis; hepatotoxicity

Monitoring	Treatment should not be initiated unless patients can be adequately monitored for toxic effects throughout the duration of therapy.	
	Pre-treatment Assessment	Full Blood Count, Urea and Electrolytes, Liver Function Tests TPMT level checked and results must be back before treatment commences.
	After commencing treatment	FBC, LFT every 2 weeks for first 8 weeks, every month for 3 months and thereafter every 3 months.
	Cessation of Treatment	Platelets <120,000 White Blood Cells <3.5, Neutrophils < 2.0 LFTs twice the upper limit of normal (AST or ALP)
	Dose reduction	If WBC <4.0, Neutrophils <2.5 Halve dose Reduce dose if patient suffering from nausea, rash or recurrent infections
	If there is an isolated rise in MCV- investigate other causes (B12, folate, TFTs or alcohol consumption). An isolated high MCV is not an indication to stop treatment.	

	Azathioprine	Mercaptopurine
Drug Interactions	As per BNF May 2015 online. For more information please refer to the SmPC	As per BNF May 2015 online. For more information please refer to the SmPC

Agent	Notes
Allopurinol	enhanced effects and increased toxicity of azathioprine when given with allopurinol (reduce dose of azathioprine to one quarter of usual dose)
Captopril	increased risk of anaemia or leucopenia when azathioprine given with captopril especially in renal impairment
Coumarins	azathioprine possibly reduces anticoagulant effect of coumarins **Note:** Change in patient's clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect anticoagulant control
Enalapril	increased risk of anaemia when azathioprine given with enalapril especially in renal impairment
Febuxostat	avoidance of azathioprine advised by manufacturer of febuxostat
Ribavirin	myelosuppressive effects of azathioprine possibly enhanced by ribavirin
Sulfamethoxazole	increased risk of haematological toxicity when azathioprine given with sulfamethoxazole (as co-trimoxazole)
Trimethoprim	increased risk of haematological toxicity when azathioprine given with trimethoprim (also with co-trimoxazole)

Agent	Notes
Allopurinol	Enhanced effects and increased toxicity of mercaptopurine when given with allopurinol (reduce dose of mercaptopurine to one quarter of usual dose)
Coumarins	Mercaptopurine possibly reduces anticoagulant effect of coumarins **Note:** Change in patient's clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect anticoagulant control
Dairy Products	Plasma concentration of mercaptopurine possibly reduced by dairy products —manufacturer of mercaptopurine advises give at least 1 hour before or 2 hours after dairy products
Febuxostat	Avoidance of mercaptopurine advised by manufacturer of febuxostat
Sulfamethoxazole	Increased risk of haematological toxicity when mercaptopurine given with sulfamethoxazole (as co-trimoxazole)
Trimethoprim	Increased risk of haematological toxicity when mercaptopurine given with trimethoprim (also with co-trimoxazole)
Clozapine	Avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis) **Note:** Avoid concomitant use of clozapine with drugs that have a substantial potential for causing agranulocytosis

Reference

SmPC Mercaptopurine
SmPC Imuran
Guidelines for the management of inflammatory bowel disease in adults - Gut (2011) Mowat C, Cole A, Windsor A, et al.

I agree to participate in this shared care agreement for the treatment of the below named patient with azathioprine or mercaptopurine for inflammatory bowel disease refractory to 5ASA treatment and/or steroid dependent

General Practitioner
Name (please print)_____Signature _____Date_____

Hospital Specialist/Consultant
Name (please print)_____Signature_____Date_____

Patient's name	Date of birth	Sex	Home Address	Hospital Number
				NHS Number

Please keep a copy of this agreement for your own records and forward the original to the above named Consultant at: