Azathioprine

(either alone or more usually in combination with corticosteroids and/or other drugs and procedures)

ESCA: For the treatment of systemic lupus erythematosus / dermatomyositis, polymyositis and pemphigus vulgaris

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 in systemic lupus erythematosus / dermatomyositis and polymyositis 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 systemic lupus erythematosus / dermatomyositis and polymyositis 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 systemic lupus erythematosus / dermatomyositis and polymyositis
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
5. Initiate treatment and stabilise dose of azathioprine
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 via Yellow Card Scheme https://yellowcard.mhra.gov.uk
9. Ensure clear backup arrangements exist for GPs, for advice and support (please complete contact details in appendix 1)

General Practitioner responsibilities						
1. Reply to the request for shared care as soon as practicable i.e. within 10 working days						
2. Prescribe azathioprine at the dose recommended						
3. Adjust the dose as advised by the specialist.						
4. 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
5. Monitor patient's response to treatment; make dosage adjustments if agreed with specialist						
6. 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						
7. Refer back to specialist if condition deteriorates						
8. Report serious adverse events to specialist and MHRA via the Yellow Card Scheme https://yellowcard.mhra.gov.uk						
9. 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. Attend regularly for required blood tests and annual health checks.
3. Share any concerns in relation to treatment with azathioprine with the specialist, clinical nurse specialist or GP
4. Report any adverse effects to the specialist or GP whilst taking azathioprine
5. Attend regular outpatient appointments with the specialist

Please enter Specialist contact details and patient specific information in Appendix 1

SUPPORTING INFORMATION

Indication	For the treatment of systemic lupus erythematosus / dermatomyositis and polymyositis	
Dosage and Administration	starting dosage	In general, is from 1 to 3 mg/kg body weight/day, and should be adjusted, within these limits, depending on the clinical response (which may not be evident for weeks or months) and haematological tolerance. When therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the maintenance of that response. If no improvement occurs in the patient's condition within 3 months, consideration should be given to withdrawing azathioprine
	maintenance dosage	Range from less than 1 mg/kg body weight/day to 3 mg/kg body weight/day, depending on the clinical condition being treated and the individual patient response, including haematological tolerance.
Renal Impairment **Hepatic impairment**	In patients with renal and/or hepatic insufficiency, dosages should be given at the lower end of the normal range.	
Patients with NUDT15 variant	Patients with inherited mutated NUDT15 gene are at increased risk for severe azathioprine toxicity. These patients generally require dose reduction; particularly those being NUDT15 variant homozygotes. Genotypic testing of NUDT15 variants may be considered before initiating azathioprine therapy. In any case, close monitoring of blood counts is necessary.	

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.
	• 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.	

Side Effects	Very common	Depression of bone marrow function; leucopenia.
	Common	Nausea (dose related), diarrhoea, headache, arthralgia. These symptoms often improve over time. Rash or mouth ulcers may respond to a dose reduction otherwise treatment should be discontinued. Thrombocytopenia.
	Less common	Hair Loss, neutopenia, leucopenia, pancreatitis, hepatitis- discontinue treatment. For a full list of ADRs refer to the product SPC. Influenza and Pneumovax vaccination is

		recommended.
Monitoring	Pre-treatment assessment	Full Blood Count, Urea and Electrolytes, Liver Function, renal function, C-Reactive protein Tests TPMT level checked and results must be back before treatment commences.
		From BAD:- Hepatitis B and C serology HIV serology, especially in high-risk groups VZV serology (if no history of varicella)
	After commencing treatment	FBC, LFT every 2 weeks for first 8 weeks, every month for 3 months and thereafter every 3 months.
	TPMT range	**Azathioprine maintenance dose (mg kg)1 daily)**
	Absent	In general unsuitable for azathioprine
	Intermediate	1.0-1.5
	Normal	2.0-3.0
	Actions to be taken: (*Based on BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists (2008))*	
	WBC < 3.5 x 10^9/L	*Withhold azathioprine ; consider discussing with specialist team.*
	Neutrophils < 2.0 x 10^9/L	*Withhold azathioprine ; consider discussing with specialist team.*
	Platelets < 150 x 10^9/L	*Withhold azathioprine ; consider discussing with specialist team.*
	MCV > 105 fl	Check serum folate and B12 & TSH. Treat any underlying abnormality. If results normal discuss with specialist team.
	LFT (AST & ALT) greater than 2 times the upper limit of normal	*Withhold azathioprine ; consider discussing with specialist team.*
	Rash or oral ulceration	*Withhold azathioprine ; consider discussing with specialist team.*
	Abnormal bruising or severe sore throat	*Withhold until FBC results available and discuss with the specialist team.*
	Other (From BAD)	*Advise on the need for pneumococcal vaccine and a yearly influenza vaccination.* *Discuss the possible increased risk of malignancy with longterm use* *Give advice on sunscreens and sun avoidance* *Caution regarding avoidance of pregnancy*

Drug Interactions (severe interaction as outlined in BNF, please see BNF and SPC for more detail)

Medication	Interaction	Severity of interaction	Evidence for interaction	Action
Allopurinol	Allopurinol potentially increases the risk of haematological toxicity when given with azathioprine.	Severe	Study	Manufacturer advises adjust azathioprine dose.
Bacillus Calmette-Guérin vaccine	Bacillus Calmette-Guérin vaccine is predicted to increase the risk of generalised infection (possibly life-threatening) when given with azathioprine (high-dose).	Severe	Theoretical	Public Health England advises avoid (refer to Green Book).
Captopril	Captopril is predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine.	Severe	Anecdotal	
Enalapril	Enalapril is predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine.	Severe	Anecdotal	
Febuxostat	Febuxostat is predicted to increase the exposure to azathioprine.	Severe	Theoretical	Manufacturer advises avoid.
Fosinopril	Fosinopril is predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine.	Severe	Anecdotal	
Imidapril	Imidapril is predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine.	Severe	Anecdotal	
Influenza vaccine (live)	Influenza vaccine (live) is predicted to increase the risk of generalised infection (possibly life-threatening) when given with azathioprine (high-dose).	Severe	Theoretical	Public Health England advises avoid (refer to Green Book).
Lisinopril	Lisinopril is predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine.	Severe	Anecdotal	
Measles, mumps and rubella vaccine, live	Measles, mumps and rubella vaccine, live is predicted to increase the risk of generalised infection (possibly life-threatening) when given with azathioprine (high-dose).	Severe	Theoretical	Public Health England advises avoid (refer to Green Book).
Moexipril	Moexipril is predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine.	Severe	Anecdotal	
Perindopril	Perindopril is predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine.	Severe	Anecdotal	
Quinapril	Quinapril is predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine.	Severe	Anecdotal	
Ramipril	Ramipril is predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine.	Severe	Anecdotal	
Rotavirus vaccine	Rotavirus vaccine is predicted to increase the risk of generalised infection (possibly life-threatening) when given with azathioprine (high-dose).	Severe	Theoretical	Public Health England advises avoid (refer to Green Book).
Trandolapril	Trandolapril is predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine.	Severe	Anecdotal	
Typhoid vaccine, oral	Typhoid vaccine, oral is predicted to increase the risk of generalised infection (possibly life-threatening) when given with azathioprine (high-dose).	Severe	Theoretical	Public Health England advises avoid (refer to Green Book).
Varicella-zoster vaccine	Varicella-zoster vaccine is predicted to increase the risk of generalised infection (possibly life-threatening) when given with azathioprine (high-dose).	Severe	Theoretical	Public Health England advises avoid (refer to Green Book).
Yellow fever vaccine, live	Yellow fever vaccine, live is predicted to increase the risk of generalised infection (possibly life-threatening) when given with azathioprine (high-dose).	Severe	Theoretical	Public Health England advises avoid (refer to Green Book).

References

British Association of Dermatologists - Guidelines for prescribing azathioprine 2011
BNF Online
SmPC azathioprine

Appendix 1:

Effective Shared Care Agreement (ESCA)

Azathioprine

For the treatment of systemic lupus erythematosus / dermatomyositis and polymyositis / pemphigus vulgaris

Please refer to BSSE APC formulary website for complete document.

BACK-UP ADVICE AND SUPPORT (To be completed by Specialist team)

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

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

Hospital Specialist/Consultant
Name (please print)_____Signature_____Date_____

To be completed by the General Practitioner:

I agree to participate in this shared care agreement for the treatment of the below named patient with *azathioprine in systemic lupus erythematosus / dermatomyositis and polymyositis / pemphigus vulgaris*

General Practitioner
Name (please print)_____Signature _____Date_____

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

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