Azathioprine (in conjunction with prednisolone)

ESCA: For the treatment of Interstitial lung disease

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 conjunction with prednisolone) for Interstitial lung disease 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 Interstitial lung disease 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 Interstitial lung 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 (in conjunction with prednisolone)
5. Initiate treatment and stabilise dose of Azathioprine (in conjunction with prednisolone)
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 (in conjunction with prednisolone) 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 (in conjunction with prednisolone) with the specialist, clinical nurse specialist or GP
3. Report any adverse effects to the specialist or GP whilst taking Azathioprine (in conjunction with prednisolone)
4. Attend regular outpatient appointments with the specialist

BACK-UP ADVICE AND SUPPORT

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

Based on MTRAC template
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Interface Lead Pharmacist
Birmingham CrossCity CCG

SUPPORTING INFORMATION

Indication (Unlicensed)	Azathioprine tablets are used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and procedures which influence the immune response. Azathioprine is usually used together with steroids. Using Azathioprine can sometimes allow a lower dose of steroids to be taken. In respiratory disease, it is used in the treatment of conditions such as fibrosis, vasculitis and sarcoidosis. It is usually given over months to years and benefit may not be noted for several weeks.
Dosage and Administration	Azathioprine (2 mg/kg, maximum 150 mg/ day) with prednisolone (see below for dose) • Appropriate counselling should be given to all patients started on specific regimes.
Agent	Azathioprine tablets
Renal Impairment	In patients with renal insufficiency, dosages should be given at the lower end of the normal range
Hepatic impairment	In patients with hepatic insufficiency, dosages should be given at the lower end of the normal range
Contra-indications / Special precautions	**Contraindications:-** In patients known to be hypersensitive to azathioprine. Hypersensitivity to 6-mercaptopurine (6-MP) 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.

<table>
<tr><td rowspan="2">Side Effects</td><td>Very common</td><td>Depression of bone marrow function; leucopenia.</td></tr>
<tr><td>Common</td><td>Thrombocytopenia.</td></tr>
<tr><td>Monitoring</td><td colspan="2">Treatment should not be initiated unless patients can be adequately monitored for toxic effects throughout the duration of therapy.</td></tr>
<tr><td>Pretreatment Assessment</td><td colspan="2">Full Blood Count, Urea and Electrolytes, Liver Function Tests, Renal, C-reactive protein</td></tr>
<tr><td>After commencing treatment</td><td colspan="2">FBC, LFT every week for first month then every 2 weeks for the second month and thereafter every month until stable after which monitor every 3 months.</td></tr>
<tr><td>Disease monitoring</td><td colspan="2">Occasional ESR/CRP helps assessment</td></tr>
<tr><td>Cessation of treatment (seek advice)</td><td colspan="2">• Platelets <120.000
• WBC <3.5 N <2.0
• LFTs 2x upper normal limit</td></tr>
<tr><td>Dose reduction</td><td colspan="2">Side effects:- nausea, diarrhoea rash, recurrent infection</td></tr>
<tr><td>Important notes</td><td colspan="2">• Live vaccines should not be administered
• Influenza and Pneumovax vaccines are recommended
• Patients without immunity who are exposed to chickenpox or shingles should be administered Varicella Zoster Immunoglobulin
• Effective contraception should be recommended during therapy
• Patient should be counselled to observe for signs of bone marrow suppression i.e inexplicable bruising, bleeding or infection</td></tr>
<tr><td>Drug interaction (significant interaction as outlined in BNF, please see BNF and SPC for more detail)</td><td colspan="2">As per BNF May 2015 online. For more information please refer to the SmPC
<table>
<tr><td>Allopurinol</td><td>enhanced effects and increased toxicity of azathioprine when given with allopurinol (reduce dose of azathioprine to one quarter of usual dose)</td></tr>
<tr><td>Coumarins</td><td>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</td></tr>
<tr><td>Febuxostat</td><td>avoidance of azathioprine advised by manufacturer of febuxostat</td></tr>
<tr><td>Ribavirin</td><td>myelosuppressive effects of azathioprine possibly enhanced by ribavirin</td></tr>
<tr><td>Sulfamethoxazole</td><td>increased risk of haematological toxicity when azathioprine given with sulfamethoxazole (as co-trimoxazole)</td></tr>
<tr><td>Trimethoprim</td><td>increased risk of haematological toxicity when azathioprine given with trimethoprim (also with co-trimoxazole)</td></tr>
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Agent	Prednisolone (Non EC)
Indication	**Suppression of inflammatory and allergic disorders**
Dosage and Administration	The lowest effective dose should be used for the minimum period in order to minimise side effects Prednisolone (tapering from 0.5 mg/day to 10–20 mg/ day) with azathioprine (see above for dose)

Contra-indications / Special precautions	**Contraindications**
	Hypersensitivity to any ingredients in the formulation.
	Systemic infections unless specific anti-infective therapy is employed.
	Patients with ocular herpes simplex due to the possibility of perforation.
	Cautions
	• Patients should carry "steroid treatment" cards which give clear guidance on the precautions to be taken to minimise risk and provide details of prescriber, drug, dosage and duration of treatment.
	• Adrenal suppression:- Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment.
	• Patients/and or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure, although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.
	• Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.
	• Caution is necessary when corticosteroids, including prednisolone, are prescribed to patients with the following conditions and frequent patient monitoring is necessary:
	  • Diabetes mellitus or in those with a family history of diabetes.
	  • Glaucoma or in those with a family history of glaucoma.
	  • Hypertension or congestive heart failure.
	  • Liver failure.
	  • Epilepsy.
	  • Osteoporosis: This is of special importance in post-menopausal females who are at particular risk.
	  • Patients with a history of severe affective disorders and particularly those with a previous history of corticosteroid induced psychoses.
	  • Peptic ulceration.
	  • Previous steroid myopathy.
	  • Renal insufficiency.
	  • Tuberculosis: Those with a history of, or X-ray changes characteristic of tuberculosis. The emergence of active tuberculosis can, however, be prevented by the prophylactic use of antituberculous therapy.
	  • Recent myocardial infarction (rupture).
	  • Chickenpox: Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunisation with varicella/zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants special care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

	• Measles: Patients are advised to avoid exposure to measles, medical advice should be sought if exposure occurs. Propylaxis with intramuscular normal immunoglobulin may be needed. • Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised. • The effect of corticosteroids may be enhanced in patients with hypothyroidism in those with chronic liver disease with impaired hepatic function. • Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished. • Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. **Withdrawal** In patients who have received more than physiological doses of systemic corticosteroids (approximately 7.5mg prednisolone or equivalent) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose equivalent to 7.5mg of prednisolone is reached, dose reduction should be slower to allow the HPA-axis to recover. Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 40mg daily of prednisolone, or equivalent for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be considered even after courses lasting 3 weeks or less: • Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks, • When a short course has been prescribed within one year of cessation of long-term therapy (months or years), • Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy, • Patients receiving doses of systemic corticosteroid greater than 40mg daily of prednisolone, • Patients repeatedly taking doses in the evening. During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily reintroduced.	
Side Effects	Common	Irritability, depressed and labile mood, suicidal thoughts, psychotic reactions, mania, delusions, hallucinations, and aggravation of schizophrenia. behavioural disturbances, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia.
Monitoring	See cautions	

Drug interaction (significant interaction as outlined in BNF, please see BNF and SPC for more detail)	Prednisolone belongs to **Corticosteroids** and will have the following interactions:

Note: Interactions do not generally apply to corticosteroids used for topical action (including inhalation) unless specified	
Aldesleukin	avoidance of corticosteroids advised by manufacturer of aldesleukin
Amphotericin	increased risk of hypokalaemia when corticosteroids given with amphotericin —avoid concomitant use unless corticosteroids needed to control reactions **Note:** Close monitoring required with concomitant administration of nephrotoxic drugs or cytotoxics
Coumarins	corticosteroids may enhance or reduce anticoagulant effect of coumarins (high-dose corticosteroids enhance anticoagulant effect) **Note:** Change in patient's clinical condition, particularly associated with liver disease, inter current 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
Fosphenytoin	metabolism of corticosteroids accelerated by fosphenytoin(reduced effect)
Phenobarbital	metabolism of corticosteroids accelerated by phenobarbital (reduced effect)
Phenytoin	metabolism of corticosteroids accelerated by phenytoin(reduced effect)
Primidone	metabolism of corticosteroids accelerated by primidone(reduced effect)
Rifamycins	metabolism of corticosteroids accelerated by rifamycins(reduced effect) **Note:** Interactions do not apply to rifaximin
Ritonavir	plasma concentration of corticosteroids possibly increased by ritonavir —increased risk of adrenal suppression
Vaccines	high doses of corticosteroids impair immune response to vaccines — avoid concomitant use with live vaccines

References

- Prednisolone SmPC
- Prednisolone BNF
- Azathioprine SmPC
- Azathioprine BNF
- Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008;63;v1-v58

I agree to participate in this shared care agreement for the treatment of the below named patient with Azathioprine (in conjunction with prednisolone) for Interstitial lung disease

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: