There is a new NEL-wide SCG for Azathioprine and Mercaptopurine for all indications which supersedes this document. Please refer to the new NEL-wide SCG for up to date information on use of Azathioprine, and continue to use this (existing) version for Mycophenolate. Access the NEL-wide Azathioprine and Mercaptopurine here: https://primarycare.northeastlondon.icb.nhs.uk/home/meds/nel-wide-non-mental-health/

BHR CCG's and BHRUT NHS Trust Shared Care Guidelines

AZATHIOPRINE & MYCOPHENOLATE MOFETIL
IN RESPIRATORY MEDICINE

DOCUMENT TO BE SCANNED INTO ELECTRONIC RECORDS AND FILED IN NOTES

Patient Full Name:	**NHS No:**
Date of Birth: `	**Hospital Number:**
Name of Referring Consultant:	**Contact number:**

INTRODUCTION

Azathioprine and Mycophenolate Mofetil are immunosuppressant agents used in inflammatory interstitial lung disease (ILD). Their use is widely established in treating these conditions and is supported by the British Thoracic Society (BTS).

Azathioprine is metabolised by the enzyme thiopurine methyltransferase (TPMT). TPMT activity is a mandatory test performed prior to commencement of azathioprine. Approximately 11% of patients have intermediate TPMT activity and are at greater risk of adverse drug reactions on standard doses and 0.3% have no detectable TPMT activity and are at risk of suffering life-threatening complications even when treated with low doses of either drug.

Drug name	Indication	Oral Dose and administration	Adverse effects
Azathioprine	**Unlicensed indications:** Inflammatory interstitial lung diseases where corticosteroids alone are not effective in controlling the disease: e.g. connective tissue disease-associated ILD (CTD-ILD), Idiopathic pneumonitis with autoimmune features (IPAF), nonspecific interstitial pneumonia (NSIP), hypersensitivity pneumonitis (HP), pulmonary sarcoidosis	**High TPMT level (>150microU/L):** Dose- 1mg to 3 mg/kg daily Drug should be started at half target dose for *first week* to minimise side effects **Normal TPMT level (68 – 150microU/L):** Dose- 0.5mg to 1.5mg/kg daily **Deficient (<10microU/L) - Low 20 – 67microU/L) TPMT level:** Avoid usage of azathioprine	• Dose related bone marrow suppression • Liver impairment • Cholestatic jaundice • Hypersensitivity reactions (malaise, dizziness, vomiting, diarrhoea, fever, rigors, rash, interstitial nephritis) • Rarely pancreatitis, or pneumonitis • Nausea • Alopecia See BNF for further information

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Mycophenolate Mofetil (MMF)	**Unlicensed indications:** Inflammatory interstitial lung diseases where corticosteroids alone are not effective in controlling the disease: e.g. connective tissue disease-associated ILD (CTD-ILD), Idiopathic pneumonitis with autoimmune features (IPAF), nonspecific interstitial pneumonia (NSIP), hypersensitivity pneumonitis (HP)	Dose range is between 1g and 3 g daily, dependant on indication and patient, determined by Respiratory consultant	• Nausea, vomiting, constipation, diarrhoea & indigestion • Anaemia • Prone to infections • Excessive bleeding • Bruising of skin • Long-term use of MMF can increase the risk of developing skin cancers in fair-skinned. See BNF for further information

Cautions

Azathioprine:

- Thiopurine methyltransferase (TPMT) status
- Monitoring of FBC, U&E, LFT (see monitoring standards below)
- Reduce dose in elderly, hepatic & renal impairment
- Increased risk of haematological toxicity with co-trimoxazole/trimethoprim
- Patients must avoid 'live' vaccines such as oral polio, MMR, BCG, nasal Flu vaccine and yellow fever
- Patients should avoid contact with people who have active chickenpox or shingles and should report any such contact urgently to their GP or specialist
- Careful assessment of risk versus benefit should be carried out before use during pregnancy and breast-feeding.
- Any other interacting drugs (refer to the latest BNF Edition)
- Avoid prescribing allopurinol in patients on azathioprine due to a clinically significant interaction that can lead to increased toxicity. If concomitant prescription of allopurinol is required, then 25% of the original dose of azathioprine must be given

Mycophenolate Mofetil (MMF):

- Avoid sun exposure and protect your skin with a sun screen, which has a high protection SPF (SPF 30 or more) to protect against UVB, and the UVA circle logo and/or 4 or 5 UVA stars to protect against UVA.
- Women must not become pregnant or breast feed during MMF treatment and must use contraceptive measures during treatment and for 6 weeks after the last dose of MMF.
- Men to use barrier contraceptive methods during the treatment and for 90 days after the last dose.
- MMF may interact with other medication e.g. antacids, anti-epileptics, antibiotics (e.g. metronidazole, norfloxacin, rifampicin), antivirals (e.g. aciclovir) and some antipsychotics (e.g. Clozapine).
- Avoid live vaccines during MMF treatment. If immunisation with a live vaccine requires, MMF should be stopped 6 months before and until 2 weeks after the vaccination. Flu vaccines (not nasal Flu vaccine) and Pneumovax are safe and recommended.

Contra-indications

Azathioprine:

a) Hypersensitivity to azathioprine or to any of the excipients
b) Severe infections
c) Severely impaired hepatic or bone-marrow function.
d) Thiopurine methyltransferase (TPMT) deficiency
e) Pancreatitis
f) Concomitant use of any live vaccines especially BCG, smallpox, yellow fever
f) Pregnancy- Treatment should not generally be initiated during pregnancy. Careful assessment of risk versus benefit.
g) Lactation. (May use if potential benefit outweighs risk)

Mycophenolate Mofetil (MMF)

a) Hypersensitivity to MMF or to any other excipients
b) Severe infections
c) Malignancy
d) Severely impaired hepatic or bone-marrow function.
e) Concomitant use of any live vaccines
f) Pregnancy- Treatment should not generally be initiated during pregnancy.
g) Lactation

Initiating monitoring standards for Azathioprine & Mycophenolate Mofetil (MMF) to be undertaken at BHRUT NHS Trust

PARAMETER	BLOOD RESULT	ACTION
Pre-treatment	FBC, U&Es, LFTs, TPMT phenotype Varicella Zoster serology	Results to be known before drug is commenced
Monitoring	FBC, LFT, U&E	At initiation and after any dose changes (monitored by hospital) - Every week for 4 weeks. Thereafter at least every 3 months, until patient clinically stable

Monitoring standards for Azathioprine & Mycophenolate Mofetil (MMF) to be undertaken by GP

PARAMETER	BLOOD RESULT	ACTION
Monitoring	FBC, LFT, U&E	Every 3 months

Actions for GPs on monitoring patients blood results & symptoms

Please see recommendations table below for general medical management of a patient presenting with the following blood results & symptoms:

BLOOD RESULT	ACTION
Neutrophils < 1.5 x 10^9/L AST/ALT > 4 fold rise (from upper normal limit)	**STOP** Azathioprine & Mycophenolate Mofetil Contact specialist hospital clinician
Neutrophils < 2.0 x 10^9/L Lymphocytes < 0.5 x 10^9/L Platelets < 150 x 10^9/L AST/ALT > 2 fold rise (from upper normal limit)	Discuss with specialist hospital clinician
GFR 20-50ml (Mild) renal impairment GFR 10-20ml/min- (Moderate) renal impairment GRF <10ml/min (Severe) renal impairment	Discuss with specialist hospital clinician
MCV > 105 fl	Check B12, TFT and Folate. GP to start supplementation if low
SYMPTOMS	**ACTION**
Rash, abnormal bruising or bleeding, Severe or persistent sore throat, infection, fever, rigors, oral ulceration Jaundice Abdominal pain suggestive of pancreatitis	**STOP** Azathioprine and Mycophenolate Mofetil Discuss with Dermatology nurse or specialist hospital clinician

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Exposure to Varicella	If patient is non-immune and in contact with varicella or shingles, they will require Varicella Zoster immunoglobulin within the first 10 days of exposure. Please contact Consultant Microbiologist for advice. Supplies of this can be obtained from the Health Protection Agency (HPA) (contact details are available from the HPA website (http://www.hpa.org.uk)"

AZATHIOPRINE & MYCOPHENOLATE MOFETIL

SHARED CARE

Sharing of care assumes communication between the specialist, GP and the patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy.

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

SHARED CARE RESPONSIBILITIES

Consultant

1. Doctor to check interactions with existing therapies before initiating treatment
2. Initiate treatment and prescribe until patient is on a stable dose (minimum 1 month's treatment) and the GP formally agrees to shared care
3. If dose change required, recall patient to monitor until stable
4. Send a letter to the GP requesting shared care for this patient.
5. Clinical and laboratory supervision of the patient at routine clinic follow-up on a regular basis.
6. Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated
7. Evaluation of any reported adverse effects by GP or patient.
8. Advise GP on review, duration or discontinuation of treatment where necessary.
9. Inform GP of patients who do not attend clinic appointments within 2 weeks
10. Ensure that backup advice is available at all times.
11. Provide appropriate written or verbal information to patient, including the need for regular blood monitoring

General Practitioner

1. Monitor patient's overall health and well-being.
2. Prescribe the drug treatment as described after the first three months of stabilisation.
3. Monitor blood results (FBC, LFT U&E) in line with recommendations in this document after the first three months of stabilisation.
4. Report any adverse events to the consultant, where appropriate.
5. Report any adverse events to the CSM, where appropriate.
6. Help in monitoring the progression of disease.

CCG

1. To provide feedback to the Trust via Trust Medicines Optimisation Group
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
3. To support trusts in resolving issues that may arise as a result of shared care.

Patient

1. Report promptly any adverse effects to their GP and/or specialist whilst taking azathioprine/ mycophenolate.
2. Ensure they have a clear understanding of their treatment.
3. Report any changes in disease symptoms to GP and/or specialist whilst taking azathioprine /mycophenolate
4. Discuss with GP and/or specialist of any change of circumstance that could affect management of disease e.g. plans for pregnancy whilst taking azathioprine/ mycophenolate, recent exposure to active chickenpox or shingles.

Costs

Drug Product	Mims online (exc.VAT) (Accessed 01/02/2017)
Mycophenolate Mofetil 500mg tablet s (50 tabs)	£6.17
Mycophenolate Mofetil 250mg capsules (100 caps)	£82.26
Azathioprine 50mg tablets (56 tabs)	£2.21
Azathioprine 25mg tablets (28 tabs)	£1.66

Contact Numbers for advice and support

Barking, Havering and Redbridge University Hospitals NHS Trust	
Consultant via switchboard Registrar on-call out of hours	Queens Hospital- 01708 435000 Bleep via switchboard
Pharmacy Medicines Information Department	01708 435 418
BHR CCG Medicines Management Team.	0208 822 3074
FAX number Queens Hospital	01708 503 104

References

1. BNF 72. September 2016- March 2017
2. Mims online
3. www.medicines.org.uk
4. Renal drug handbook, 3rd Edition, Ashley C & Currie A, 2009
5. (British Thoracic Society) Interstitial Lung Disease Guideline, Thorax 2008; 63, v1-v58
6. http://www.bad.org.uk/shared/get-file.ashx?id=108&itemtype=document
7. http://www.bad.org.uk/search?search=mycophenolate
8. http://www.bad.org.uk/shared/get-file.ashx?id=42&itemtype=document

Refer to the relevant BHR CCG website to obtain the latest version of this guideline

http://www.barkingdagenhamccg.nhs.uk/About-us/Medicines-management/shared-care-guidelines.htm
http://www.haveringccg.nhs.uk/About-us/medicines-management/shared-care-guidelines.htm
http://www.redbridgeccg.nhs.uk/About-us/Medicines-management/shared-care-guidelines.htm

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APPENDIX 1

Barking, Havering and Redbridge University Hospitals NHS Trust

This form will be completed by the Hospital Specialist and given to the patient.

Shared Care information Form

You have been prescribed ……..t**ablets**
for ……..
This treatment should be continued until stopped by your doctor

Your GP has been given all the necessary information regarding your condition and treatment.

The date for your next hospital appointment is ……

The success and safety of your treatment also **depends on you.**

- You will have been given information from the Respiratory department, which tells you about your treatment and condition
- Avoid excessive alcohol consumption
- Do not take any over-the-counter medicines, herbal, complementary or alternative medicines and treatments without getting advice from your doctor
- Avoid contact with chicken pox or shingles. If you do, please inform your GP/ Consultant no later than 10 days from exposure
- Avoid driving and hazardous work until you have learned how azathioprine or mycophenolate mofetil affects you, as these drugs can occasionally cause dizziness.
- Azathioprine and mycophenolate mofetil increase the skin's sensitivity to sunlight and the risk of developing some forms of skin cancer. Use sun block and wear a hat and light clothing when out in strong sunshine. Do **not** use sunlamps or sun beds.
- You will need to have blood tests at least every three months
- Your GP/ Practice Nurse needs to see you every ……

If you experience any of the following side-effects, urgently see your GP:

- Mouth ulcer, sore throat, sore mouth
- Feeling generally unwell
- Feeling sick, upset stomach, diarrhoea.
- Rashes – new rash or severe itching anywhere on the body.

Stop treatment and get immediate medical advice if you develop:

- An infection with fever and or chills or a severe sore throat
- Sudden shortness of breath (breathlessness)
- The whites of your eyes or skin become yellow
- Severe itching of the skin
- New unexplained bleeding or bruising
- Severe and continuing abdominal pain or diarrhea or vomiting

If you think you are pregnant contact the Dermatology nurse or specialist

If you have any concerns about your treatment contact your GP or the hospital.

Direct-dial telephone numbers for the department are……

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APPENDIX 2

Barking, Havering and Redbridge University Hospitals NHS Trust

Mycophenolate Mofetil Shared Monitoring Agreement Letter

Name of GP ……..… Address ……
Drop code of GP……. ……..…
..……

Dear GP

Re: Patient's name……..……Date of birth……..……

Hospital number……..……NHS number……..……

Indication for treatment……

Patient is on **Mycophenolate Mofetil …...…mg tablets**

Take…… tablets (……mg) ……..times per day

This patient is being treated with mycophenolate for the above condition. This treatment will be long term. I hope that you will agree to share the care of this patient with the hospital.

Enclosed is a copy of the shared care monitoring guidelines for mycophenolate mofetil to be retained in the patient's notes. It is safer for monitoring and prescribing to be done by the same clinician. It is not possible for secondary care to do all the prescribing. Should you agree to take over responsibility for monitoring, we will send a letter containing the details of the patient's treatment plan, the dose to be prescribed and all relevant blood results.

The patient has been given drug information regarding Mycophenolate Mofetil	Please tick ☐
The patient has been initiated and is on a stable dose of treatment.	Please tick ☐
The patient has been counselled about the need for regular blood test monitoring	Please tick ☐
The patient has been advised to seek urgent medical attention in the event of a febrile illness.	Please tick ☐

You must ensure access to blood results to **enable you to prescribe further Mycophenolate Mofetil**

Please sign below and return this letter by fax to the Hospital Specialist if you agree to take over shared monitoring for this patient.

Hospital site to send fax to: Queens Hospital

Many thanks

Hospital Specialist	GP
Signature……..	Signature……..
Name ……..……..	Name ……..
Date……..	Date……..…..……..

If you are not taking on the monitoring responsibility for this patient please state the reason why and return this letter to the Hospital Specialist

……

You will retain the responsibility to check the blood results prior to prescribing. This should be available via electronic access, or please provide your drop code to enable the patient's blood results to be sent to you.

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APPENDIX 3

Barking, Havering and Redbridge University Hospitals NHS Trust

Azathioprine Shared Monitoring Agreement Letter

Name of GP ……..… Address ……
Drop code of GP…… ……
……

Dear GP

Re: Patient's name……..……Date of birth…….……

Hospital number……..……NHS number……

Indication for azathioprine treatment…….……

Patient is on **Azathioprine …….mg tablets**

Take…… tablets (……mg) …….. times per day

This patient is being treated with Azathioprine for the above condition. This treatment will be long term. I hope that you will agree to share the care of this patient with the hospital.

Enclosed is a copy of the shared care monitoring guidelines for Azathioprine to be retained in the patient's notes. It is safer for monitoring and prescribing to be done by the clinician. It is not possible for secondary care to do all the prescribing.
Should you agree to take over responsibility for monitoring, we will send a letter containing the details of the patient's treatment plan, the dose to be prescribed and all relevant blood results.

The patient has been given drug information regarding Azathioprine	Please tick ☐
The patient has been initiated and is on a stable dose of treatment.	Please tick ☐
The patient has been counselled about the need for regular blood test monitoring	Please tick ☐
The patient has been advised to seek urgent medical attention in the event of a febrile illness.	Please tick ☐

You must ensure access to blood results to **enable you to prescribe further azathioprine.**

Please sign below and return this letter by fax to the Hospital Specialist if you agree to take over shared monitoring for this patient.

Hospital site to send fax to: Queens Hospital

Many thanks

Hospital Specialist	GP
Signature……..	Signature……..
Name ……..……..	Name ……..
Date……..	Date……..……..

If you are not taking on the monitoring responsibility for this patient please state the reason why and return this letter to the Hospital Specialist

……

You will retain the responsibility to check the blood results prior to prescribing. This should be available via electronic access, or please provide your drop code to enable the patient's blood results to be sent to you

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