MYCOPHENOLATE MOFETIL for Interstitial Lung Disease

Referral Criteria

- These guidelines are for patients over 16 years of age with Interstitial Lung disease (ILD).
- Shared Care is only appropriate if it provides the optimum solution for the patient.
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patients' GP
- Safe prescribing must be accompanied by effective monitoring
- When transfer is agreed, the patient will be given a supply of mycophenolate sufficient for 4 week maintenance therapy
- Respiratory Consultants at Princess Alexandra Hospital are supported by colleagues at Papworth and ULCH Hospitals, Specialist Centre for ILD
- **The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.**

SHARED CARE RESPONSIBILITIES

Consultant

1. Ensure that patient understands risks and benefits of medication and has read appropriate information leaflet.
2. Ensure the patient understands the shared care agreement and has signed the Patient Agreement Letter (page 8-9)
3. Perform baseline tests (see Monitoring section) and provide results to GP
4. Ensure all recommendations from MHRA advice December 2015 Mycophenolate mofetil, mycophenolic acid: new pregnancy-prevention advice for women and men are in place for the patient prior to treatment starting, see below
5. Initiate treatment and prescribe until the GP formally agrees to share care (as a minimum, supply the first month treatment and until patient is stabilised).
6. Promptly send a letter to the GP requesting shared care for this patient.
7. Review the patient in outpatients as clinically appropriate and advise the GP promptly after these reviews on when to adjust the dose, stop treatment or consult with the specialist.
8. Inform GP, by letter, of each clinic attendance and action taken for the management of the patient ensuring current dose, most recent blood results and frequency of monitoring are stated.
9. Evaluate any reported adverse effects by GP or patient.
10. Inform GP of patients who do not attend clinic appointments, admin to contact patient to rearrange.
11. Ensure that backup advice is available at all times. (see Contacts section)
12. Report any adverse effects to the GP and CHM see link Yellow Card MHRA

General Practitioner

1. Monitor patient's overall health and well-being.
2. Respond to the request for Shared Care as soon as practicable. If concerns regarding shared care, urgently contact the Consultant and complete attached letter (page 7) with clinical reasons and return to Consultant and Pharmacy department.
3. Ensure compatibility with other concomitant medication.
4. Ensure patient has effective contraception in line with MHRA advice December 2015
5. Prescribe at the dose recommended.
6. Monitor U&E, creatinine, FBC and LFTs at recommended frequencies (see Action and Advice) and refer if abnormal.
7. Adjust the dose as advised by the specialist.
8. Stop treatment on advice of specialist or immediately if any urgent need to stop treatment arises.
9. Report any adverse events to the specialist and CHM. Yellow Card MHRA
10. Inform specialist of any change in the medical condition of patient which may have effect on disease / medications.
11. Ensure patient is offered an annual flu vaccination and a one off pneumococcal vaccination

Patient

1. Report to specialist or GP if there is not a clear understanding of their treatment and discuss any concerns in relation to treatment

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2. Report any adverse effects to their GP and/or specialist whilst taking Mycophenolate, especially unexplained bruising/bleeding, fever, infections or mouth ulcers which should be reported immediately.
3. Report any changes in disease symptoms to GP and/or specialist whilst taking Mycophenolate.
4. Take effective contraception as advised by Specialist and GP
5. Alert GP immediately should pregnancy occur.
6. Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy whilst taking Mycophenolate.
7. Try to avoid contact with chickenpox and shingles if no definite history of chickenpox, and report any such contact to urgently to their GP and/or consultant
8. Inform GP or specialist of any other medicines being taken including over-the-counter products.
9. Attend for regular reviews and blood monitoring tests

CONTACT NUMBERS FOR ADVICE AND SUPPORT

Princess Alexandra Hospital NHS Trust – Respiratory	
Consultant via switchboard:	01279 444455 ext 7419

Princess Alexandra Hospital NHS Trust - Pharmacy	
Medicines Information (for medicines related queries)	01279 827054

CLINICAL INFORMATION

Prescribed Indications covered by this Shared Care Agreement

This SCA is for the unlicensed indication of Interstitial Lung disease only

Therapeutic Summary

Mycophenolate mofetil (MMF) is a pro-drug of mycophenolic acid. It is a reversible inhibitor of inosine monophosphate dehydrogenase and thus inhibits purine synthesis, with potent cytostatic effects on both T- and B-lymphocytes. It does not inhibit production of interleukins as does ciclosporin and tacrolimus.

Different brands and formulations of Mycophenolate have small differences in bioavailability, but this is not a problem in this group of patients. (Transplant patients need to be prescribed the brand specified by the transplant centre)

Time to response is usually between 6 weeks and 3 months.
See SPC for full details http://www.medicines.org.uk/emc/medicine/1680

Dose and Route of Administration

Interstitial Lung disease

- Typical dose 1-2g daily, maximum dose 3g daily
- Dosage advised by hospital specialist but typically a gradual increase in dosage eg
  - Week 1: 500mg **once** daily. Check FBC. If tolerated -
  - Week 2: 500mg **twice** daily. Check FBC, U&E. If tolerated -
  - Week 3: 1g morning, 500mg evening. Check FBC. If tolerated -
  - From 4 weeks: 1g **twice** daily
- Time to response 6-12 weeks

Further information can be found in the Summary of Product Characteristics (SPC):
http://www.medicines.org.uk/emc/medicine/1679

Adverse Effects

Very common	(≥ 1 in 10)
Common	(≥ 1 in 100 and < 1 in 10)
Uncommon	(≥ 1 in 1000 and < 1 in 100)
Rare	(≥ 1 in 10000 and < 1 in 1000)

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System organ class		Adverse drug reactions
Infections and infestations	Very common	Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster
	Common	Pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Very common	-
	Common	Skin cancer, benign neoplasm of skin
Blood and lymphatic system disorders	Very common	Leucopenia, thrombocytopenia, anaemia
	Common	Pancytopenia, leukocytosis
Metabolism and nutrition disorders	Very common	-
	Common	Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia
Psychiatric disorders	Very common	-
	Common	Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia
Nervous system disorders	Very common	-
	Common	Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia
Cardiac disorders	Very common	-
	Common	Tachycardia
Vascular disorders	Very common	-
	Common	Hypotension, hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Very common	-
	Common	Pleural effusion, dyspnoea, cough
Gastrointestinal disorders	Very common	Vomiting, abdominal pain, diarrhoea, nausea
	Common	Gastrointestinal haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence, eructation
Hepatobiliary disorders	Very common	-
	Common	Hepatitis, jaundice, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Very common	-
	Common	Skin hypertrophy, rash, acne, alopecia,
Musculoskeletal and connective tissue disorders	Very common	-
	Common	Arthralgia
Renal and urinary disorders	Very common	-
	Common	Renal impairment
General disorders and administration site conditions	Very common	-
	Common	Oedema, pyrexia, chills, pain, malaise, asthenia,
Investigations	Very common	-
	Common	Hepatic enzyme increased, blood creatinine increased, blood lactate dehydrogenase increased, blood urea increased, blood alkaline phosphatase increased, weight decreased

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Cautions

Immunosuppression: Patients are at risk of opportunistic infections including life threatening meningitis, endocarditis, tuberculosis and atypical mycobacterial infections**.** Patients who have not had chicken pox and are in contact with anyone with the virus are advised to contact either their own GP or the specialist department to have VZ antibody status checked. If antibodies are negative, it is recommended for these patients to have VZ immunoglobulin. Please see Human Varicella-Zoster Immunoglobulin (VZIG) Doc for further information and contact details
Cancer risk: Patients receiving mycophenolate are at increased risk of lymphomas and skin malignancies. Avoiding excessive exposure to the sun and use of high factor sunscreen are recommended.
Vaccines: live vaccines should be avoided.
Genetic deficiencies: Mycophenolate mofetil is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. On theoretical grounds therefore it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
Renal impairment: Reduce dose if significant renal impairment, see monitoring section

Contraindications

Hypersensitivity to mycophenolate, myophenolic acid or to any of the excipients.
Pregnancy
Breastfeeding.

Pregnancy and Lactation

Mycophenolate mofetil, mycophenolic acid: new pregnancy-prevention advice for women and men
Mycophenolate mofetil and its active metabolite mycophenolic acid are associated with a high rate of serious birth defects and increased risk of spontaneous abortion.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/485099/Drug_Safety_Update_Dec_2015.pdf

- Mycophenolate mofetil or mycophenolic acid should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection
- Physicians should ensure that women and men taking mycophenolate mofetil and mycophenolic acid understand: the risk of harm to a baby; the need for effective contraception; the need to plan for pregnancy and change treatment as necessary; and the need to immediately consult a physician if there is a possibility of pregnancy
- Mycophenolate mofetil or mycophenolic acid treatment should only be initiated in women of child bearing potential when there is a negative pregnancy test result to rule out unintended use in pregnancy.
- Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended. The second test should be done 8–10 days after the first one and immediately before starting mycophenolate mofetil. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient.
- Mycophenolate mofetil or mycophenolic acid should only be given to women of childbearing potential who are using highly effective contraception
- Women should use 2 forms of effective contraception during treatment and for 6 weeks after stopping treatment.
    - The pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected by co-administration of mycophenolate, CellCept® ref. SPC Roche.
    - No interaction is listed in the BNF between combined oral contraceptives or progesterone only contraceptives with mycophenolate.
- Men (including those who have had a vasectomy) should use condoms during treatment and for at least 90 days after stopping treatment. This advice is a precautionary measure due to the genotoxicity of these products. UPDATED CONTRACEPTION ADVICE FOR MALE PATIENTS FEB 18.
- Female partners of male patients treated with mycophenolate mofetil or mycophenolic acid should use highly effective contraception during treatment and for 90 days after the last dose

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- Patients should be instructed not to stop treatment but to consult their physician immediately should pregnancy occur.
- Breast feeding is contra-indicated

Interactions with other medications

As mycophenolate metabolites undergo extensive enterohepatic recirculation, any drugs which may interfere with this pathway should be avoided:

- Antacids containing magnesium or aluminum hydroxide – reduces absorption of MMF
- Cholestyramine should not be taken at the same time of day as this will impair the absorption of mycophenolate mofetil.
- Probenicid
- Aciclovir & ganciclovir
- Rifampicin –reduces plasma concentrations of active metabolite of mycophenolate.
- Metronidazole and norfloxacin – possibly reduce bioavailability of mycophenolate.

See current BNF for more information.

MONITORING STANDARDS FOR MYCOPHENOLATE AT PRINCESS ALEXANDRA HOSPITAL NHS TRUST

The following standards have been agreed for the monitoring of Mycophenolate in all patients at Princess Alexandra Hospital NHS Trust.

Pre-treatment by Specialist	FBC, U&Es including eGFR, LFTs, chest X-ray Blood pressure, fasting lipids. Negative pregnancy test in those of child bearing potential	
Ongoing monitoring by GP	FBC & LFTs	Weekly until dose stable for 4 weeks then fortnightly for 2 months, then monthly even after patient is stabilized on treatment.
	Lipids	6 monthly
	Pregnancy test	If there is a break in contraception ensure negative pregnancy test in those of child bearing potential

Action and Advice

If a GP has taken blood tests for the general medical management of a patient and blood test results fall into the categories below or the patient reports one of the adverse events below, these are recommendations for considering the withdrawal of Mycophenolate therapy:

Blood Test Results	
WBC < 3.5 x 10^9/l	Withhold until discussed with specialist team
Neutrophils < 2.0 x 10^9/l	Withhold until discussed with specialist team
Platelets < 150 x 10^9/l	Withhold until discussed with specialist team
Lipids	Discuss abnormal result with specialist team
> 2-fold rise in AST, ALT (from upper limit of reference range)	Withhold until discussed with specialist team
Mild-to-moderate renal impairment† (creatinine clearance; mild = 20–50 mL/minute; moderate = 10–20 mL/minute)	Withhold until discussed with specialist team.
Symptoms	
Unexplained rash	Withhold until discussed with specialist team
Abnormal bruising or bleeding	Withhold until FBC results available & discuss with specialist
Severe sore throat	Withhold until FBC results available & discuss with specialist

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Swigris JJ, Olson AL, Fischer A, Lynch DA, Cosgrove GP, Frankel SK, Meehan RT, Brown KK
Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. Chest. 2006 Jul;130(1):30-6.
https://www.ncbi.nlm.nih.gov/pubmed/16840379

J Rheumatol. 2013 May;40(5):640-6. 2013 F.A. Brown et al
Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease.
https://www.ncbi.nlm.nih.gov/pubmed/23457378

Further Information

This document does not replace the SPC and BNF and should be read in conjunction with it.

Further information can be found in the Summary of Product Characteristics (SPC):
http://www.medicines.org.uk/emc/medicine/1679

Suggestions for Drug Monitoring in Adults in Primary care
http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Drug%20monitoring%20document%20Feb%202014.pdf

West Essex Shared Care Guidelines
https://westessexccg.nhs.uk/your-health/medicines-optimisation-and-pharmacy/shared-care-medicines

CKS
http://cks.nice.org.uk/dmards#!scenario

Risk Minimisation Materials
www.medicines.org.uk/emc/.

MHRA and in particular the advice for mycophenolate
https://www.gov.uk/drug-safety-update

GP response to Shared Care Agreement

(only complete & send if NOT participating in shared care)

This shared care agreement has been approved by the Medicines Management Optimisation Programme Board November 2016

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Patient Name:	NHS No:
Consultant:	Medicine requested for shared care: **Mycophenolate Mofetil**

I will **NOT** be undertaking the GP responsibilities as described in the agreed shared care agreement. My clinical reasons for declining shared care for this patient are listed in the box below:

Yours sincerely

{GP name}

{Surgery}

Please send a copy of this response to:
1. The specialist/consultant requesting shared care
2. **ANONYMISED COPY OF THIS FORM ONLY** to the E-MAIL: **tpa-tr.ClinicalPharmacy@nhs.net**

(sending a copy of this form to the PAH pharmacy will help to identify any inappropriate requests for shared care e.g. indication not covered, hospital monitoring requirements not fulfilled. It will also help to inform the CCG Medicines Optimisation Team of the reasons shared care is not being undertaken by GPs allowing for changes to be made in future updates to improve patient safety)

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P14064

The Princess Alexandra Hospital NHS
NHS Trust

Hamstel Road
Harlow, Essex
CM20 1QX

Tel: 01279 444455

Information for patients:

SHARED CARE: Agreement information and confirmation

Patient name:

.....

Medicine:

.....

We would be grateful if you would take time to read this information as it will help us work with you to manage your condition and ensure safe prescribing of the specific medicine listed above.

What is a Shared Care Agreement (SCA)?

A Shared Care Agreement (SCA) enables the care you have for a specific condition to be shared between the hospital and your GP.

The agreement means that the medicine the hospital has started, can be continued by your GP, so you won't have to visit the hospital to collect your medicine.

The SCA gives information on your medicine, guidance on the prescribing and monitoring responsibilities for your consultant (in the hospital), your GP and you. For an SCA, to work everyone involved must understand it and communicate effectively.

Your consultant and your GP will need to sign the agreement and if you agree to this approach, we would ask you to sign this letter, to indicate your agreement to have your care managed in this way.

How does shared care work?

Your consultant and GP share responsibility for your care.

The consultant is a specialist in your condition and will start prescribing your medicine, making sure it is suitable for you. There will come a point in your treatment when you may not need to be monitored by the consultant as often and this monitoring can be done by your GP.

Once your GP has agreed to the SCA, they will be able to prescribe the same medicine for you at the dose recommended by the consultant.

The organisation which regulates GPs, the General Medical Council, says that 'When a GP prescribes a medicine, the GP needs to satisfy themselves that the prescription is needed, appropriate for the patient and within the limits of their competence'.

So, your GP can only issue a prescription if the consultant and you keep to the responsibilities you have agreed (see below). If responsibilities are not kept or if the GP no longer feels it is safe to prescribe the medicine, he/she will explain the reasons to you and your consultant, then prescribing responsibilities will be transferred back to the hospital.

What do I need to do to ensure the SCA can continue?

- **Attend hospital outpatients**
  You must still attend the hospital for regular reviews as directed by your consultant (these may be less frequent than before). If you do not attend your hospital appointments, your GP will not be able to continue issuing prescriptions for this medication.
- **Attend GP appointments**
  You must attend any appointments you have with your GP in relation to this medicine, so they can look after you effectively.
- **Have blood tests as you have been advised to**
  Your consultant should have informed you

continued overleaf

MOPB Approved Jan 2017 Review date Jan 2019. The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics and British National Formulary.

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if and how often you need to have blood monitoring tests. You can usually have your blood taken at an appropriate clinic and not need to go to the hospital.

- If you do not have the blood monitoring tests as advised by your consultant, your GP will no longer be able to issue you with prescriptions as it would not be safe to do so.

What do I do if I am having side-effects to the medicine?

Your consultant should have informed you of the common side-effects to expect and what to do if you experience them. If you think you may be having side-effects from a medicine report these directly to your consultant. Your GP may need to seek advice from your consultant before issuing you with another prescription; this is to ensure it is safe for you to continue on the medication.

What if my disease symptoms change or get worse?

Report any changes in disease symptoms or circumstances that could affect management of your disease to your consultant.

What about the other medicines I take?

Inform your GP and the consultant of all other medicines you are taking, including those you may have bought yourself. Do not take new medicines (including those you could buy) until you have discussed this with your pharmacist, GP or consultant.

If you would like to go ahead with a shared care agreement for the specific medication identified on page 1, please sign below to confirm that you:

- Understand the shared care agreement.
- Are happy to have your care for this aspect of your health managed by a shared care agreement.
- You agree to attend regular review appointments as requested.
- You agree to have blood tests as required.

Patient's signature .....

Date .....

Print name .....

If at any point in time you would like this shared care agreement to stop, please talk to your GP.

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