

# SHARED CARE GUIDELINE

## DRUG: MYCOPHENOLATE MOFETIL

<p><b>Introduction</b></p>	<p><b>This protocol only applies to the unlicensed indications listed below. Transplant protocols should be followed for licensed indications.</b></p> <p><b>Unlicensed:</b> Severe rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, connective tissue diseases with severe / organ-threatening manifestations, interstitial lung disease (not to be used in idiopathic pulmonary fibrosis IPF), vasculitides, as maintenance post cyclophosphamide in patients for whom azathioprine is contra-indicated or is inappropriate.</p> <p><b>Background:</b> Mycophenolate mofetil (MMF) is a pro-drug of the active metabolite of mycophenolic acid. It is a suppressor of T and B cell proliferation and adhesion and inhibits inosine monophosphate dehydrogenase that eventually blocks the progression to DNA synthesis and proliferation.</p> <p><b>There are two preparations of mycophenolic acid in the UK; mycophenolate mofetil and mycophenolate sodium. The two salts should not be interchanged or substituted because they have differing pharmacokinetic profiles. Please note that this guideline relates to mycophenolate mofetil only. Prescribers should clearly prescribe mycophenolate mofetil <u>NOT</u> mycophenolic acid/mycophenolate sodium.</b></p>
<p><b>Dose &amp; Administration<sup>1</sup></b></p>	<p><b>Typical dose:</b> 1 to 2 grams/daily (in divided doses).</p> <p><b>Starting dose:</b> 500mg daily for the 1st week, 500mg twice daily for the 2nd week and increase it gradually by 500mg each week until the optimal or maximum tolerated dose is reached.</p> <p>(For interstitial lung disease the starting dose is 250-500mg daily increasing by 250mg per week up to 1-1.5g twice daily.<sup>6</sup>)</p> <p><b>Maximum dose:</b> Up to 3 grams/day.</p> <p><b>Time to response:</b> 6 weeks to 3 months.</p>
<p><b>Secondary Care Responsibilities</b></p>	<ul style="list-style-type: none"> <li>• Discuss the benefits and side effects of treatment with the patient. Ensure that the patient understands which warning signs and symptoms to report.</li> <li>• Ensure that women and men understand the need for effective contraception and to immediately consult a physician if there is a possibility of pregnancy.<sup>4</sup> (See cautions section below and MHRA warning (Ref 4) for more information)</li> <li>• Ensure that the patient is aware that the use of the drug for this condition is unlicensed. Make a clear, accurate and legible record of medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine (<a href="#">as per GMC guidance</a>).</li> <li>• Perform pre-treatment screening (chest X-ray [only if pre-existing lung disease], height, weight, BP, FBC, LFT's, CrCl/ calculated GFR, albumin and pregnancy test in women of childbearing potential).</li> <li>• Patients should be assessed for co-morbidities, including evaluation for respiratory disease and screening for occult viral infection.</li> <li>• Provide the patient with prescriptions for mycophenolate mofetil until on stable dose and they have undergone monthly monitoring for a minimum of 3 months.</li> <li>• Provide the patient with a monitoring and dosage record booklet and ensure that the patient knows when and where to attend for monitoring. Encourage the patient to take responsibility for ensuring that results of tests are entered in the monitoring booklet.</li> <li>• Arrange shared care with the patient's GP and continue to provide treatment until shared care arrangements have been confirmed.</li> <li>• Review the patient to monitor the patient's response to therapy. Advise the GP of the secondary care monitoring and follow up arrangements.</li> <li>• Conduct laboratory monitoring (see below) TWO WEEKLY until dose stable for SIX weeks, then every MONTH for THREE months</li> </ul>

	<ul style="list-style-type: none"> <li>Request copies of test results for the patient's GP by completing the "copy to" section on the pathology form (where available or follow local protocols).</li> <li>Advise the GP when to stop treatment.</li> <li>Ensure that clear backup arrangements exist for GPs to obtain advice.</li> </ul>
<b>Primary Care Responsibilities</b>	<ul style="list-style-type: none"> <li>Provide the patient with prescriptions for mycophenolate mofetil once on stable dose and having undergone monthly monitoring for a minimum of 3 months.</li> <li>Arrange on-going monitoring at the recommended frequencies (see MONITORING below) ensure that test results are recorded in the monitoring booklet. Request copies of test results for the patient's consultant by completing the "copy to" section on the pathology form (where available or follow local protocols).</li> <li>Report any adverse events to the consultant or specialist nurse and stop treatment on their advice or immediately if an urgent need arises (see MONITORING below).</li> <li>Report any worsening of control of the condition to the consultant or specialist nurse.</li> </ul>
<b>Immunisations</b>	<ul style="list-style-type: none"> <li>Annual flu vaccine is recommended</li> <li>Pneumococcal vaccination recommended</li> <li>In patients exposed to chicken pox or shingles, if required, passive immunisation should be considered for varicella. Refer to Green book: <a href="#">Varicella: the green book, chapter 34 - Publications - GOV.UK</a></li> <li>Live vaccines should be avoided specialist advice has been sought.</li> </ul>
<b>Drug Interactions</b>	<ul style="list-style-type: none"> <li>Rifampicin - reduces plasma concentration of active metabolite of mycophenolate</li> <li>Antacids – absorption of mycophenolate reduced</li> <li>Metronidazole possibly reduces bioavailability of mycophenolate</li> <li>Norfloxacin possibly reduces bioavailability of mycophenolate</li> <li>Cholestyramine should not be taken at the same time of day as it will impair the absorption of mycophenolate</li> <li>Oral iron should not be taken at the same time of day as it will impair the absorption of mycophenolate</li> <li>Aciclovir / Ganciclovir / Valaciclovir / Valganciclovir – mycophenolate increases aciclovir / valaciclovir plasma levels and possibly increases plasma concentration of ganciclovir and valganciclovir.</li> </ul>
<b>Cautions</b>	<ul style="list-style-type: none"> <li>Active serious digestive system disease (risk of haemorrhage, ulceration and perforation).</li> <li>Elderly (increased risk of infection, gastrointestinal haemorrhage and pulmonary oedema)</li> <li>Patients should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.</li> <li>Avoid exposure to strong sunlight as there is an increased susceptibility to skin cancer.</li> <li>Mycophenolate Mofetil and its active metabolite are associated with a high rate of serious birth defects and spontaneous abortion. (See <a href="#">MHRA Drug Safety Alert</a>)<sup>4</sup> <ul style="list-style-type: none"> <li>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</li> <li>Mycophenolate mofetil or mycophenolic acid should only be given to women of childbearing potential who are using highly effective contraception</li> <li>Women should use 2 forms of effective contraception during treatment and for 6 weeks after stopping treatment</li> <li>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</li> <li>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</li> </ul> </li> </ul>

<b>Contra-indications</b>	<ul style="list-style-type: none"> <li>• Mycophenolate should not be given to women who are pregnant, or likely to become pregnant. It should only be initiated in women of child bearing potential when there is a negative pregnancy test. See also cautions (above) and MHRA alert (Ref 4) for more information on the need for effective contraception for men and women during treatment and for six weeks following discontinuation of therapy<sup>4</sup></li> <li>• Mycophenolate is contra-indicated in women who are breastfeeding.</li> <li>• Hypersensitivity to mycophenolate mofetil or mycophenolic acid.</li> </ul>
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**This guidance does not replace the SPC's, which should be read in conjunction with this guidance.**

**Monitoring**

**The team responsible for prescribing the medication should also hold responsibility for monitoring.**

Treatment Status	FBC	LFT	Albumin	Creatinine/ calculated GFR
Initial monitoring until on stable dose for 6 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks
For next three months	Every month	Every month	Every month	Every month
Thereafter, *	Every month	Every month	Every month	Every month

**\*Please note:** If the patient is also being treated with **leflunomide**, increased monthly monitoring is required, as specified in the leflunomide shared care guidance. (Where other biologic/DMARDs are used in combination with mycophenolate mofetil, the standard monitoring requirements, as outlined above, continue to apply).

As per secondary care responsibilities, for clarity the frequency of monitoring should be specified in the initial shared care request.

**N.B. Secondary care will be responsible for:**  
FBC, LFTs and CrCl and albumin every TWO WEEKS until dose stable for SIX weeks, then every MONTH for THREE months.

**Primary care will then take ongoing responsibility for:**  
FBC, LFTs and CrCl and albumin every MONTH. <sup>1&3&5</sup>

Dose increases should be monitored by FBC, creatinine / calculated GFR, albumin and LFTs every 2 weeks until on stable dose for 6 weeks and then revert to previous schedule.

Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis.

**Laboratory adverse event\***

<b>WBC</b>	< 3.5 x 10 <sup>9</sup> /L or less than the lower limit of the reference as per lab
<b>Neutrophils</b>	< 1.6 x 10 <sup>9</sup> /L or less than the lower limit of the reference as per lab
<b>Eosinophils</b>	>0.5 x 10 <sup>9</sup> /L or greater than the upper limit of the reference as per lab
<b>Platelets</b>	< 140 x 10 <sup>9</sup> /L or less than the lower limit of the reference as per lab
<b>AST, ALT</b>	> 100 U/l
<b>Albumin</b>	<30g/L
<b>MCV*</b>	> 105 fL
<b>U&amp;E (including creatinine)</b>	Increase in creatinine of >30% over 12months or CrCl <60ml/min
<b>Potassium</b>	>5.5mmol/L

<b>Adverse Effects</b>	<p>* Withhold and check vitamin B12, folate and TSH. If abnormal, treat any underlying abnormality. If normal, discuss with the specialist team.</p> <p>STOP treatment unless otherwise advised by secondary care (For patients with SLE neutropenia can be a manifestation of disease and therefore in some instances it may be appropriate to continue treatment outside the above reference range on specialist advice).</p> <p>As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results e.g. gradual decreases in white blood cells or albumin, or increasing liver enzymes.</p> <p><b>Bruising with or without sore throat - Check FBC immediately and discuss with specialist team.</b></p> <p>Recurrent infection – measure serum immunoglobulin levels, discuss with the specialist team if low.</p> <p>Persistent cough or dyspnoea – discuss with the specialist team, bronchiectasis or pulmonary fibrosis should be considered</p>
<b>Adverse Effects</b>	<p>Taste disturbance, gingival hyperplasia, nausea, constipation, flatulence, anorexia, weight loss, vomiting, abdominal pain, gastro-intestinal inflammation, ulceration, and bleeding, hepatitis, jaundice, pancreatitis, stomatitis, oedema, tachycardia, hypertension, hypotension, vasodilatation, cough, dyspnoea, insomnia, agitation, confusion, depression, anxiety, convulsions, paraesthesia, myasthenic syndrome, tremor, dizziness, headache, influenza-like syndrome, infections, hyperglycaemia, renal impairment, malignancy (particularly of the skin), blood disorders (including leucopenia, anaemia, thrombocytopenia, pancytopenia, and red cell aplasia, disturbances of electrolytes and blood lipids, arthralgia, alopecia, acne, skin hypertrophy, and rash; <i>also reported</i> intestinal villous atrophy, progressive multifocal leukoencephalopathy. As per the SPC there have been isolated cases of interstitial lung disease &amp; pulmonary fibrosis with mycophenolate, some of which have been fatal.</p>

## Acknowledgements to

University Hospitals of Morecombe Bay

### References

1. The electronic medicines compendium. Mycophenolate Mofetil 250mg Capsules. Summary of medicines characteristics. SPC <https://www.medicines.org.uk/emc/medicine/24288>. Accessed December 2015
2. NICE CKS. DMARDs Scenario: Mycophenolate. Last revised July 2015. Accessed December 2015 <http://cks.nice.org.uk/dmards#!scenario:9>
3. BSR/BHPR Non-Biologic DMARD Guidelines 2017.
4. MHRA. Drug Safety Update. Mycophenolate Mofetil, Mycophenolic acid: new pregnancy-prevention advice for women and men. Issued December 2015. Accessed December 2015. <https://www.gov.uk/drug-safety-update/mycophenolate-mofetil-mycophenolic-acid-new-pregnancy-prevention-advice-for-women-and-men>
5. NICE CKS DMARDs Last revised in July 2015, Scenario: Mycophenolate mofetil (MMF). Accessed May 2017. <https://cks.nice.org.uk/dmards#!scenario:9>
6. GMMMG Shared Care Protocol for mycophenolate mofetil for interstitial lung disease. Version 1: 17/11/2016. Accessed May 2017. <http://gmmmg.nhs.uk/docs/ip/GMMMG-SCP-Mycophenolate-for-Interstitial-Lung-Disease-GMMMG-approved-18-11-16.doc>
7. Ledingham et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology. 2017;56:865 – 868.

# RELEVANT CONTACT LIST

Speciality	
Name and Title	Tel. No.



## Optional Shared Care Agreement form

### Request by Specialist Clinician for the patient's GP to enter into a shared care agreement

**PLEASE NOTE:** The use of this form is not compulsory, but the same information must be communicated between the specialist service and primary care in advance of entering into a shared-care agreement.

### **Part 1 - To be signed by Consultant / Associate Specialist / Speciality Trainee or Specialist Nurse (who must be a prescriber)**

<b>Dear Doctor:</b>	Click or tap here to enter text.
<b>Name of Patient:</b>	Click or tap here to enter text.
<b>Address:</b>	Click or tap here to enter text.
	Click or tap here to enter text.
	Click or tap here to enter text.
<b>Date:</b>	Click or tap to enter a date.
<b>Patient NHS Number:</b>	Click or tap here to enter text.
<b>Patient Hospital Number:</b>	Click or tap here to enter text.
<b>Diagnosed Condition:</b>	Click or tap here to enter text.

**I request that you prescribe:**

- (1) Click or tap here to enter text.
- (2) Click or tap here to enter text.
- (3) Click or tap here to enter text.
- (4) Click or tap here to enter text.

for the above patient in accordance with the LMMG shared care guideline(s) (Available on the LMMG website).

<b>Last Prescription Issued:</b>	Click or tap to enter a date.
<b>Next Supply Due:</b>	Click or tap to enter a date.
<b>Date of last blood test (if applicable):</b>	Click or tap to enter a date.
<b>Date of next blood test (if applicable):</b>	Click or tap to enter a date.
<b>Frequency of blood test (if applicable):</b>	Click or tap here to enter text.

I confirm that the patient has been stabilised and reviewed on the above regime in accordance with the Shared Care guideline.

If this is a Shared Care Agreement for a drug indication which is unlicensed or off label, I confirm that informed consent has been received from the patient.

I will accept referral for reassessment at your request. The medical staff of the department are available if required to give you advice.

### Details of Specialist Clinicians

<b>Name:</b>	Click or tap here to enter text.
<b>Date:</b>	Click or tap to enter a date.
<b>Position:</b>	Choose an item.
<b>Signature:</b>	Click or tap here to enter text.

(An email from the specialist clinician will be taken as the authorised signature)  
In all cases, please also provide the name and contact details of the Consultant.

When the request for shared care is made by a Specialist Nurse, it is the supervising consultant who takes medicolegal responsibility for the agreement.

<b>Consultant</b>	Click or tap here to enter text.
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#### Contact Details

<b>Telephone Number</b>	Click or tap here to enter text.
<b>Extension</b>	Click or tap here to enter text.
<b>Email Address</b>	Click or tap here to enter text.

### **Part 2 - To be completed by Primary Care Clinician (GP)**

I agree to prescribe and monitor Click or tap here to enter text. for the above patient in accordance with the LMMG shared care guideline(s) commencing from the date of next supply / monitoring (as stated in Part 1 of the agreement form).

<b>Name:</b>	Click or tap here to enter text.
<b>Date:</b>	Click or tap to enter a date.
<b>Signature:</b>	Click or tap here to enter text.

*Please sign and return a copy **within 14 calendar days** to the address above **OR***

If you **do not** agree to prescribe, please sign below and provide any supporting information as appropriate:

I **DO NOT** agree to enter in to a shared care agreement on this occasion.

<b>Name:</b>	Click or tap here to enter text.
<b>Date:</b>	Click or tap to enter a date.
<b>Signature:</b>	Click or tap here to enter text.
<b>Further information:</b>	Click or tap here to enter text.