

SHARED CARE GUIDELINE

DRUG: MYCOPHENOLATE MOFETIL

<p>Introduction</p>	<p>This protocol only applies to the unlicensed indications listed below. Transplant protocols should be followed for licensed indications.</p> <p>Unlicensed: 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>Background: 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>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.</p>
<p>Dose & Administration¹</p>	<p>Typical dose: 1 to 2 grams/daily (in divided doses).</p> <p>Starting dose: 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.⁶)</p> <p>Maximum dose: Up to 3 grams/day.</p> <p>Time to response: 6 weeks to 3 months.</p>
<p>Secondary Care Responsibilities</p>	<ul style="list-style-type: none"> • Discuss the benefits and side effects of treatment with the patient. Ensure that the patient understands which warning signs and symptoms to report. • Ensure that women and men understand the need for effective contraception and to immediately consult a physician if there is a possibility of pregnancy.⁴ (See cautions section below and MHRA warning (Ref 4) for more information) • 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 (<u>as per GMC guidance</u>). • 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). • Patients should be assessed for co-morbidities, including evaluation for respiratory disease and screening for occult viral infection. • Provide the patient with prescriptions for mycophenolate mofetil until on stable dose and they have undergone monthly monitoring for a minimum of 3 months. • 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. • Arrange shared care with the patient's GP and continue to provide treatment until shared care arrangements have been confirmed. • Review the patient to monitor the patient's response to therapy. Advise the GP of the secondary care monitoring and follow up arrangements.

	<ul style="list-style-type: none"> • Conduct laboratory monitoring (see below) TWO WEEKLY until dose stable for SIX weeks, then every MONTH for THREE months • 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). • Advise the GP when to stop treatment. • Ensure that clear backup arrangements exist for GPs to obtain advice.
Primary Care Responsibilities	<ul style="list-style-type: none"> • Provide the patient with prescriptions for mycophenolate mofetil once on stable dose and having undergone monthly monitoring for a minimum of 3 months. • Ensure that the patient understands which warning signs and symptoms to report. • 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). • 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). • Report any worsening of control of the condition to the consultant or specialist nurse.
Immunisations	<ul style="list-style-type: none"> • Annual flu vaccine is recommended • Pneumococcal vaccination recommended • In patients exposed to chicken pox or shingles, if required, passive immunisation should be considered for varicella. Refer to Green book: Varicella: the green book, chapter 34 - Publications - GOV.UK • Live vaccines should be avoided
Drug Interactions	<ul style="list-style-type: none"> • Rifampicin - reduces plasma concentration of active metabolite of mycophenolate • Antacids – absorption of mycophenolate reduced • Metronidazole possibly reduces bioavailability of mycophenolate • Norfloxacin possibly reduces bioavailability of mycophenolate • Cholestyramine should not be taken at the same time of day as it will impair the absorption of mycophenolate • Oral iron should not be taken at the same time of day as it will impair the absorption of mycophenolate • Aciclovir / Ganciclovir / Valaciclovir / Valganciclovir – mycophenolate increases aciclovir / valaciclovir plasma levels and possibly increases plasma concentration of ganciclovir and valganciclovir.
Cautions	<ul style="list-style-type: none"> • Active serious digestive system disease (risk of haemorrhage, ulceration and perforation). • Elderly (increased risk of infection, gastrointestinal haemorrhage and pulmonary oedema) • Patients should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression. • Avoid exposure to strong sunlight as there is an increased susceptibility to skin cancer. • Mycophenolate Mofetil and its active metabolite are associated with a high rate of serious birth defects and spontaneous abortion. (See MHRA Drug Safety Alert)⁴ <ul style="list-style-type: none"> ○ 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 ○ 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 ○ 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 ○ 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

Contra-indications	<ul style="list-style-type: none"> • 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 therapy⁴ • Mycophenolate is contra-indicated in women who are breastfeeding. • Hypersensitivity to mycophenolate mofetil or mycophenolic acid.
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This guidance does not replace the SPC's, which should be read in conjunction with this guidance.

Monitoring	<p>The team responsible for prescribing the medication should also hold responsibility for monitoring.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #0070C0; color: white;"> <th>Treatment Status</th> <th>FBC</th> <th>LFT</th> <th>Albumin</th> <th>Creatinine/calculated GFR</th> </tr> </thead> <tbody> <tr> <td>Initial monitoring until on stable dose for 6 weeks</td> <td>Every 2 weeks</td> <td>Every 2 weeks</td> <td>Every 2 weeks</td> <td>Every 2 weeks</td> </tr> <tr> <td>For next three months</td> <td>Every month</td> <td>Every month</td> <td>Every month</td> <td>Every month</td> </tr> <tr> <td>Thereafter, *</td> <td>Every month</td> <td>Every month</td> <td>Every month</td> <td>Every month</td> </tr> </tbody> </table> <p>*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).</p> <p>As per secondary care responsibilities, for clarity the frequency of monitoring should be specified in the initial shared care request.</p> <p>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.</p> <p>Primary care will then take ongoing responsibility for: FBC, LFTs and CrCl and albumin every MONTH. ^{1&3&5}</p> <p>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.</p> <p>Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis.</p> <p>Laboratory adverse event*</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tbody> <tr> <td style="text-align: center;">WBC</td> <td>< 3.5 x 10⁹/L or less than the lower limit of the reference as per lab</td> </tr> <tr> <td style="text-align: center;">Neutrophils</td> <td>< 1.6 x 10⁹/L or less than the lower limit of the reference as per lab</td> </tr> <tr> <td style="text-align: center;">Eosinophils</td> <td>>0.5 x 10⁹/L or greater than the upper limit of the reference as per lab</td> </tr> <tr> <td style="text-align: center;">Platelets</td> <td>< 140 x 10⁹/L or less than the lower limit of the reference as per lab</td> </tr> <tr> <td style="text-align: center;">AST, ALT</td> <td>> 100 U/l</td> </tr> <tr> <td style="text-align: center;">Albumin</td> <td><30g/L</td> </tr> <tr> <td style="text-align: center;">MCV*</td> <td>> 105 fL</td> </tr> <tr> <td style="text-align: center;">U&E (including creatinine)</td> <td>Increase in creatinine of >30% over 12months or CrCl <60ml/min</td> </tr> <tr> <td style="text-align: center;">Potassium</td> <td>>5.5mmol/L</td> </tr> </tbody> </table> <p>* Withhold and check vitamin B12, folate and TSH. If abnormal, treat any underlying abnormality. If normal, discuss with the specialist team.</p>	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	WBC	< 3.5 x 10 ⁹ /L or less than the lower limit of the reference as per lab	Neutrophils	< 1.6 x 10 ⁹ /L or less than the lower limit of the reference as per lab	Eosinophils	>0.5 x 10 ⁹ /L or greater than the upper limit of the reference as per lab	Platelets	< 140 x 10 ⁹ /L or less than the lower limit of the reference as per lab	AST, ALT	> 100 U/l	Albumin	<30g/L	MCV*	> 105 fL	U&E (including creatinine)	Increase in creatinine of >30% over 12months or CrCl <60ml/min	Potassium	>5.5mmol/L
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Adverse Effects	<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>Bruising with or without sore throat - Check FBC immediately and discuss with specialist team.</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>
Adverse Effects	<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 & 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.
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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

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