Lancashire & South Cumbria Medicines Management Group

SHARED CARE GUIDELINE

DRUG: MYCOPHENOLATE MOFETIL

Introduction	**This protocol only applies to the unlicensed indications listed below. Transplant protocols should be followed for licensed indications.** **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), vasculitidies, as maintenance post cyclophosphamide in patients for whom azathioprine is contra-indicated or is inappropriate. **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. **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 NOT mycophenolic acid/mycophenolate sodium.**
Dose & Administration[1]	**Typical dose:** 1 to 2 grams/daily (in divided doses). **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. (For interstitial lung disease the starting dose is 250-500mg daily increasing by 250mg per week up to 1-1.5g twice daily.[6]) **Maximum dose:** Up to 3 grams/day. **Time to response:** 6 weeks to 3 months.
Secondary Care Responsibilities	• 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 (See cautions section below and MHRA warning 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 (as per GMC guidance). • 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. • Conduct laboratory monitoring (see below) TWO WEEKLY until dose stable for SIX weeks, then every MONTH for THREE months

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	• 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	• Provide the patient with prescriptions for mycophenolate mofetil once on stable dose and having undergone monthly monitoring for a minimum of 3 months. • 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	• Annual flu vaccination is recommended. • Pneumococcal vaccination is recommended • COVID-19 vaccination is 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 including shingles unless specialist advice has been sought. See 'Green Book' for details of vaccines in patients who may be immunosuppressed. **Live vaccines should be avoided until specialist advice has been sought.**
Drug Interactions	Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with enterohepatic recirculation, e.g. ciclosporin, to others devoid of this effect, e.g. tacrolimus, sirolimus, belatacept, or vice versa. Drugs which interfere with mycophenolate's enterohepatic cycle (e.g. cholestyramine, antibiotics) should be used with caution due to their potential to reduce the plasma levels and efficacy of Mycophenolate. It is recommended that Mycophenolate should not be administered concomitantly with azathioprine because such concomitant administration has not been studied. **Other clinically significant interactions:** Rifampicin decreases the concentration of Mycophenolate. Manufacturer advises monitor and adjust dose.
Cautions	**Neoplasms** As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. **Infections** Patients treated with immunosuppressants, including Mycophenolate, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. There is a risk of hypogammaglobulinaemia or bronchiectasis when used in combination with other immunosuppressants. Measure serum immunoglobulin levels if recurrent infections develop, and consider bronchiectasis or pulmonary fibrosis if persistent respiratory symptoms such as cough and dyspnoea develop – **see monitoring section.**

	Mycophenolic acid has a cytostatic effect on B- and T-lymphocytes, therefore an increased severity of COVID-19 may occur, and appropriate clinical action should be considered. **Blood and immune system** Patients receiving Mycophenolate should be monitored for neutropenia – **see monitoring section for details.** Cases of pure red cell aplasia (PRCA) have been reported in patients treated with Mycophenolate in combination with other immunosuppressants – **see monitoring section.** **Patients receiving Mycophenolate should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow failure – see monitoring section also** **Gastro-intestinal** Mycophenolate has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation. Mycophenolate should be administered with caution in patients with active serious digestive system disease. Mycophenolate is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. 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. **Special populations** Elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals.
Contra-indications	• Mycophenolate should not be given to patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients. Hypersensitivity reactions to mycophenolate have been observed. • Mycophenolate should not be given to women of childbearing potential who are not using highly effective contraception. • Mycophenolate treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy. • Mycophenolate should not be used in pregnancy. • Mycophenolate should not be given to women who are breastfeeding.
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.

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*

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

* Withhold and check vitamin B12, folate and TSH. If abnormal, treat any underlying abnormality. If normal, discuss with the specialist team.

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).

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.

	Bruising with or without sore throat - Check FBC immediately and discuss with specialist team. Recurrent infection – measure serum immunoglobulin levels, discuss with the specialist team if low. Persistent cough or dyspnoea – discuss with the specialist team, bronchiectasis or pulmonary fibrosis should be considered. **Patients receiving Mycophenolate should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow failure**
Adverse Effects	**Common or very common:** Acidosis; alopecia; anaemia; appetite decreased; arthralgia; asthenia; bone marrow disorders; chills; constipation; cough; depression; diarrhoea; drowsiness; dyslipidaemia; dyspnoea; electrolyte imbalance; fever; gastrointestinal discomfort; gastrointestinal disorders; gastrointestinal haemorrhage; headache; hyperglycaemia; hypertension; hypotension; increased risk of infection; insomnia; leucocytosis; leucopenia; malaise; nausea; neoplasms; oedema; oral disorders; pain; pancreatitis; paraesthesia; renal impairment; respiratory disorders; seizure; sepsis; skin reactions; tachycardia; thinking abnormal; thrombocytopenia; tremor; vomiting; weight decreased. **Uncommon:** Agranulocytosis. **Frequency not known:** Endocarditis; hypogammaglobulinaemia; malignancy; meningitis; neutropenia; polyomavirus-associated nephropathy; progressive multifocal leukoencephalopathy (PML); pure red cell aplasia. **Specific side-effects:** **Common or very common:** With intravenous use: Hepatitis; muscle tone increased. With oral use: Anxiety; burping; confusion; dizziness; gout; hepatic disorders; hyperbilirubinaemia; hyperuricaemia; neuromuscular dysfunction; taste altered; vasodilation

Acknowledgements to
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References

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RELEVANT CONTACT LIST

Speciality	
Name and Title	Tel. No.

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