SHARED CARE GUIDELINE

DRUG: MYCOPHENOLATE MOFETIL

Introduction	**This protocol only applies to the Off- Label indications listed below. Transplant protocols should be followed for licensed indications.** **Off- Label indications:** Severe rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, connective tissue diseases with severe / organ-threatening manifestations, vasculitides, as maintenance post cyclophosphamide in patients for whom azathioprine is contra-indicated or is inappropriate, atopic eczema, bullous dermatoses, chronic actinic dermatitis, dermatomyositis, photoallergy, psoriasis, pyoderma gangrenosum. **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.**
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. **Maximum dose:** Up to 3 grams/day. **Time to response:** 6 weeks to 3 months.
Secondary Care Responsibilities	1. Discuss the benefits and side effects of treatment with the patient. Ensure that the patient understands which warning signs and symptoms to report. 2. 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) 2. Ensure that the patient is aware that the use of the drug for this condition equates to 'off-label' use of a licensed product. Make a clear, accurate and legible record of medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed/off-label medicine (as per GMC guidance). 3. Perform pre-treatment screening (chest X-ray, FBC, LFT's, U&E's, pregnancy test in women of childbearing potential). 4. 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. 5. Initiate treatment with mycophenolate, continue for at least 3 months and until the patient is stable. 6. Arrange shared care with the patient's GP and continue to provide treatment until shared care arrangements have been confirmed. 7. Review the patient regularly to monitor the patient's response to therapy. Advise the GP of the secondary care monitoring and follow up arrangements. 8. Request copies of test results for the patient's GP by completing the "copy to" section on the pathology form. 9. Advise the GP on dose adjustments and when to stop treatment. 10. Ensure that clear backup arrangements exist for GPs to obtain advice.

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Primary Care Responsibilities	1. Provide the patient with prescriptions for mycophenolate mofetil. 2. Ensure that the patient understands which warning signs and symptoms to report. 3. 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. 4. 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). 5. Report any worsening of control of the condition to the consultant or specialist nurse.
Immunisations	• 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
Monitoring Required in Primary Care	FBC weekly until dose stable for 4 weeks then fortnightly for 2 months, then monthly, even after the patient is stabilized on treatment. [1&3] **Laboratory adverse event*** **Seek advice if:** **WBC < 3.5 x 10^9/L or less than the lower limit of the reference as per lab** **Neutrophils < 2. 0 x 10^9/L or less than the lower limit of the reference as per lab** **Platelets < 150 x 10^9/L or less than the lower limit of the reference as per lab** **AST, ALT*> 2 times the upper limit of reference range** *LFTs should be checked at baseline as per the SPC/BSR guidance but routine monitoring of LFTs after this is not required unless otherwise specified by the initiating specialist 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). *If routine blood tests are within the laboratory range but give rise to concerns, (e.g. because of a notable change from baseline or a downward trend) then discuss with the specialist team. **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 (n.b. cough is also a recognised side effect of mycophenolate mofetil)
Adverse Effects	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; *also reported* 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.

Cautions	• 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. (Patients should be advised to wear protective clothing and use a sunscreen with a high protection factor when outdoors).
	• **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]
	  ○ 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

Drug Interactions	• 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 – mycophenolate increases aciclovir plasma levels (significant only in renal impairment).
Contra-indications	• 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[4] • Mycophenolate is contra-indicated in women who are breastfeeding. • Hypersensitivity to mycophenolate mofetil or mycophenolic acid.
This guidance does not replace the SPCs, which should be read in conjunction with this guidance.	

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 guideline for disease-modifying anti-rheumatic drug therapy in consultation with the British Association of Dermatologists http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmard_therapy.pdf
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