SHARED CARE GUIDELINE

Mycophenolate for use in Neurology

Implementation Date: June 2018 **Review Date: June 2021**

This guidance has been prepared and approved for use within Sunderland and South Tyneside in consultation within the CCGs, and Secondary Care Trust.
The guideline sets out the details of the transfer of prescribing and respective responsibilities of GPs and specialist services within shared care prescribing arrangements. It is intended to provide sufficient information to allow GPs to prescribe this treatment within a shared care setting

Approved by:

Committee	Date
SCCG medicines optimisation and guideline group	20.6.18
STS APC – review date extended to December 2020	August 2020
STS APC – review date extended to June 2021	February 2021

Instructions for completion:

- ☐ Consultant to counsel patient on medication and ensure patient has been provided with information leaflet
- ☐ Consultant to ensure all clinical details completed on this document
- ☐ Consultant to ensure patient understands proposed monitoring and prescribing arrangements if a shared care agreement is entered into
- ☐ GP to complete final section of form and return to specialist prescriber within 28 days
- ☐ GP to retain copy of document on patient record within surgery

Clinical details:

SHARED CARE GUIDELINE					
Non-proprietary name	Mycophenolate mofetil	Brand name	Cellcept	Licensed Yes/No	*No*
Dosage form and strength	Oral tablets (500mg), capsules (250mg) and suspension (1g/5mL). Dose and frequency of administration should be stated clearly on the prescription			BNF class	8.2.1
Indication	Unlicensed: Myasthenia gravis, Neuromyelitis optica, Autoimmune limbic encephalitis, neurosarcoidosis, CNS vasculitis, inflammatory myositis, Chronic inflammatory demyelinating polyradiculopathy (CIDP)				
Dosage and Administration	**Typical dose:** • 1–2 g/day. • **Starting dose**: 500mg daily for the 1st week, • 500 mg twice daily for the 2nd week and increase it gradually by 500 mg each week until the optimal or maximum tolerated dose is reached. **Maximum dose**: Up to 3 g/day **Time to response:** 6 weeks to 3 months Dose and frequency should be stated clearly on the prescription				
Eligibility criteria for shared care	Patients must be under the care of CHS consultant neurologist Must have diagnosis consistent with indications above who have been stable on their maintenance dose of mycophenolate for three months				
Excluded patients	Not for patients under the age of 16 years. Patients in whom mycophenolate is contraindicated or not tolerated				

<table>
<tr><td>Initiation</td><td>Shared care to be initiated once patient has been stable on maintenance dose for three months</td></tr>
<tr><td>Monitoring</td><td>

Baseline assessment
The following should be performed prior to starting mycophenolate

- Routine bloods including FBC, (ESR optional),U&E, LFTS, HIV, Hepatitis B & C
- BMI
- Chest x-ray if any concern regarding latent TB
- Lung function tests plus further investigations if concern of chronic lung disease
- Pregnancy test should be performed in women of reproductive age

Assessment for acute infection, including urine analysis

Ongoing blood test monitoring according to high risk or low risk patients according to monitoring schedules below.

<u>Monitoring of high risk patients</u>

- The patient is ‘high risk’ if any of the following apply:
- Extremes of weight: BMI <18 or >30kg/m2
- Renal impairment: CKD stage III or above
- Pre-existing liver disease (including NAFLD)
- Significant other co-morbidity (e.g. malignancy)
- Age >80 years
- Previous DMARD toxicity.

Routine Bloods: FBC, U&E, ALT, Albumin, eGFR **— every four weeks**.

<u>For patients who are NOT high risk:</u>
Routine Bloods: FBC, U&E, ALT, Albumin eGFR

- Once on a stable dose: monthly blood tests for 3 months
- Then: at least every 12 weeks for the duration of treatment
- Following a dose increase bloods should be checked 2 weekly for 6 weeks, then revert back to previous schedule

Laboratory abnormalities requiring action
The abnormalities in table below should trigger action/review. **<u>If any abnormal blood test results are obtained, withhold the medication and discuss with the patient’s consultant neurologist</u>**. Do not forget to consider the possibility that the abnormal blood result may be unrelated to the immunosuppressant medication.

Test	Result
White cell count	<3.5 * 10^9/l (or downward trend over 2 consecutive tests)
Neutrophils	<1.6 * 10^9/l
Unexplained eosinophilia	>0.5 * 10^9/l
Platelet count	<140 * 10^9/l
MCV	> 105 f/l
Creatinine/ eGFR	Creatinine increase >30% over 12 months and/or GFR <60ml/min/1.73m2
ALT (and or AST)	>100 U/L
Albumin	Unexplained reduction in albumin to <30g/l

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Infections	**Infections** Patients treated with immunosuppressants are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). During serious infections, the IA should be temporarily discontinued, until the patient has recovered from the infection. It is usually appropriate to continue them in minor infections (e.g. a treated, uncomplicated UTI or URTI). It is very important to be observant about any new symptoms of infection as the reported incidence of cytomegalovirus infection is slightly higher. The incidence of infection and sepsis is somewhat similar to that typically observed in the transplant population. • Increased risk of infections (particularly if used in combination with other immunosuppressants) • In addition, hypogammaglobulinaemia with recurrent infections has been reported in patients taking MMF with other immunosuppressants – product literature advises that patients with recurrent infections on MMF should have their immunoglobulin levels checked • Bronchiectasis has been reported in patients taking MMF with other immunosuppressants • Reactivation of latent infection e.g. TB, hepatitis B or C, herpes zoster • If the patient develops recurrent infections or respiratory symptoms this should be investigated as mycophenolate has been associated with hypogammaglobulinaemia, bronchiectasis and pulmonary fibrosis (MHRA alert January 2015) If the patient develops recurrent infections or respiratory symptoms this should be investigated as mycophenolate has been associated with hypogammaglobulinaemia, bronchiectasis and pulmonary fibrosis (MHRA alert January 2015). If recurrent infections or respiratory symptoms are present, refer back to specialist Patient should be seen by GP/clinician within 12 hours of onset of infective symptoms.
Vaccinations	Live vaccinations are not recommended. Vaccinations against influenza and pneumococcus should be recommended. If herpes zoster occurs stop MMF and prescribe aciclovir. If patient is in contact with chicken pox, contact the neurology team (may need zoster immune globulin).
Pregnancy and breastfeeding	Contact specialist. It is generally advised to ensure that the patients are NOT pregnant before the drug is commenced and advised to use contraception for at least 6 weeks after discontinuation of treatment. It is not recommended for mothers who are breast feeding (manufacturer's advice). Reproductive issues: • MMF is teratogenic and it should not be taken during pregnancy nor while breast-feeding • Women of child-bearing age should use appropriate contraception whilst taking the drug. Hormonal methods of contraception should be supplemented with a barrier method • Women should not attempt to get pregnant until at least 6-12 weeks after stopping MMF The European Medicines Agency updated its advice for men and mycophenolate (15 December 2017): either the male patient or his female

	partner use reliable contraception during mycophenolate treatment and for at least 90 days after stopping treatment. • Limited evidence suggests no increased risk of teratogenicity in men The manufacturers of MMF have produce risk materials for healthcare professionals and patients to reflect the above advice https://www.medicines.org.uk/emc/product/1102/rmms
Perioperative use	Steroid exposure should be minimised prior to surgical procedures and increases in steroid doses to prevent adrenal insufficiency are not routinely required
Cancer risk	Patients receiving long-term IAs are at increased risk of developing a malignancy. There is no evidence as to whether MMF use in patients with neurological conditions increases cancer risk. An increased incidence of non-Hodgkin's lymphoma has been documented in transplant patients receiving MMF. The majority of malignancies are B cell lymphoma associated with Epstein-Barr virus. However, concomitant treatment with drugs such as azathioprine, ciclosporin or tacrolimus can increase the probability of lymphoma. **Skin cancer advice** • There is probably an increase in skin cancers in patients on any form of immunosuppression. This is also related to skin types and duration of sun exposure. In view of this we would recommend sun protection with sun tan lotion/ hats and avoiding burning. • Patients should be vigilant with regards to suspicious or changing skin lesions and should report them to their GP or hospital consultant as a matter of urgency. In patients with prior skin cancer, it may be appropriate to involve the dermatologists, with consideration of a skin screening programme.
Specialist Responsibilities	• The decision to initiate immunosuppressive therapy must be made in conjunction with the patient/carer and be supervised by an expert in the condition in question • Patients must be provided with education about their treatment • Patient will be provided with an mycophenolate patient information leaflet • Patients must be assessed for contra-indications and co-morbidities • Where appropriate, patients should be advised about the impact of the immunosuppressive agent (IA) on fertility, pregnancy and breastfeeding • Vaccinations against pneumococcus and influenza are recommended • Interactions between the proposed IA and current medication should identified and actioned • Direct the patient to report any sign of infection or side effect to their GP or hospital clinic • Conduct baseline monitoring • Prescribe medication until responsibility agreed to be transferred to patients GP • Complete checklist contained in this guidance prior to transfer • Supply general immunosuppressant background information to GP as per this guidance • Request GP participate in shared care in writing no sooner than patient has been stable on same dose for 3 months • Pre-agreed quantity of medication supplied at point of transfer, info regarding initial quantities to be supplied by GP

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The secondary care specialist will communicate with the patient and GP when treatment is changed and/or needs to be changed by GP on future prescriptions, and/or when any changes to the monitoring are required, usually within 24 hrs
Conduct routine monitoring as per schedule while prescribing responsibility with specialist – this could be during initiation or at any point in time where the responsibility has been transferred back to the specialist
Observe advice relating to vaccination, perioperative use, infections etc contained in this document
Specialist responsible for ongoing disease monitoring– clinical response to therapy will be assessed by the hospital physician in all cases and communicated to the GP

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<tr><td>GP Responsibilities</td><td>

The GP should reply to the request for shared care as soon as possible, but always within 28 days, either accepting shared care or informing the specialist why shared care is not felt appropriate in this case.
If GP declines shared care responsibilities it is still the GPs responsibility to record on the primary care record that the drug is being prescribed by secondary care
Shared care to be initiated once patient has been stable on maintenance dose for three months.
Prescribe medication as per document
Conduct routine monitoring as per schedule on page 2
Observe advice relating to vaccination, perioperative use, infections etc. contained in this document

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<tr><td>Contraindications, Precautions, CKD advice, haematological advice and Adverse Effects</td><td>
Contra-indications
Known hypersensitivity to the product
Suspected local or systemic infection
Pregnancy and breast feeding (see below)
Bone marrow failure, with unexplained anaemia and cytopenia
Pre-existing blood dyscrasias
Severe acute or chronic infections
Hereditary deficiency of the enzyme hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan or Kelley-Seegmiller syndrome

Precautions
Very frail and elderly patients
Active serious gastro-intestinal disease.
Hereditary deficiency of hypoxanthine-guanine (presents with early onset gout)
Localised or systemic infection.

Chronic kidney disease (CKD)
In renal disease, IAs that are renally excreted accumulate, and some IAs are nephrotoxic. Mycophenolate is not felt to be nephrotoxic but does accumulate in renal failure. Patients with CKD should be graded as per NICE definition of CKD (table 1) and have IA dose reductions as per recommendations by the British Society of Rheumatology (BSR) (table 2). GPs should contact specialist for advice in the case of CKD or abnormal CrCl/eGFR results.

Table 1: NICE Definitions of CKD
<table>
<tr><th>Degree of Impairment</th><th>Calculated GFR ml/min/1.73m2</th></tr>
<tr><td>Normal, Stage I</td><td>>90 (other evidence of kidney damage)</td></tr>
<tr><td>Mild, Stage II</td><td>60-89 (other evidence of kidney</td></tr>
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Contraindications, Precautions, CKD advice, haematological advice and Adverse Effects

	damage)
Moderate, Stage III	30-59
Severe, Stage IV	15-29
Established renal failure, Stage V	<15

Table 2: Recommended dose adjustment in CKD by the BSR

			Recommended adjustment (% of standard dose)		
Drug	Accumulates in renal failure	Nephrotoxic	CKD III	CKD IV	CKD V
Azathioprine	No	No	Normal dose	75-100	50-100
Methotrexate	Yes	Yes	50%	Contraindicated	
Mycophenolate	Yes	No	Normal dose	1g BD maximum	

Hematological

- Suppression of haemopoisis/myelosuppression
- Neutropenia and cases of pure red cell aplasia reported Abnormal bruising with or without sore throat may indicate bone marrow failure. Severe neutropenia occurs in 0.5% patients receiving MMF in the full dose.
- STOP the drug. Check FBC immediately also discuss with specialist team. Temporary suspension of MMF for 10–14 days will usually result in recovery of the cell count. Once the cell count recovers, the drug can be re-administered in half the previous dose and gradually increased until a stable dose is attained without any toxic effect.
- It is often difficult to assess the exact cause of leucopenia or neutropenia because many causes may lead to the development of these disorders such as additional immunosuppressive regimens, concomitant medications and viral infections or combination of all the above. It is most commonly seen within the first 6 months.
- Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MMF in combination with other immunosuppressants. PRCA may resolve with dose reduction or cessation of MMF (Roche communication May 2009).

Adverse Effects

Nausea, diarrhoea GI inflammation, ulceration and bleeding, abdominal cramps and dyspepsia. (STOP drug if evidence of GI bleeding),cough, dyspnoea, hyperglycaemia, tremor, dizziness, headache, flu-like syndrome hepatitis, jaundice, pancreatitis, hypertension, hypotension, tachycardia, insomnia, blood disorders (including leucopenia, anaemia, thrombocytopenia, pancytopenia and red cell aplasia), disturbances of electrolytes and lipids, malignancy (particularly of the skin), renal impairment, progressive multifocal leukoencephalopathy, interstitial lung disease, pulmonary fibrosis, alopecia, rash, uro-genital (sterile haematuria, urinary tract infection, renal tubular necrosis).
Clinician should review severity of side effect and contact specialist for advice if needed.

For a full list of contraindications/precautions/side effects please consult either the current BNF or SPC

<table>
<tr><td>Communication/ Contact Details</td><td>Contact the patient’s Consultant Neurologist at Sunderland Royal Hospital. In their absence please contact the consultant neurologist on-call.
Neurology department: 0191 5656256</td></tr>
<tr><td>Common Drug Interactions</td><td>Interactions:
Live vaccines should not be given.
Antacids: Containing aluminium and magnesium hydroxide cause a decrease in the absorption of MMF by 33% and bioavailability by 17%. Antacids/PPIs impair mycophenolate absorption and should be taken 1hr prior or 2hrs after.
Cholestyramine: May decrease the absorption of MMF and bio-availability by 40%.
Azathioprine: The manufacturers state that mycophenolate mofetil should not be given with azathioprine as concurrent use has not been studied and both drugs may cause bone marrow suppression. If concurrent use is unavoidable it would seem prudent to increase the frequency of routine monitoring.
Rifampicin: decreases the concentration of MMF; manufacturer advises monitor and adjust dose.
Probenecid: Prevents renal tubular secretion and causes an increase in plasma concentration of MMF.
Aciclovir: causes increase in the concentration of both MMF and aciclovir. However, the increase is significant only in renal impairment.
Other drug interactions include metronidazole, ganciclovir, iron, ciclosporin A, telmisartan and sevelamer.
For a full list of interactions please consult the current BNF or SPC.</td></tr>
<tr><td>Caveats</td><td>This document should be read in conjunction with the general guidance on immunosuppression attached</td></tr>
<tr><td>Checklist and References</td><td>Weight: _____ BP:_____
Starting dose:_____ twice daily
<table><tr><th></th><th>YES</th><th>NO</th></tr><tr><td>Received education and written information about their treatment?</td><td></td><td></td></tr><tr><td>Advised of potential adverse effects of drug including allergy</td><td></td><td></td></tr><tr><td>Advised about reproductive issues as above</td><td></td><td></td></tr><tr><td>Assessed for contraindication to drug</td><td></td><td></td></tr><tr><td>Evaluated for chronic lung disease? If chronic lung disease present: had lung function tests, CXR +/- high resolution CT chest and respiratory referral</td><td></td><td></td></tr><tr><td>Assessed if any risk of latent TB, if so, CXR performed</td><td></td><td></td></tr><tr><td>Smoking status checked and cessation advice given if necessary</td><td></td><td></td></tr><tr><td>Evaluated for liver disease and any causes addressed and managed if necessary.</td><td></td><td></td></tr><tr><td>Evaluated for renal disease and any dose reduction made if necessary (dose of 1g BD maximum in CKD stages IV and V)</td><td></td><td></td></tr><tr><td>Discussed possible risk of increased malignancy</td><td></td><td></td></tr><tr><td>Made aware of the national screening programmes for cervical, breast, bowel and prostate cancer</td><td></td><td></td></tr><tr><td>Given skin cancer advise and assessed whether had previous/current skin cancer, and, if so, consideration made as to whether to refer to dermatologist</td><td></td><td></td></tr><tr><td>Screening blood tests performed: FBC, U&Es, LFTs, HIV, hepatitis B and C</td><td></td><td></td></tr><tr><td>Pregnancy test</td><td></td><td></td></tr></table></td></tr>
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	Assessed if any symptoms of acute infection (MMF inadvisable)		
	Urinalysis		
	Recommended yearly flu and pneumococcal vaccination		
	Assed whether had previous history of chickenpox. If not, consider testing VZV IgG and vaccination if necessary		
	Counselled that live vaccines not recommended. There is no guidance as to whether it is safe to administer the shingles) vaccine. Therefore, if possible, eligible patients should be vaccinated at least 4 weeks prior to commencing therapy. (Patients at 70 years of age as part of the national vaccination programme.)		
	Counselled that if develops persistent cough or breathlessness, fever, sore throat, abnormal bleeding/bruising, rashes or jaundice to stop medication and seek immediate medical advice		
	Counselled that if has recurrent infections, seek medical advice (immunoglobulins should be checked)		
	Discussed need for monitoring		

References

1. British Society for Rheumatology guideline for the prescription and monitoring of non-biologic disease modifying anti-rheumatic drugs. Ledingham J, Gullick N, Irving K et al 2017, Oxford University Press.
2. Myasthenia gravis: Association of British Neurologists' management guidelines. Sussman J, Farrugia ME, Hill M et al. Pract neurol 2015;15:199-206.
3. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Palace J, Newsom-Davis J, Lecky B. Neurology 1998;50(6):1778-83.
4. EFNS guidelines on diagnosis and management of neuromyelitis optica. Sellner J, Boggild M, Clanet M et al. Eur J Neurol 2010;17:1019-32.
5. Use of azathioprine for non-thymoma myasthenia and risk of cancer: a nationwide case-control study in Denmark. Pederse EG, Pottegard A, Hallas J et al. Eur J Neurol 2013;20:942-948.
6. Risk of non-melanoma skin cancer in myasthenia patients treated with azathioprine. Pederse EG, Pottegard A, Hallas J et al. Eur J Neurol 2014;21:454-458.
7. BSR and BHPR guideline on prescribing drugs in pregnancy and breast-feeding- Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Flint J, Panchal S, Hurrell A et al. Rheumatol 2016;55:1693-97.
8. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> Accessed: 11/1/18
9. Cellcept 250 mg capsules SPC (Date of last update: 3/12/15). electronic Medicines Compendium (eMC). http://www.medicines.org.uk/emc/. Accessed on 11/1/18

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to full prescribing data in the SPC or the BNF.

Shared Care Request/Confirmation **Private and Confidential**

Patient information:

To be completed by specialist prescriber:

		Patient details (use hospital label if preferred)	
Consultant	……	**Name**	……
Department	……	**Address**	……
Hospital	……		……
		Postcode	..... **Sex** ……..
		NHS or Hosp. Reg. No.	…… **DoB** ……..

Treatment Requested for Prescribing in Accordance with Shared Care Arrangement:

To be completed by specialist prescriber:

Drug name	
Dose	
Frequency	
Indication	
Other information	

Name (print)…….… Signature (of specialist prescriber)……..…….. Date……..

Acceptance/rejection of treatment under Shared Care Agreement:

To be completed by GP:

Please tick one box

I ACCEPT the proposed shared care arrangement for this patient ❑

or

I ACCEPT the proposed shared care arrangement with the caveats below ❑

or

I DO NOT ACCEPT the proposed shared care arrangement for this patient ❑

My caveats / reason(s) for not accepting include: ……
……

Name (print)……..… Signature (of GP)……..……..... Date….

N.B. Participation in this shared care arrangement implies that prescribing responsibility is shared between the specialist prescriber and the patient's GP