NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT

Shared care guidelines for use of Mycophenolate mofetil / Mycophenolic acid for Adult Solid Organ Transplant Patients

Monitoring level Amber 1 - perform higher level of monitoring e.g. 6 monthly review

Generic and Proprietary/Brand Name	
• Mycophenolate mofetil – available as generic products from several manufacturers • Mycophenolic acid (as Mycophenolate sodium) • CellCept®, Myfenax® – treatment is interchangeable between mycophenolate mofetil brands and generics • Myfortic® (Mycophenolic acid (as Mycophenolate sodium)) – not interchangeable with other mycophenolate salts	
Indications for shared care	
• Post adult solid organ transplant • Shared-care will only be considered appropriate at least three months post-transplant and only when the immunosuppression regimen is stable, co-morbid conditions such as hypertension are being treated.	
Specialist Prescribing and Monitoring Responsibilities – summary. Full details in main body of document	**GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities – summary. Full details in main body of document**
• Review patient in clinic. • Inform the patient of side effects and long term monitoring before initiating treatment. • Prescribe mycophenolate for at least three months until the immunosuppression regimen is stable, co-morbid conditions such as hypertension are being treated and there is no longer a need for the patients to be seen as frequently in clinic. • When the patient is near completing a satisfactory initiation period, the physician will write to the GP to request they take over prescribing. • Inform the patient/carers of the arrangements being made to share care with their GP, including information on who will be monitoring each aspect of therapy. • Inform the GP of the results taken at each clinic visit. **Initial monitoring:** • Urea & electrolytes (including calcium & phosphate) • Blood pressure • Liver function tests • Full blood count • Mid-stream urine (for Culture & Sensitivities) • Lipid screening	• Prescribe mycophenolate mofetil / mycophenolic acid once the patient has been stabilised on therapy and side effects have been excluded as far as possible by the hospital. • If the GP has concerns over the prescribing of mycophenolate mofetil / mycophenolic acid they will contact the physician as soon as possible. • Avoid drug interactions • Avoid live vaccines • It is vital that doses are not changed without first consulting the physician. • • Identify adverse effects and treat or report to physician where appropriate • If a patient presents with a likely infection an urgent FBC and urea & electrolytes should be taken (see section on indication for referral back to specialist) • Alert the specialist to any identified non-compliance with immunosuppressants • Carry out tests as requested in writing by the specialist

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At each clinic appointment the above tests will be taken, the frequency of which is determined by clinical need (Lipid screening for total cholesterol is taken quarterly) The specialist will also evaluate any adverse events reported by the GP.	

Patient Information

- To be taken on an empty stomach
- The tablets or capsules should not be opened or crushed but swallowed whole
- Patients should not donate blood during treatment or for at least 6 weeks following discontinuation of mycophenolate mofetil or mycophenolic acid.

Please refer to mycophenolate mofetil, CellCept and Myfortic Patient Information Leaflets; available at http://www.medicines.org.uk/emc/

Specialist Contact Details

- Dr. Mark Andrews, Consultant Nephrologist via secretary on 01603 286659
- Dr. Mahzuz Karim, Consultant Nephrologist via secretary on 01603 288930
- NNUH Langley Ward on 01603 289974

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.
- **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment
Mycophenolate mofetil is available as generic formulations which are interchangeable with Cellcept®. For patients prescribed mycophenolic acid, they should receive the Myfortic® brand which is not interchangeable with any other form of mycophenolate. Immunosuppressive agent - mycophenolate is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.
Licensed use and agreed local off-label use
Mycophenolate mofetil (various brands) and Myfortic® are indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. The combination with tacrolimus is not licensed but is well established in renal treatment protocols. NB: Mycophenolate mofetil (various brands) and Myfortic® should not be indiscriminately interchanged or substituted due to differing pharmacokinetic profiles.
Criteria for Patient Selection
For adult patients who have undergone a solid organ transplant. Addenbrooke's Hospital (primary transplant centre) tailor their immunosuppression regimen to their estimate of the 'immunological risk' of the transplant. Mycophenolate is given to patients at high immunological risk and those with delayed graft function (dose and duration according to Addenbrooke's protocols) unless contraindicated. Mycophenolate is also used in patients with intolerance to azathioprine. Patient care is transferred to the NNUH three months post-transplant. Within the NNUH mycophenolate is used in accordance with Addenbrooke's protocols. Mycophenolate is also used when a person develops a proven intolerance to calcineurin inhibitors, such as nephrotoxicity leading to risk of chronic allograft dysfunction, or in situations where there is very high risk of nephrotoxicity necessitating minimisation or avoidance of calcineurin inhibitor. **NICE guidance https://www.nice.org.uk/guidance/ta481 states under recommendation 1.3:** Mycophenolate mofetil, when used as part of an immunosuppressive regimen, is recommended as an initial option to prevent organ rejection in adults having a kidney transplant. Treatment should normally be started with the least expensive product. However, treatment can be started with an alternative dosage form if the least expensive product is not suitable (for example, if the person is not able to swallow capsules as a result of a disability or they are unable to have a particular ingredient because of allergy or religious reasons). **NICE TA 481 also states:**

The use of mycophenolate mofetil (with tacrolimus) is outside the terms of the marketing authorisation for mycophenolate mofetil. If (this combination is) prescribed, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.

Form and strength of preparation

- Mycophenolate mofetil 250mg capsules and 500mg tablets
- Mycophenolate mofetil suspension 1g/5ml
- Mycophenolic acid / Mycophenolate sodium 180mg and 360mg gastro-resistant tablets

Side Effects and Management

Link to BNF

Link to SPC

Drug Interactions

Link to BNF

Link to SPC

Cautions and Contraindications

Link to BNF

Link to SPC

Initiation of therapy and ongoing dose regimen

Consultant at the Norfolk and Norwich University Hospital or Addenbrooke's Hospital.

Mycophenolate Mofetil

The adult dose is 1g twice daily orally. Many patients will start at 500mg twice daily and the dose titrated up in the transplant clinic. Patients may be on a lower dose if they have not tolerated the higher dose. Gastro-intestinal adverse-effects may be limited by splitting doses (e.g. 500mg four times daily).

Myfortic® (Mycophenolic acid)

Once established, the recommended dose is 720mg twice daily orally.

Administration Information

As above

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

Long-term therapy

Baseline assessment and ongoing monitoring – by Specialist

Initial monitoring:

- Urea & electrolytes (including calcium & phosphate)
- Blood pressure
- Liver function tests
- Full blood count
- Mid-stream urine (for Culture & Sensitivities)
- Lipid screening

At each clinic appointment the above tests will be taken, the frequency of which is determined by clinical need (Lipid screening for total cholesterol is taken quarterly)

The specialist will also evaluate any adverse events reported by the GP.

Interim tests may be required between clinic visits. If this is the case the specialist will write to the GP stating which test is to be taken and at what time. The specialist will provide the patient directly with an ICE form to receive phlebotomy from their nearest service.

GP / Community Team or other Primary Care monitoring responsibilities

- Identify adverse effects and treat or report to physician where appropriate
- If a patient presents with a likely infection an urgent FBC and urea & electrolytes should be taken (see section on indication for referral back to specialist)
- Alert the specialist to any identified non-compliance with immunosuppressants
- Carry out tests as requested in writing by the specialist

Consultant / Specialist prescribing responsibilities

- Review patient in clinic.
- Inform the patient of side effects and long term monitoring before initiating treatment.
- Prescribe mycophenolate for at least three months until the immunosuppression regimen is stable, co-morbid conditions such as hypertension are being treated and there is no longer a need for the patients to be seen as frequently in clinic.
- Inform the GP when mycophenolate is initiated. When the patient is near completing a satisfactory initiation period, the physician will write to the GP to request they take over prescribing.
- Inform the patient/carers of the arrangements being made to share care with their GP, including information on who will be monitoring each aspect of therapy.
- Inform the GP of the results taken at each clinic visit. Any action required will be taken by the physician and information on any changes to medication will be given in the accompanying letter.

GP prescribing responsibilities

- Prescribe mycophenolate mofetil / mycophenolic acid once the patient has been stabilised on therapy and side effects have been excluded as far as possible by the hospital.
- If the GP has concerns over the prescribing of mycophenolate mofetil / mycophenolic acid they will contact the physician as soon as possible.
- Avoid drug interactions
- Avoid live vaccines

It is vital that doses are not changed without first consulting the physician.

***CellCept* / *Myfenax* / generic mycophenolate mofetil and *Myfortic* should not be indiscriminately interchanged or substituted due to differing pharmacokinetic profiles.**

Indications for referral back to Specialist

- Neutropenia (white cell count <4 * 10^9/L, neutrophils <1.3 * 10^9/L (Cellcept®, Myfenax, mycophenolate mofetil) or <1.5 * 10^9/L (Myfortic® mycophenolic acid) or indices falling rapidly.
- Pure Red Cell Aplasia (PRCA) identified by lab report.
- Significant decline in renal function.
- Frequent symptomatic diarrhoea.
- Concerns by GP or patient.

Pregnancy, paternal exposure and breastfeeding

All patients should be informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The specialist team should be contacted if a patient becomes pregnant or is planning to become pregnant or breastfeed.

Pregnancy:

Mycophenolate is contraindicated during pregnancy or breastfeeding. Contraception should be used for 6 weeks after stopping the drug.

Because of the genotoxic and teratogenic potential of mycophenolate mofetil, people of childbearing potential must use at least one highly effective form of contraception before and during treatment and for six weeks after stopping mycophenolate unless abstinence is the chosen method of contraception. Two forms of contraception used simultaneously are preferred. See MHRA Drug safety update and letter sent to healthcare professionals. See also more recent advice:
MHRA Drug Safety Update: Medicines with teratogenic potential: what is effective contraception and how often is pregnancy testing needed?
Faculty of Sexual and Reproductive Healthcare statement on contraception for women using known teratogenic drugs or drugs with potential teratogenic effects.

Methods of contraception which are considered 'highly effective' in this context include the long-acting reversible contraceptives (LARC) copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS) and progestogen-only implant (IMP) and male and female sterilisation, all of which have a failure rate of less than 1% with typical use. (Note that patients using IMP must not take any interacting drugs that could reduce contraceptive effectiveness).
Information for healthcare professionals:
https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-MYCOPHENOLATE-MOFETIL-IN-PREGNANCY/
Information for patients and carers: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Mycophenolate/

Breastfeeding:
Mycophenolate should not be prescribed for people who are breastfeeding
Information for healthcare professionals: https://www.sps.nhs.uk/medicines/mycophenolate-mofetil/

Paternal exposure:
Limited evidence does not indicate an increased risk of malformations or miscarriages in pregnancies where the father is taking mycophenolate. However, mycophenolate is genotoxic and the risk cannot be fully excluded. It is therefore recommended that male patients or their female partners use reliable contraception during treatment, and for at least 90 days after stopping mycophenolate. See MHRA Drug Safety Update: Mycophenolate mofetil, mycophenolic acid, updated contraception advice for male patients (Feb 2018)

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Document history:

Version	Date	Author / Editor	Status	Comment
1.	Jan 2007	Dr Mark Andrews, Consultant in Renal Medicine, Hannah Waller, Specialist Clinical Pharmacist Renal Medicine, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Due for review January 2009
2.	March 2009	Dr Mark Andrews, Consultant in Renal Medicine, Claire O'Dwyer, Specialist Clinical Pharmacist Renal Medicine, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	2 year review. Change of author. Clarification regarding monitoring for MMF patients. The current procedure in place involves the consultant writing to the GP requesting their involvement should there be a need for additional tests between clinic visits. They also communicate dose changes, test results or any other issues etc by letter after the clinic visit. The SCA details monitoring carried out by the specialists. GPs are not obliged to carry out any other monitoring other than those lists in the SCA under GP monitoring and GP prescribing responsibilities. Results of tests carried out here are available to read on the ICE system. If a GP however, prescribes an acute prescription for the patient, one which may possibly interact with MMF then it is their responsibility to monitor the FBC or to ask for advice. Due for review March 2011
3.	Sept 2009	Dr Mark Andrews, Consultant in Renal Medicine, Claire O'Dwyer, Specialist Clinical Pharmacist Renal Medicine, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Revised to include information on MHRA reports on cases of pure red cell aplasia (PRCA) associated with its use. Text added under **Side Effects** and **Indications for referral back to specialist**
4.	Sept 2012	Dr Mark Andrews, Consultant in Renal Medicine, Claire O'Dwyer, Specialist Clinical Pharmacist Renal Medicine,	Superseded	Arzip® brand of mycophenolate mofetil added, which is interchangeable with CellCept®. Treatment with mycophenolic

		NNUH / Fiona Marshall TAG Lead Pharmacist		acid / mycophenolate sodium (Myfortic®) is not interchangeable with any brand of mycophenolate mofetil. Approved by the TAG on 6th September 2012.
5.	Oct – Nov 2014	Dr Mark Andrews, Consultant in Renal Medicine, NNUH / Fiona Marshall TAG Lead Pharmacist, NEL CSU (Anglia)	Superseded	Updated into current TAG template format. Clinical content reviewed by the NNUH. Entry regarding timetable for repatriation of prescribing responsibility added to Additional information. **November 2014:** The TAG recommended adding under the specialist monitoring section "The specialist will provide the patient directly with an ICE form to receive phlebotomy from their nearest service".
6.	May 2016	As per v5. above	Superseded	Continued need reviewed by the TAG – repatriation not complete and homecare services not yet established. Use to be extended by another year – revisit May 2017. Need for GPs to monitor trends in blood results removed since is responsibility of the specialist. *Arzip*® brand removed – no longer available. *Myfenax*® brand added.
7.	Nov 2017	As per v5. above	Current	Continued need reviewed by the TAG – repatriation not complete. Use to be extended by another 6 months – revisit May 2018. Link to current NICE guidance updated. Interactions section updated in line with BNF.
8.	Feb 2018	As per v5. above	Draft	Under "**Contraindications and precautions**" guidance added regarding the need for effective contraception in patients taking MMF and their partners as per MHRA drug safety warning (Feb 2018) Under "**Patient Information**" advice added that patients

				should not give blood during, and for at least 6 weeks after stopping MMF.
8.1	Mar18	Dr Mahzuz Karim, Consultant Nephrologist, and Nicholas Weavers, Pharmacist, added to authors	Draft	Reviewed by NNUH renal specialists and key Renal Association guidance reference also provided: https://renal.org/wp-content/uploads/2018/02/Full-Update.pdf Supported by the TAG / D&TC 15th March 2018.
9.0	Aug 2021	Jen Carroll, TAG Lead Technician	FINAL	Discussed at August 2021 TAG meeting. Review dates extended for a year from meeting due to covid pressures
10.0	Jan 2024	Jen Carroll, TAG Lead Technician	Draft	Updated to new template. Title and indication amended to 'solid organ transplant' 'Pregnancy, paternal exposure and breastfeeding' section updated as per RMOC shared care guidance