



**SHARED CARE PRESCRIBING GUIDELINE: Continuation  
Continuation of Advagraf<sup>®</sup> (tacrolimus modified release {MR})  
for the prevention of organ rejection in adult liver transplant  
recipients in existing patients only  
(i.e. those already being prescribed this drug in primary care)**

**NOTES to the GP**

The information in the shared care guideline has been developed in consultation with the boroughs under South East London CCG and it has been agreed that it is suitable for shared care.

This document should provide sufficient information to enable you to make an informed decision regarding the clinical and legal responsibility for prescribing **Advagraf** (tacrolimus MR) for the prevention of organ rejection in adult liver transplant recipients.

Due to a planned repatriation of immunosuppressants in the future, shared care is **not** appropriate for new patients. **Shared care will only be requested for existing patients who are already being prescribed this drug in primary care by their GP practice.** Having a shared care agreement in place will help support safer prescribing in primary care and clarify responsibilities of clinicians and patients.

The questions below will help you confirm this:

- § Is the patient already being prescribed **Advagraf** (tacrolimus MR) for this clinical indication by your practice?
- § Is the patient's condition predictable or stable?
- § Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care prescribing guideline?
- § Have you been provided with relevant clinical details including monitoring data?

**If you can answer YES to all these questions** (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility.

**If the answer is NO to any of these questions** you should contact the requesting consultant or your local Borough Medicines Management Team. There may be implications for the patient where the invitation to share care is declined. For example, the patient may need to be changed to an alternative treatment regimen. It would not normally be expected that shared care prescribing would be declined on the basis of cost.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. **It is important that patients are consulted about treatment and are in agreement with it.**

Prescribing should follow requirements in the South East London Interface Prescribing Policy.

**The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use. The patient's best interests are always paramount.**

**Once you have read the shared care guideline and considered the information above, please complete the GP decision form on the next page and email back to the requesting clinician if you are in agreement to participation in shared care.**



## GP DECISION FORM

This shared care agreement outlines suggested ways in which the responsibilities for **continuing** to manage the prescribing of **Advagraf** (tacrolimus MR) for the prevention of organ rejection in adult liver transplant recipients can be shared between the specialist and general practitioner (GP). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is 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.

<b>AGREEMENT TO PARTICIPATE IN SHARED CARE</b>	
<b>Advagraf (tacrolimus MR) for the prevention of organ rejection in adult liver transplant recipients already being prescribed this drug in primary care (i.e. <b>existing patients only</b>)</b>	
<b>Consultant/Specialist Name:</b>	<b>Patient name:</b>
<b>Consultant/Specialist signature:</b>	<b>Patient Hospital Number:</b>
	<b>Patient NHS Number:</b>
<b>Date completed:</b>	<b>Patient Agreement:</b>
<b>Hospital requesting shared care:</b>	Patient agrees to shared care £
	Patient does not agree to shared care £
<b>GP Name:</b>	
<b>This is to confirm that I agree to continue participation in shared care Advagraf (tacrolimus MR) for the prevention of organ rejection in adult liver transplant recipients for this patient as outlined in this shared care document</b>	
<b>GP Signature:</b>	
<b>Date signed:</b>	
<b>ACTION</b>	
<b>1. HOSPITAL CONSULTANT</b>	<b>Tick to confirm</b>
§ Explain shared care to patient and obtain agreement	Date agreement obtained: _____ <input type="checkbox"/>
§ Indicate requesting hospital	<input type="checkbox"/>
§ Complete and sign agreement	<input type="checkbox"/>
§ Email full shared care guideline (including signed agreement to GP)	<input type="checkbox"/>
§ Place original in patient's notes	<input type="checkbox"/>
<b>2. GP PRACTICE</b>	
§ If <b>in agreement</b> to participate in shared care, sign and email this sheet back <b>within 2 weeks</b> of receipt of <b>request from specialist</b> to the <a href="mailto:kch-tr.liverpharmacy@nhs.net">liver</a> pharmacy team (kch-tr.liverpharmacy@nhs.net)	
§ If <b>you do not agree</b> to participate in shared care, contact consultant and local Borough Medicines Management Team within 2 weeks of receipt to discuss. If after discussion it is agreed not to undertake shared care for this patient, both the consultant and the local Borough Medicines Management team should be informed.	
§ Once decision reached file a copy in the patient's medical notes.	



## Advagraf (tacrolimus MR) capsules for the prevention of organ rejection in adult liver transplant recipients already being prescribed this drug in primary care (i.e. **existing patients only**)

Advagraf (tacrolimus MR) is one of the first line immunosuppressants post liver transplant.

### CIRCUMSTANCES WHEN SHARED CARE IS APPROPRIATE

- Prescribing responsibility will only be transferred when the consultant and the GP are in agreement that the patient's condition is stable or predictable.
- Shared care will only be requested for **existing** patients who are already being prescribed this drug in primary care by their GP practice. Having a shared care agreement in place will help support safer prescribing in primary care and clarify responsibilities of clinicians and patients.
- The hospital will provide the patient with a supply of therapy for at least the first 3 months post discharge.

### 2. AREAS OF RESPONSIBILITY

#### Consultant / Specialist Team responsibilities

- Establish or confirm diagnosis and assess patient suitability for treatment.
- Baseline monitoring tests:
  - Liver function tests including aspartate transaminase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin and albumin
  - Urea and electrolytes including magnesium
  - Full Blood Count
  - Clotting – INR
  - Tacrolimus trough level
- Discuss treatment with patient and ensure they have a clear understanding of it. Where appropriate obtain signed consent.  
*Information provided to patient*
  - Detailed patient education program including self-medication program on ward prior to discharge
  - Post-transplant patient education booklet which includes diet and lifestyle advice.
- Email a signed shared care guideline with patient details completed to GP for consideration of shared care request.
- Acceptance of shared care should NOT be assumed. Confirmation to participate is required from GP.
- It is the responsibility of the initiating hospital clinic to contact GP.
- Initiate treatment and provide a supply of therapy for at least the first 3 months post discharge.
- Prescribe and monitor treatment according to local guideline or formulary until patient's condition is stable or predictable.

#### After agreement to shared care

- Inform GP when patient's condition is stable or predictable and > 3 months post-transplant.
- Inform GP of abnormal monitoring results and any changes in therapy.
- Evaluate adverse events reported by GP or patient.
- Carry out ongoing monitoring and follow up in line with page 5 and 6 of this shared care guideline, including continued need for therapy.
- To review patient at the request of GP should any problems arise (side-effects / lack of efficacy) within 2 weeks.
- To communicate promptly with the GP if immunosuppression treatment is changed within 3 working days.
- To report any suspected adverse effects to the MHRA: <http://www.yellowcard.gov.uk>.

### General Practitioner responsibilities

- Consider shared care proposal within 2 weeks of receipt.
- If in agreement to continue shared care prescribing responsibility, confirmation to the requesting consultant is required within 2 weeks of receipt of this shared care request by completing and emailing the agreement on page 2.
- If do not agree to shared care discuss with requesting consultant or local Borough medicines management team within 2 weeks of receipt of shared care request.

#### After agreement to shared care

- Prescribe dose as recommended once the patient's condition is stable or predictable and > 3months post-transplant. To adjust dose as advised by the specialist.
- Prescribe tacrolimus by brand, in this case Advagraf.
- Monitor general health of patient and check adverse effects as appropriate.
- Inform Transplant Specialist of suspected adverse effects and also report to the MHRA via yellow card scheme via <http://www.yellowcard.gov.uk> if necessary.
- Stop treatment on advice of specialist.
- Check compatibility interactions when prescribing new or stopping existing medication. If advice is needed from the specialist team, please see communication information on page 8.
- Carry out monitoring and follow up according to page 6 of this shared care guideline.
- Discuss any abnormal results with specialist consultant and agree any action required.
- Refer to Transplant Specialist urgently if patient non-compliance with immunosuppression is suspected.
- Only ask specialist to take back prescribing if unmanageable problems arise, for example erratic blood levels or nonadherence.
- To refer back to specialist if the patient's condition deteriorates.
- Add SNOMED code for shared care prescribing "415522008"

### Patient's / Carer's responsibilities

- § To contact the specialist or GP if he or she does not have a clear understanding of any aspect of the treatment.
- § To inform prescribing specialist, GP and other healthcare professionals of any other medication being taken, including over the counter products, alternative therapies or recreational drugs.
- § To inform community pharmacists that they are using Advagraf (tacrolimus MR) before purchasing medication over-the-counter
- § To attend all hospital and GP appointments
- § To take medicines as agreed and take steps to ensure that no doses are missed and not to share medicines with others
- § To read the patient information leaflet included with the medication.
- § To report any adverse effects or warning symptoms to GP or hospital specialist
- § To inform GP and hospital of any changes in addresses or telephone contact numbers.

## 3. CLINICAL INFORMATION

**NOTE:** The information here is not exhaustive. Please also consult the current Summary of Product Characteristics (SPC) for Advagraf (tacrolimus MR) prior to prescribing for up to date prescribing information, including detailed information on adverse effects, drug interactions, cautions and contraindications (available via [www.medicines.org.uk](http://www.medicines.org.uk)).

### Indication(s)

Prevention of organ rejection following liver transplantation.

### Place in Therapy

Tacrolimus is the first line immunosuppressant post liver transplant. Advagraf (tacrolimus MR) is an extended release formulation of tacrolimus that is used when once daily administration is preferable for the patient. Conversion to once-daily Advagraf (tacrolimus MR) should only be done under the supervision of a Transplant Consultant. It is often prescribed as part of a dual immunosuppressant regimen, consisting of Advagraf (tacrolimus) and prednisolone. Immunosuppressant regimens will be adapted to the individual patient, with some patients being maintained on tacrolimus mono-therapy and other patients requiring the addition of extra immunosuppressive agents such as mycophenolate, azathioprine or sirolimus.

### Dose & route of administration

The dose will be advised by the Transplant Consultant. Doses are adjusted according to individual patient requirements and trough Advagraf (tacrolimus MR) levels taken 20 hours after last Advagraf dose.

Some patients may be switched from Prograf to Advagraf. On conversion to Advagraf (tacrolimus MR), therapeutic drug monitoring must be carried out within 2 weeks of conversion, and the dose will be titrated to achieve tacrolimus levels equivalent to those achieved with Prograf (tacrolimus) and stable graft function. Initially post-transplant the target trough tacrolimus level is 5-10 microgram/L reducing over time if liver function tests remain satisfactory. Target tacrolimus levels are individualised to each patient taking a number of factors into consideration such as liver and renal function.

### Brand prescribing of Prograf (Tacrolimus) or Advagraf (tacrolimus MR)

Tacrolimus prescribing is **brand specific** due to varying bioavailability between formulations. There are currently two formulations of branded tacrolimus; **Prograf** (tacrolimus) are immediate release capsules usually prescribed **TWICE daily** (except for a small minority of patients requiring very small doses i.e. <1 milligram daily, whereby Prograf will be prescribed once daily). **Advagraf** (tacrolimus MR) are prolonged release capsules which are **always** taken **ONCE daily**. Prograf and Advagraf are not freely interchangeable. When changes are made a proportion of patients will require dose adjustments to ensure that tacrolimus levels are optimal. Switching between brands is possible under the supervision of a transplant specialist, with therapeutic drug monitoring being undertaken before and within two weeks after conversion.

Tacrolimus is also available in generic formulations and under **no circumstances** should a patient on branded tacrolimus be switched to a generic formulation without confirmation by the Specialist Transplant Physician. There is significant clinical risk to the patient if this advice is not followed.

Advagraf is available as 500microgram, 1milligram, 3milligram and 5milligram capsules. .

### Duration of treatment

Lifelong.

### Criteria for stopping treatment

Only after discussion with Transplant Consultant.

### Monitoring Requirements including frequency

#### Transplant Consultant:

The following will be monitored and reviewed by the Transplant Consultant at each liver post-transplant outpatient appointment;

- Clinical assessment including examination of suspicious skin lesions.
- Bloods are taken for trough tacrolimus level, FBC, INR, urea and creatinine, eGFR and LFTs (aspartate transaminase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin and albumin, INR). Additional tests may be required for individual patients.
- Immediately post-transplant, clinic appointments will be weekly. The interval between appointments will be gradually increased based on individual patient needs. All post-transplant patients will be reviewed at least annually in the liver outpatient clinic.

#### GP:

Provide an annual review of the following to monitor for adverse effects of medication:

- Monitor patient's overall health and wellbeing
- Blood pressure – Monitoring of hypertension should be as per NICE guidelines. Amlodipine is the antihypertensive of choice in hypertension secondary to tacrolimus. For patients with other indications for antihypertensive therapy, treatment should be as per NICE guidelines. ACE inhibitors, amlodipine, beta-blockers or alpha-blockers are considered suitable therapeutic options. There is an increased risk of hyperkalaemia and renal impairment with concomitant use of ACE inhibitors (or angiotensin II receptor antagonists) and tacrolimus. Baseline electrolytes (serum creatinine, estimated glomerular filtration rate and potassium) should be obtained before initiation of an ACE inhibitor, within 2 weeks of treatment initiation and at regular intervals during treatment i.e. annually. Treatment options can be discussed with the Transplant Consultant if required.
- Fasting blood glucose. Refer to Transplant Consultant for consideration of immunosuppression alteration. If no alteration in immunosuppression is possible, diabetes should be managed as per NICE guideline 17 and NICE guideline 28.

- Renal function – electrolytes (serum creatinine, glomerular filtration rate and potassium) annually. Refer to Transplant Specialist for prompt consideration of alteration in immunosuppression for any patient with an eGFR < 65mls/min.
- Skin care – Skin cancers account for the commonest malignancies after liver transplantation. Suggested preventative measures include:
  - Patients should carry out regular self-examination and report any new lesions to ensure early detection and ablation of premalignant lesions. Any suspicious lesions require prompt specialist referral.
  - Patients should avoid direct sun exposure, use appropriate clothing for outdoor activities and apply sunscreens with high sun protection factor. Guidelines for patients can now be found on the web (<http://www.scopenetwork.org>, <http://www.itsec.org>).
- Liver function – any deterioration in liver function (e.g. deterioration in AST, ALP, GGT, bilirubin, albumin and INR) should necessitate immediate liaison with the Transplant Centre.
- Tacrolimus trough levels should be checked if clinical suspicion of toxicity (signs and symptoms predominantly include tremor), nonadherence, and interacting medication is commenced or any other cause for concern. Blood samples (3ml of blood in an EDTA tube) should be sent to Phillip Morgan, IDM Service, Institute of Liver Studies, King's College Hospital, Denmark Hill, SE5 9RS, for assay. There is no charge for tacrolimus assays.
- Influenza vaccine: annual immunisation with influenza vaccine is strongly recommended for all post-transplant patients who are taking immunosuppressant medications such as tacrolimus.
- Pneumococcal vaccine is recommended for all adults who are immuno-compromised. Revaccination is not recommended. Confirm patient's vaccine status.
- Report any suspected adverse effects to the MHRA: <http://www.yellowcard.gov.uk>.

## Follow up arrangements

### Transplant Consultant:

- Frequency of outpatient appointments is dependent on individual patient progress. Each patient will be reviewed annually as a minimum. Following each outpatient clinic or inpatient stay, any medication changes will be communicated to the patient and the GP by letter within 3 working days. The patient will be informed by telephone of any changes in drug doses that need to be made on an urgent basis.
- Assess need for further investigation.

### GP:

- Monitor patients overall health and wellbeing.
- Carry out monitoring requirements as detailed above annually or at more frequent intervals dependent on individual patient needs.

## Practical issues including other relevant advice/information

**Reminder: The information here is not exhaustive. Please also consult the current Summary of Product Characteristics (SPC) for Advagraf (tacrolimus MR) prior to prescribing for up to date prescribing information, including detailed information on adverse effects, drug interactions, cautions and contraindications (available via [www.medicines.org.uk](http://www.medicines.org.uk)).**

### Adverse drug reactions

**N.B These are common adverse effects but this list is not exhaustive.** Refer to British National Formulary for list of all potential adverse effects.

**Nephrotoxicity.** Early acute toxicity can occur in the post-operative period or renal toxicity with long-term use may be seen. If eGFR < 65mls/min refer to Specialist Transplant Physician for consideration of alteration in immunosuppression.

**Neurotoxicity.** Headache, tremor usually only occur on initiation and resolve within a few days. Paraesthesia may be related to hypomagnasaemia and should be treated with a short course of magnesium supplements if not severe. Tremors may indicate toxic tacrolimus levels. Blood should be taken to check tacrolimus level. For unresolved or severe neurotoxic reactions refer to Specialist Transplant Physician.

**Nausea, diarrhoea** can occur initially. Refer if persistent or severe.

**Hypertension.** Treat as per guidance in monitoring section. If hypertension remains uncontrolled refer to Specialist Transplant Physician.

**Skin care.** Patients receiving immunosuppressants are at increased risk of lymphomas and other malignancies of the skin. Avoiding excessive exposure to the sun and high factor sun screens are advised. See advice under monitoring.

**Cardiac effects.** Cardiomyopathy has been reported in children receiving tacrolimus after transplantation. Refer to specialist if cardiomyopathy secondary to tacrolimus suspected.

**Electrolyte disturbance,** especially hyperkalaemia is common. If problematic refer to specialist for consideration

of alteration in immunosuppressant.

### **Important Drug Interactions**

**N.B These are the common drug interactions but this list is not exclusive.**

Refer to BNF for list of all potential drug interactions with Advagraf (tacrolimus MR). The Liver Team at King's would appreciate the opportunity to discuss the introduction of any new drug which may interfere with the metabolism of Advagraf (tacrolimus MR) before it is initiated. The Liver Pharmacy Team can be contacted for advice on 0203 299 9000 extension 35714 or 0203 299 9000 (switchboard) and ask to page 699581.

Tacrolimus is metabolised via the cytochrome P450 3A4 enzyme system. Concomitant use of drugs known to affect this enzyme system can increase/decrease the metabolism of tacrolimus and affect tacrolimus levels.

**The following drugs should not be initiated** by a GP unless discussed with the Specialist;

Drugs that <u>induce</u> cytochrome P450 3A4 and <b>REDUCE</b> tacrolimus levels	Drugs that <u>inhibit</u> cytochrome P450 3A4 and <b>INCREASE</b> tacrolimus levels
Rifampicin	Erythromycin and Clarithromycin
Carbamazepine	Protease inhibitors e.g. ritonavir
Phenobarbitone	"Azole" antifungal e.g. fluconazole *, itraconazole, ketoconazole, voriconazole, posaconazole
Phenytoin	Calcium channel antagonists e.g. Diltiazem, Verapamil

Other interacting medication;

- **NSAIDs** are contra-indicated in patients taking Advagraf (tacrolimus MR). Paracetamol and/or a weak/moderate opioid should be used instead.
- **ACE inhibitors and Angiotensin II inhibitors** can be used but there is an increased risk of hyperkalaemia with concomitant tacrolimus use. Baseline electrolytes (serum creatinine, estimated glomerular filtration rate and potassium) should be obtained before initiation of an ACE inhibitor, within 2 weeks of treatment initiation and at regular intervals during treatment i.e. annually.
- **Diuretics** such as potassium sparing diuretics and aldosterone antagonists increase the risk of hyperkalaemia when administered with tacrolimus.
- **St. John's Wort** is known to increase tacrolimus levels. Herbal medicines may have an effect on drug levels. Avoid concomitant use.
- **Grapefruit juice and Seville Oranges** inhibit cytochrome P450 and increase plasma tacrolimus concentration.

### **Diarrhoea and vomiting**

Absorption/metabolism of tacrolimus may be affected by diarrhoea and/or vomiting. Levels should be checked if there is a significant increase in frequency/looseness of stools persisting for 48 hours, as the dose may need to be adjusted. **N.B. Diarrhoea may cause tacrolimus levels to rise to toxic levels.**

### **Vaccines**

Live vaccines are contra-indicated and should be avoided. For further information on vaccines see BNF, chapter 14 for a list of live vaccines.

Please contact the Liver Transplant Pharmacist for further advice on vaccines.

### **Contraception**

Please contact the Liver Team at King's regarding contraception advice.

### **Pregnancy**

In general, immunosuppression should be continued during pregnancy. All patients who wish to become or who are pregnant should be reviewed by a Transplant Consultant for consideration of immunosuppressive regimen choice and/or dose adjustment. It is essential to maintain adequate immunosuppression levels during pregnancy and pregnancy can dramatically affect immunosuppressant drug handling.

**Breastfeeding**

All liver transplant patients who are pregnant will be reviewed by a Transplant Consultant and the decision on whether it is safe for a patient to breastfeed will be guided by them depending on the specific immunosuppressant regimen that the patient is on.

**Information provided to the patient**

- Detailed patient education program including self-medication program on ward prior to discharge
- Post-transplant patient education booklet including information about brand prescribing and how to obtain further supplies.

**Evidence Base for treatment and key references**

1. British National Formulary 70. September 2019-March 2020
2. Summary of Product Characteristics. Prograf 0.5mg capsules. Accessed via [www.medicines.org.uk](http://www.medicines.org.uk). Last updated 27/9/2019
3. Summary of Product Characteristics. Advagraf 0.5mg capsules. Accessed via [www.medicines.org.uk](http://www.medicines.org.uk). Last updated 27/9/19
4. Immunisation against infectious disease: The Green Book. Accessed via [www.dh.gov.uk](http://www.dh.gov.uk). Updated September 2014
5. NICE guidance NG136 Hypertension in adults: Diagnosis and Management August 2019.

**4. COMMUNICATION AND SUPPORT**

**NOTE:** King's College Hospital NHS Foundation Trust is the only Trust in SEL that manages this patient group.

<b>King's College and Princess Royal Hospitals switchboard: 0203 299 9000</b>	
<p><b><u>Consultant/specialist team - Liver Transplantation</u></b>                      Professor Michael Heneghan                      Dr. Kosh Agarwal                      Dr. Varuna Aluvihare                      Dr. Abid Suddle                      Dr Deepak Joshi                      Professor Sanchez Fueyo                      Dr Marianne Samyn</p>	<p>Consultant Hepatology Transplant Secretary                      Tel: 0203 299 4952</p>
<p><b><u>Consultant Surgical Team – Liver Transplantation</u></b>                      Professor Nigel Heaton                      Mr. Andreas Prachalias                      Mr. Parthi Srinivasan                      Mr. Hector Vilca-Melendez                      Mr Krishna Menon                      Mr Wayel Jassem                      Miss Miriam Cortes</p>	<p>Consultant Surgical Transplant Secretary                      Tel: 0203 299 3762</p>
<p><b><u>Immediate medical advice, and out of hours</u></b>                       Transplant Registrar</p>	<p>Tel: 0203 299 9000                       Bleep 142 or out-of-hours via switchboard (0203 299 9000)</p>
<p><b><u>Immediate general advice, and out of hours</u></b>                       Transplant Co-Ordinators</p>	<p>Tel: 0203 299 4024                      or out of hours via switchboard (0203 299 9000),                      Aircall 842688 via switchboard (0203 299 9000)</p>
<p><b><u>Medication – Prescribing advice, interactions, availability of medicines</u></b>                       Transplant Pharmacist: Lindsay Smith</p>	<p>Pharmacy Department Secretary; 0203 299 3347                      699581 via switchboard (0203 299 9000)                      Direct extension: 0203 299 5714                      Email: <a href="mailto:kch-tr.liverpharmacy@nhs.net">kch-tr.liverpharmacy@nhs.net</a></p>
<p><b><u>Transplant ward</u></b>                       Todd ward</p>	<p>Tel: 0203 299 3310</p>
<p><b><u>Immunosuppressant Drug Monitoring</u></b>                      Phillip Morgan</p>	<p>Tel: 020 3299 3147</p>