**Indication:**
Prophylaxis of transplant rejection in kidney recipients

Tacrolimus is an immunosuppressant drug with a narrow therapeutic index. It is currently the first line immunosuppressant for renal transplant recipients. It is sometimes used in combination with mycophenolate, depending on immunological risk and induction therapy (monoclonal antibody). These regimes allow the avoidance of maintenance corticosteroid in most patients.

Tacrolimus is never used in combination with ciclosporin.

**Formulations:**
There are three different formulations of tacrolimus:
- **Adoport and Prograf**, are immediate-release capsules that are taken twice daily, every 12 hours, once in the morning and once in the evening;
- **Advagraf** is a prolonged-release capsule that is taken once daily in the morning.
- **Modigraf** granules are used to prepare immediate-release oral suspension which is taken twice daily, once in the morning and once in the evening;

**Note:** Tacni® and Vivadex® are also listed in the BNF but are not currently initiated for transplant patients in our region.

**Prescribing notes**
- When prescribing tacrolimus, all prescribers should state the brand name, formulation (i.e. capsule or modified release capsule), the dose and the frequency (once daily or twice daily).
- Formulations and brands are NOT interchangeable. Any changes in formulation or brand must be supervised closely by the Consultant nephrologist.

**Dosage & administration:**

**Dosage**
Detailed information is available in the product data sheet (SPC).

Patients are most commonly on a twice daily immediate-release preparation.
The initial dose of tacrolimus normal-release is titrated to achieve the desired trough blood level.

The level required to prevent rejection without causing toxicity is considered to be between 5 and 14 micrograms/L. Renal physicians will generally try to obtain blood levels between 9 and 14 micrograms/L in the early post-transplant period. Lower levels will be maintained thereafter depending on immunological risk.

Doses required to achieve this level vary between patients, though typically a range of 1 mg to 4 mg twice daily is common in adults taking an immediate-release formulation at three months post-transplant.

**Alternative preparations** - If switching treatment between preparations, the renal consultant will advise on dose switches. Brand name must be specified whenever tacrolimus is prescribed. This is in line with the CSM recommendations.

**Administration**

- On blood monitoring days, the morning dose should be omitted until after the blood is sampled.
- Capsules should be taken immediately following removal from the packaging. Patients should be advised not to swallow the desiccant.
- Capsules should be taken on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption.

**Contraindications & Warnings:**

- **Contraindications**
  - Hypersensitivity to tacrolimus, macrolides or any of the other excipients of the formulation.
  - Concomitant use of ciclosporin

- **Warnings**
  - Suspected non-compliance with immunosuppression therapy is serious and can lead to loss of the graft function. The patient should be referred to the renal physician urgently.
  - Pregnancy – patients discovered or planning to become pregnant should be started on folic acid 400 micrograms daily and referred to the renal physician at the earliest opportunity. Tacrolimus should be continued until specialist advice is sought.

**Interactions:**

- The manufacturers of tacrolimus advise that the combined oral contraceptive (COC) should **not** be used with tacrolimus. This is due to a theoretical risk that the COC is less effective when taken concurrently with tacrolimus. There have been no reported problems of this in clinical practice and therefore the renal physicians continue to recommend the COC as a viable method of birth control in patients on tacrolimus.

- The patient’s renal function should be taken into consideration when co-prescribing for renal transplant patients.

- Tacrolimus is metabolised by cytochrome P450 and therefore interacts with
several drugs that are also metabolised by this group of liver enzymes.

The following drugs should not be initiated by a GP unless discussed with the renal physician:

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect on tacrolimus blood level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin and clarithromycin</td>
<td>Increased</td>
</tr>
<tr>
<td>Diltiazem, nicardipine, verapamil, felodipine</td>
<td>Increased</td>
</tr>
<tr>
<td>Fluconazole, itraconazole, ketoconazole</td>
<td>Increased</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Decreased</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Decreased</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Decreased</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Decreased</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Decreased</td>
</tr>
<tr>
<td>St John's wort</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

Other interacting agents:
- Patients should not drink **grapefruit juice or eat grapefruit**, because it can increase in tacrolimus levels.
- NSAIDs (and other nephrotoxic drugs) should be used with extreme caution.
- Potassium-sparing medicines may exacerbate tacrolimus-induced hyperkalaemia and should only be initiated with regular monitoring of U&Es.
- Avoid the use of live vaccines

Appendix 1 of the BNF is a useful guide to whether any drug is likely to cause a problem. If there is a clinical need to use such drugs then this is best undertaken in the renal clinic with careful monitoring of tacrolimus levels.

For full list see SPC at [www.medicines.org.uk/EMC](http://www.medicines.org.uk/EMC)

### Adverse Effects:

The monitoring of adverse effects will not usually require additional routine appointments unless a problem is anticipated:

- **Hypertension**
  Hypertension (BP >130/>80mmHg) is a commonly encountered adverse effect which the GP will be best placed to monitor and treat. NICE hypertension guidance for drug selection is suitable for renal transplant recipients. Patients started on ACE inhibitors or Angiotensin II receptor antagonists (and for subsequent dose increases) should have U&Es checked 14 days later. Creatinine rising by >20% or eGFR falling >15mL/min is not an absolute contra-indication, but this scenario is best managed under specialist supervision and referral to the renal physician is recommended. A dihydropyridine calcium channel blocker such as nifedipine may be used but diltiazem, nicardipine, felodipine and verapamil should not be used as they may increase plasma tacrolimus levels.

- **Headache, tremor, insomnia and visual disorders**
  These adverse effects are frequently seen. If persistent or severe, they may reflect toxic levels of tacrolimus. In this case, the patient should be referred back to the renal physician.
- **Alopecia**  
  Hair loss occurs in a small percentage of patients on tacrolimus. If this occurs, the patient should be referred back to the renal physician for adjustment of immunosuppressant.

- **Nephrotoxicity**  
  Tacrolimus exhibits an acute blood level related nephrotoxicity. Identified primarily by serum creatinine monitoring, which will be undertaken at the hospital. This may be difficult to distinguish from acute rejection but is reversed by dose reduction.

- **Hyperglycaemia**  
  High blood glucose levels and diabetes are more common with tacrolimus than ciclosporin. Blood glucose measurements are made at each clinic visit. Occasionally, insulin is required.

- **Hepatic dysfunction and hyperlipidaemia**  
  Liver function monitoring tests will be carried out at outpatient appointments. Hyperlipidaemic patients will be prescribed a statin (the monitoring of efficacy and adverse effects is then undertaken in the renal clinic).

- **Cancer risk**  
  Like all immunosuppressants, tacrolimus increases the risk of developing lymphomas and other malignancies, particularly those of the skin. The increased risk appears to be related to the degree and duration of the immunosuppression rather than to the use of specific agents.

For full list see SPC at [www.medicines.org.uk/EMC](http://www.medicines.org.uk/EMC)

### Responsibilities of the specialist initiating treatment:

#### General:
- To assess the suitability of the patient for treatment.
- To ensure that the patient/carer has received counselling and understands the therapy, its benefits, limitations, continued monitoring (where applicable), adverse effects, and is aware of actions to take if adverse effects are suspected.
- Inform the GP of the information provided to the patient.
- To review the patient at agreed intervals and copy any relevant results to the GP.
- Carry out disease and drug monitoring as listed below.
- Formally hand over to GP by letter and patient informed - send a copy (either electronically or paper copy) of the Shared Care Guideline to the GP and ask whether they are willing to participate in shared care.
- Monitor the patient for adverse events and report to the GP and, where appropriate, the Commission on Human Medicines/MHRA using the Yellow Card scheme.

#### Prescribing:
- Secondary care will prescribe tacrolimus for the first 3 months post transplant or until the immunosuppression regimen is stable.
### Disease & drug monitoring:

- Monitor bloods at each hospital appointment, the frequency of which is determined by clinical need.

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea &amp; electrolytes</td>
<td>At each hospital appointment</td>
</tr>
<tr>
<td>Full blood count</td>
<td></td>
</tr>
<tr>
<td>Mid-stream urine (for culture &amp; sensitivities)</td>
<td></td>
</tr>
<tr>
<td>Trough tacrolimus levels</td>
<td></td>
</tr>
<tr>
<td>Liver function tests</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td>Blood glucose</td>
<td></td>
</tr>
<tr>
<td>Lipid screening for total cholesterol</td>
<td>Every 6 months</td>
</tr>
</tbody>
</table>

- Discuss shared care arrangement with patient.
- Support and advise GPs as required.
- Assess response to treatment and initiate any dose changes as clinically appropriate including discontinuation of treatment.

### General and Prescribing:

- To reply to the request for shared care within 2 weeks of receipt of the Consultant letter.
- Monitor* and prescribe as recommended by the specialist. The GPs will be typically asked to take up the monitoring and prescribing of tacrolimus approximately 3 months after transplantation, or until the patient is on a stable immunosuppressant regimen.
- Ensure the correct brand of tacrolimus is used
- Alert the hospital consultant of any suspected non-compliance with immunosuppressants
- Ensure there are no drug interactions with any other medications initiated in primary care, including avoiding the use of live vaccines

*GP to monitor for side effects, drug interactions etc. Consultant will however do all routine blood monitoring.

### Disease & drug monitoring:

- Drug monitoring will normally be carried out by secondary care unless otherwise requested. GP must however ensure smear tests are up to date for female patients (3 yearly for females aged 25 to 49 and 5 yearly for females aged 50 to 65).
- Urgent referral to specialist as clinically appropriate
- To stop treatment on the advice of the specialist
- To refer back to the Specialist if the patient’s condition deteriorates.
- To identify adverse effects if the patient presents with any signs and liaise with the hospital Specialist where necessary. To report adverse effects to the Specialist and where appropriate to the Commission on Human Medicines/MHRA (Yellow Card scheme).

### General:

- Report any possible side effects to the hospital/GP.
- Ensure they have an adequate supply of medication.
- Attend appointments.
- To report to the hospital or GP if there are any questions regarding their treatment.
- To notify the hospital or GP if starting new medicines (including herbal remedies) and of the purchase of medication over the counter.
- To dispose of unused or expired medication appropriately at a community or hospital pharmacy.

**Disease & drug monitoring:**
As above – contact GP or initiating team if side effects develop (see adverse effects) and attend appointments including those for routine blood tests/investigations.

**Communication:**

**Specialist to GP:**
- The specialist will inform the GP when they have initiated tacrolimus, stating the brand the patient is taking and when there are any subsequent changes in treatment – standard clinic letter.
- When the patient is near completing a satisfactory initiation period, the renal physician will send a copy (either electronically or paper copy) of the Shared Care Guideline to the GP and ask whether they are willing to participate in shared care and take over prescribing.
- Inform the GP of the information provided to the patient.

**GP to Specialist:**
- To reply to the request for shared care within 2 weeks of receipt of the Consultant letter.
- Irrespective of whether you accept prescribing responsibility or not, you should inform the consultant of relevant medical information regarding the patient and changes to the patient’s medication regime irrespective of indication.
- Notify Consultant immediately if treatment with tacrolimus is discontinued is if non compliance is suspected.

**Contact names & details:**
If you have any concerns regarding individual patients, see consultant letter for medical contact details or contact one of the following:

<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Location</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr D Border</td>
<td>Consultant Nephrologist, York &amp; Harrogate</td>
<td>01904 725813 (Sec.)</td>
</tr>
<tr>
<td>Dr C Jones</td>
<td>Consultant Nephrologist, York &amp; Malton</td>
<td>01904 725374 (Sec.)</td>
</tr>
<tr>
<td>Dr P Laboi</td>
<td>Consultant Nephrologist, York &amp; Selby</td>
<td>01904 725813 (Sec.)</td>
</tr>
<tr>
<td>Dr K McCullough</td>
<td>Consultant Nephrologist, York</td>
<td>01904 725393 (Sec.)</td>
</tr>
<tr>
<td>Dr Richardson</td>
<td>Consultant Nephrologist, York</td>
<td>01904 725393 (Sec.)  or through switchboard on 01904 631313</td>
</tr>
<tr>
<td>Dr Than</td>
<td>Consultant Nephrologist Harrogate, &amp; York</td>
<td>01904 725393 (Sec.)</td>
</tr>
<tr>
<td>Hazel Wootton or Gillian Taylor</td>
<td>Specialist Transplant Nurses</td>
<td>01904 726617</td>
</tr>
</tbody>
</table>
Other members of the renal team may also be able to offer advice with questions or problems and can be contacted through the hospital switchboard 01904 631313 or the renal unit on 01904 725370

**Cost:**

BNF no 64 Sept 2012

Cost of a 1mg twice daily dose (immediate-release preparations) per calendar month (i.e. 28 days)

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adoport</td>
<td>£73.38</td>
</tr>
<tr>
<td>Prograf</td>
<td>£89.91</td>
</tr>
</tbody>
</table>

**Choice of brand is based on the hospital regional contract. Any changes will be managed through the hospital renal team and the GP and the patient will be notified.**

**References:**

1. Leeds Teaching Hospital NHS Trust shared care guidelines for tacrolimus (Prograf® or Advagraf®) post adult renal transplant (2009)
2. British National Formulary 64 (September 2012)
3. Summary of Product Characteristics – all products

**This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC (data sheet) or BNF for further prescribing information.**

The original Microsoft Word file of this document is located on:
York Teaching Hospital NHS Foundation Trust Pharmacy Department X:\MEDICINES INFORMATION\Shared Care Guidelines\Approved Shared Care Guidelines\TACROLIMUS (Renal Transplant) Shared Care Guideline V1.0

Shared Care Guidelines are also available electronically via [http://www.yorkandscarboroughformulary.nhs.uk/](http://www.yorkandscarboroughformulary.nhs.uk/)

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