

# Tacrolimus (*Prograf*<sup>®</sup>)

## SCG: For Transplant patients

*The following guidelines are designed to provide information relating to tacrolimus and to outline the responsibilities of the primary and secondary care teams in the prescribing of tacrolimus.*

### AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

#### Introduction:

Tacrolimus is a macrolide immunosuppressant which possesses similar but more potent immunosuppressant properties compared with ciclosporin, inhibiting cell-mediated immune responses.

At Papworth, we only prescribe the standard release formulation (brand name *Prograf*<sup>®</sup>). It should be prescribed by brand name to avoid confusion with the prolonged release preparation.

### RESPONSIBILITIES AND ROLES

#### Specialist responsibilities (Transplant Team):

1. Initially prescribe and stabilise the patient on the treatment regime and monitor transplant graft function
2. Measure tacrolimus blood levels and advise the patient and GP of dose changes
3. Provide patients with a current medication record book ("blue book")
4. Monitor efficacy of the treatment and side effects
5. Provide access to back up and support facilities
6. Evaluate any adverse events reported by the GP
7. Educate patients on their drug therapy to maximise compliance and be aware of when to seek medical attention.

#### General Practitioner's responsibilities:

1. Prescribe tacrolimus maintenance therapy according to dosage instructions from the Transplant Unit
2. Encourage patients to complete their daily medication record and document changes to therapy in their "blue book"
3. Check for possible drug interactions when newly prescribing or stopping concurrent medication
4. Report any suspected adverse events to the Transplant Unit (all potential adverse events need to be reported)
5. Monitor blood counts and discuss any abnormalities with the Transplant Unit.

#### Patient's responsibilities:

1. Complete daily medication record in their "blue book"
2. Notify GP and Transplant Unit of any suspected adverse events
3. Notify use or intended use of over the counter (OTC) and complementary/herbal medications.

## BACK-UP ADVICE AND SUPPORT

Papworth Hospital Main Switchboard	01480 830541
Transplant Unit Reception	01480 364455
Transplant Co-ordinators (On-call)	(access via switchboard)
Pharmacy Medicines Information Service	01480 364179 (Mon-Fri 9am-5pm)
Transplant Pharmacist	01480 364179 (or bleep 931)
Consultant Transplant Cardiologist	Dr J Parameshwar
	Dr C Lewis
Consultant Transplant Respiratory Physician	Dr J Parmar

Consultant and medical staff are always available to give advice and can be contacted through the main hospital switchboard on 01480 830541.

## SUPPORTING INFORMATION

### Licensed indications:

- Tacrolimus is licensed for prophylaxis of transplant rejection in liver, kidney and heart allograft recipients and allograft rejection episodes unresponsive to conventional immunosuppressive agents. Whilst it is not currently licensed for 'de novo' use in heart-lung or lung transplants it is the most commonly used immunosuppressant agent in these patient groups.

### Dosage and administration:

- The usual starting dose at Papworth for tacrolimus for heart, heart-lung and lung transplant patients is 0.1-0.2mg/kg/day, administered as two divided doses. Some of our patients, especially those with cystic fibrosis, may require three times daily doses to maintain adequate drug levels.
- It is important for patients to be instructed to take tacrolimus on an empty stomach (one hour before or 2-3 hours after a meal) to achieve maximal absorption and at the same time each day so that trough levels are representative of the true value when they return to hospital for monitoring of blood levels. Patients are instructed not to take their tacrolimus on the morning of their clinic visit so that blood levels taken represent trough concentration.

### Contraindications:

- Known hypersensitivity to tacrolimus or other macrolides

### Cautions:

- Malignancy, especially lymphomas and skin tumour are more common in immunosuppressed patients. Advise patients to limit exposure to sunlight by wearing light clothing and using a high factor sunscreen.
- Susceptibility to opportunistic infections is increased in patients receiving immunosuppression

### Therapeutic use:

- Tacrolimus may be used in patients who experience multiple episodes of rejection on ciclosporin as “rescue therapy”. It is used as an alternative to ciclosporin in patients especially those who experience severe hypertrichosis and gum hypertrophy, and in lung and heart-lung transplant patients with evidence of obliterative bronchiolitis.

### Side effects:

- All immunosuppressive agents are powerful and potentially toxic drugs, and therefore adverse events may be observed. Any adverse effects detected should be directly reported to the Transplant Unit. **It is vital that drug doses are not changed without first consulting the Transplant Unit.**
- The following are adverse events which may possibly be observed in patients taking tacrolimus. (Note: this list of adverse events is not exhaustive).

Gastrointestinal	Diarrhoea, nausea, dyspepsia, ulceration, constipation
Cardiovascular	Hypertension, tachycardia
Renal	Renal impairment
Metabolic	Hyperglycaemia, diabetes mellitus, hyperkalaemia and other electrolyte disorders
Central nervous system	Tremor, headache, insomnia, parasthesia, seizures, depression, abnormal behaviour
Haematological	Anaemia, leucopenia, thrombocytopenia, leucocytosis, abnormal red blood cell analyses
Eye disorders	Blurred vision, photophobia and other eye disorders
Ear disorders	Tinnitus
Skin disorders	Pruritis, rash, alopecia, acne, increased sweating
Musculoskeletal	Arthralgia, myalgia, limb and back pain
Hepatic	Enzyme abnormalities, cholestasis, jaundice, hepatocellular damage, hepatitis, cholangitis, increased alkaline phosphatase
General	Asthenia, fever, oedema, increase weight, distorted body temperature perception
Infection	Increased susceptibility to viral, fungal, bacterial and protozoal infections
Neoplasms (benign and malignant)	Benign and malignant neoplasms and skin malignancies

### Monitoring:

- Trough levels are taken usually aiming for levels of 8-15mcg/l in the first three months. Patients are instructed not to take their tacrolimus on the morning of their clinic visit so that blood levels taken represent trough concentrations.
- If levels are required in addition to those at clinic, the transplant unit will give written notification.
- Renal function is also checked at clinic visits.
- Monitor for drug interactions.

### Drug interactions:

- Tacrolimus is extensively bound to plasma proteins and may interact with other drugs which are similarly bound, such as oral anticoagulants and antidiabetic agents. Many drugs, including tacrolimus, are metabolised via the microsomal cytochrome P-450 enzyme system in the liver. Some drugs have the effect of inhibiting P-450 thereby increasing available degradation of tacrolimus to sub therapeutic levels. Tacrolimus itself initially inhibits the P-450 system but ultimately acts as a P-450 inducer.
- It may therefore alter the effects of other drugs which share the P-450 metabolic pathway. Herbal medications can also affect tacrolimus efficacy either by direct effect on the P-450 system or indirectly by antagonising the immunosuppressant effect of tacrolimus (e.g. Echinacea).
- For advice on tacrolimus interactions, please do not hesitate to contact Papworth Pharmacy Medicines Information Department.

The following list is not exhaustive;

- 1) **Drugs which may decrease tacrolimus levels:**  
Barbituates, carbamazepine, caspofungin, isoniazid, phenytoin, rifabutin, rifampicin, St. John's Wort.
- 2) **Drugs which may increase tacrolimus levels:**  
Bromocriptine, clarithromycin, clotrimazole, danazol, dapsone, diltiazem, ergotamine, erythromycin, ethinyloestradiol, fluconazole, gestodene, itraconazole, ketoconazole, midazolam, nocardipine, omeprazole, quinidine, ritonavir, tamoxifen, verapamil, voriconazole
- 3) **Drugs which may potentiate neurotoxicity:**  
Aciclovir, ganciclovir.
- 4) **Drugs which may potentiate hyperkalaemia:**  
ACE inhibitors, potassium sparing diuretics, potassium supplements.
- 5) **Drugs which may potentiate nephrotoxicity:**  
Aminoglycosides, amphotericin B, co-trimoxazole, NSAID's, vancomycin.
- 6) **Drugs which may potentiate hyperglycaemia:**  
Corticosteroids.
- 7) **Drugs which may be potentiated by tacrolimus:**  
Cortisone, testosterone. Tacrolimus has been shown to increase phenytoin levels.

### NB:

- **Live vaccines** are contra-indicated and should not be given to immunocompromised individuals. Other vaccines may be less effective.
- **Grapefruit juice** increases tacrolimus concentrations.
- Metabolism of steroidal based **contraceptive agents** may be inhibited, leading to increased hormone exposure.

**It is advisable to inform the Transplant Unit if one of the interacting medications is being newly prescribed or stopped so that tacrolimus blood levels can be monitored.**

### Cost:

- PCTs need to ensure that funding for post transplant drug treatment is made available for patients. **As soon as a GP is made aware of a patient requiring an expensive medicines, they are advised to discuss the funding mechanisms for it with their PCT prescribing manager.**

**Availability:**

- Tacrolimus is available from wholesalers as 0.5mg (500microgram), 1mg and 5mg capsules. Community pharmacies can obtain tacrolimus from local wholesalers within 24 hours.

**References:**

- Summary of Product Characteristics for Prograf<sup>®</sup> Capsules accessed via [emc.medicines.org.uk](http://emc.medicines.org.uk) on 14/07/2011. Last updated on 14/04/2011.
- Stockley's Drug Interactions accessed via [medicinescomplete.com](http://medicinescomplete.com) on 18/07/2011. Last updated May 2011.

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**Guidelines:**

Reviewed by: Transplant pharmacist

Approved by: Papworth Hospital Drugs and Therapeutics Committee 09/2006

Reviewed by: Transplant Pharmacist (H Chapman) – approved by Transplant Steering group 14/09/2011

Approved by: Papworth Hospital Drugs and Therapeutics Committee via Chairman's Action 18/01/2012