SHARED CARE ARRANGEMENT AND PRESCRIBING INFORMATION FOR TACROLIMUS (RENAL ADULT)

NHS Grampian

N.B. This document should be read in conjunction with the current Summary of Product Characteristics (SmPC).

Patient safety is paramount. The prescriber who prescribes the medicine legally assumes clinical responsibility for the drug and the consequences of its use.

GENERIC AND BRAND NAME (formulations and strength)

Name: Tacrolimus (Adoport® (twice daily), Prograf® (twice daily), Advagraf® (once daily)

Formulation: Capsule

Strength: Adoport® 500microgram, 750 microgram,1mg, 2mg and 5mg; Prograf® 500microgram,1mg and 5mg; Advagraf® 500microgram,1mg, 3mg and 5mg

N.B: Tacrolimus must be prescribed by brand as directed by the Renal Consultant. There are three preparations of tacrolimus available on the formulary Prograf®, Adoport® and Advagraf® are not bioequivalent. **Hence, prescribe by brand name only**.

STATUS OF MEDICINE

Licence status: Licensed (prophylaxis of transplant rejection in kidney allograft recipients)

Formulary status: Formulary

Black triangle medicine: NO

Risk minimisation materials: NO

CONDITION(S) TO BE TREATED

Prophylaxis of transplant rejection in kidney allograft patients recipients.

TYPICAL DOSAGE REGIME	
Licensed dose	See Renal Specialist for advice
Route of administration	Oral
Recommended starting dose	See Renal Specialist for advice
Titration dose/increment	See Renal Specialist for advice
Maximum dose	See Renal Specialist for advice
Situations requiring dose adjustment	See Renal Specialist for advice
Duration of treatment	See Renal Specialist for advice

RESPONSIBILITY OF ACUTE CARE/SPECIALIST SERVICE

1. **Baseline:**
   Full Blood Count (FBC); Liver Function Tests (LFTs); Blood Pressure; U&E; Creatinine; Blood Glucose Levels; BUN and Coagulation Tests.
2. Copy of results to be sent to GP.
3. Exclude pregnancy before starting therapy.
   - If contraception needed non-hormonal methods should be used.
   - Advise the patient to contact their physician immediately should pregnancy occur.
4. Initiation of therapy and recommendations for dose increments. This will be controlled by the Renal Unit.
5. Monitoring clinical response to treatment.
   - Weekly full blood counts for 4 weeks then fortnightly for 2 months then monthly for one year then 3 monthly thereafter. If stable after 2 years go to 6 monthly monitoring.
   - U&E, creatinine, blood pressure, LFT and blood glucose every 3 months.
   - Whole blood 12-hour trough tacrolimus level 7 to 14 days after each dose change.
6. Patients should be asked about the presence of sore throat, rash or abnormal bruising at each visit.

RESPONSIBILITY OF PRIMARY CARE

To preserve vital venous access, monitoring will be done by the renal service at ARI unless otherwise notified or the patient develops an intercurrent illness which would require bloods to be taken in primary care.

A Practice agreeing to prescribe Tacrolimus should:

1. Prescribe medication (**by brand name**) under the guidance of the Renal Consultant.
2. Ensure the GP is aware that the drug can cause:
   - Nephrotoxicity
   - Increase in blood pressure
   - Infection and increased risk of malignancy – benign, malignant neoplasms and skin malignancies
   - Changes to visual status and Gastrointestinal upset
   - Be aware of potential drug interactions
   - Patients should be asked about the presence of sore throat, rash or abnormal bruising at each visit.
3. Ensure that the relevant monitoring requirements have been undertaken at the correct frequency above.
4. Ensure when the patient has an intercurrent illness FBC, U+E and LFTs are done and make sure abnormal results are acted upon promptly.
5. Only continue to prescribe medication if it is being satisfactorily monitored.
6. Contact the Renal Unit/Consultant/On Call Registrar in the event of a drug reaction, monitoring abnormality, or if you are concerned in any way regarding the current treatment regime.
7. Be alert for any of the known adverse reactions.

CARE WHICH IS THE RESPONSIBILITY OF THE PRESCRIBING CLINICIAN

1. Prescribe medication (by brand name) under guidance of Consultant.
2. Check before prescribing each instalment of medication that the monitoring is up to date and that results are within the normal range.
3. Ensure no interacting medications are prescribed in primary care.
4. Monitor for concordance with therapy.
5. Report any adverse events to Consultant and MHRA using the Yellow Card System.
6. If an intercurrent illness occurs, when writing laboratory request forms always include details of the patient's medication.
7. If bloods are taken due to intercurrent illness, ensure they are monitored and contact hospital consultant to advise if results are out with range.
8. A single dose of pneumococcal polysaccharide vaccine and annual influenza vaccine should be given.

N.B. In addition to absolute values for haematological or biochemical indices a rapid change or a consistent upward/downward trend in any value should prompt caution and extra vigilance.

N.B. If something unexpected occurs contact Renal Unit/On Call Registrar or Consultant. notify the consultant if the drug is stopped.

RESPONSIBILITY OF OTHER HEALTHCARE PROFESSIONALS

N/A

RESPONSIBILITY OF THE PATIENT

- Take medication regularly as directed by the specialist/doctor.
- Attend hospital and GP clinic appointments as requested by specialist/GP practice. Failure to attend appointments may result in medication being reviewed/stopped.
- Report any adverse effects/illness to the specialist/GP and present rapidly to specialist/GP should their condition significantly worsen.
- To minimise the risk of skin cancer, exposure to sunlight and Ultra Violet light should be limited by wearing protective clothing and using sunscreen with a high protection factor.

PRESCRIBING INFORMATION

For specific product information consult the current summary of product characteristics (http://emc.medicines.org.uk/), the BNF/BNF for Children (https://www.medicinescomplete.com/mc/index.htm)

CONTRAINDICATIONS

- Hypersensitivity to tacrolimus or other macrolides.
- Hypersensitivity to any of the excipients (see SmPC).

PREGNANCY

Discuss with Consultant.

BREAST-FEEDING

Discuss with Aberdeen Maternity Hospital. Manufacturer advises avoid.

COMMON SIDE EFFECTS AND THEIR MANAGEMENT

The following are reported as common side effects:

Gastrointestinal	Diarrhoea, nausea, gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools.
Cardiovascular	Ischaemic coronary artery disorders, tachycardia, hypertension, haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders.
Renal	Renal impairment.
Metabolic	Hyperglycaemia, hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricemia, appetite decreased, metabolic acidosis, hyperlipidaemia, hypercholesterolemia, hypertriglyceridemia, other electrolyte abnormalities.
Respiratory Disorders	Dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations.
Psychiatric Disorders	Anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders.
Central Nervous System	Seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders.
Haematological	Anaemia, leucopenia, thrombocytopenia, leucocytosis, abnormal red blood cell analyses.
Eye Disorders	Blurred vision, photophobia and other eye disorders.
Ear Disorders	Tinnitus.
Skin Disorders	Pruritus, rash, alopecia, acne, increased sweating.
Musculoskeletal	Arthralgia, myalgia, limb and back pain.
Hepatic	Cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis.
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.

Abnormal Monitoring Results	Action To Be Taken
• **WBC** < 4.0 x 10^9/L	Discuss with Renal Unit/Registrar on call or Consultant
• **Neutrophils** < 2.0 x 10^9 /L	Discuss with Renal Unit/Registrar on call or Consultant
• **Platelets** < 150x10^9 /L	Discuss with Renal Unit/Registrar on call or Consultant
• **Potassium** >5.0mmol/L	Discuss with Renal Unit/Registrar on call or Consultant
• **> 2-fold rise in ALT or Alk Phos** (from upper limit of reference range) • Other significantly deranged LFT results	Discuss with Renal Unit/Registrar on call or Consultant
• Creatinine rises ≥ 30% from baseline	Discuss with Renal Unit/Registrar on call or Consultant
• Abnormal bruising, sore throat, rash, oral ulceration	Discuss with Renal Unit/Registrar on call or Consultant

COMMON DRUG INTERACTIONS (for a full list see SmPC)

Some important interactions to consider include the following:

Metabolic interactions
Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels.

It is therefore strongly recommended to closely monitor tacrolimus blood levels, as well as, QT prolongation (with ECG), renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism are used concomitantly and to interrupt or adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

Inhibitors of metabolism
Clinically the following substances have been shown to increase tacrolimus blood levels:

Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole voriconazole, and isavuconazole, the macrolide antibiotic erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir) or HCV protease inhibitors (e.g. telaprevir, boceprevir and the combination of ombitasvir and paritaprevir with ritonavir, when used with and without dasabuvir), the pharmacokinetic enhancer cobicistat, and the tyrosine kinase inhibitors nilotinib and imatinib. Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole, nefazodone and (Chinese) herbal remedies containing extracts of Schisandra sphenanthera.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, troleandomycin.

Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.

Lansoprazole and ciclosporin may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

Other interactions potentially leading to increased tacrolimus blood levels
Tacrolimus is extensively bound to plasma proteins. Possible interactions with other medicinal products known to have high affinity for plasma proteins should be considered (e.g. NSAIDs, oral anticoagulants, or oral antidiabetics).

Other potential interactions that may increase systemic exposure of tacrolimus include the prokinetic agent metoclopramide, cimetidine and magnesium-aluminium-hydroxide.

Inducers of metabolism
Clinically the following substances have been shown to decrease tacrolimus blood levels:

Strong interactions have been observed with rifampicin, phenytoin or St. John's Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.

Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

Effect of tacrolimus on the metabolism of other medicinal products
Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolised by CYP3A4 may affect the metabolism of such medicinal products.

The half-life of ciclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin. Tacrolimus has been shown to increase the blood level of phenytoin.

As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.

Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and phenazone.

Mycophenolic acid. Caution should be exercised when switching combination therapy from ciclosporin, which interferes with enterohepatic recirculation of mycophenolic acid, to tacrolimus, which is devoid of this effect, as this might result in changes of mycophenolic acid exposure. Drugs which interfere with mycophenolic acid's enterohepatic cycle have potential to reduce the plasma level and efficacy of mycophenolic acid. Therapeutic drug monitoring of mycophenolic acid may be appropriate when switching from ciclosporin to tacrolimus or vice versa.

Other interactions which have led to clinically detrimental effects
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole and trimethoprim, NSAIDs, ganciclovir or aciclovir).

Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.

As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone) should be avoided.

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

ADVERSE DRUG REPORTING

If an adverse reaction should occur, inform relevant medical practitioner as soon as possible.

Report to the MHRA using the Yellow Card System https://yellowcard.mhra.gov.uk/

REFERENCES

https://www.medicines.org.uk/emc/product/585/smpc
https://www.medicines.org.uk/emc/product/6720/smpc
https://www.medicines.org.uk/emc/product/345/smpc

ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION

In the event of concern being raised, the primary care practitioner should contact the referring Consultant via the hospital switchboard, via their secretary, by e-mail or letter, whichever is more appropriate. If the concern is urgent, and out of hours advice is required, the on call Renal Registrar may be contacted via switchboard.

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