RENAL TRANSPLANT PATIENTS ONLY

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

Clinicians must ensure they are referring to the correct SCA for specialty/situation.

This SCA is for RENAL TRANSPLANT PATIENTS ONLY. Some content and recommendations may differ from the SCA for patients receiving this treatment for conditions other than renal transplant. This is due to the specialist service clinical recommendations and monitoring requirements for managing transplant patients.

Note: 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® MR (once daily), Dailiport® MR (once daily).

Formulation: Capsule

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

Note: Tacrolimus must be prescribed by brand as directed by the Renal Consultant. Within NHS Grampian the formulations in use are Adoport®, Prograf®, Advagraf® MR and Dailiport® MR.

Tacrolimus is a drug with a narrow therapeutic index, it is vital that patients are not switched between formulations unless advised and managed by the specialist service.

These preparations are not bioequivalent therefore must be prescribed by brand name.

STATUS OF MEDICINE

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

Formulary status: Formulary

Black triangle medicine: No

Risk minimisation materials (RMM): No

CONDITION(S) TO BE TREATED UNDER THIS SCA

RENAL TRANSPLANT: 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

- Baseline:
  - Full Blood Count (FBC), Liver Function Tests (LFTs), and Urea and Electrolytes (U&Es)
  - Lipids
  - Blood glucose and blood pressure (BP)
- Copy of baseline results to be shared with Primary Care.
- 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
- Request for initiation of therapy, confirming brand to be prescribed and recommendations for dose increments to Primary Care.
- Monitoring clinical response to treatment and advising on final dose required for the patient.
- Ongoing Blood monitoring - the Renal service has the primary responsibility for **RENAL TRANSPLANT** patients blood monitoring and review of results.

  This will follow a normal schedule of:
  - full blood counts, U+E, Creatinine, blood pressure, LFT and blood glucose three times a week for first two weeks after discharge,
  - weekly until week 8,
  - alternate weeks until week 12 to 16 (depending on graft function),
  - monthly until end of first six months,
  - two to three monthly until end of first year,
  - and 3 to 6 monthly during year two and beyond if stable with satisfactory graft function,
  - lipids monitored at week 4 then every 12 months,
  - whole blood 12-hour trough tacrolimus level 7 to 14 days after each dose change.

  If any individual monitoring is to be performed out with this schedule the renal service should advise primary care accordingly, this is necessary to ensure compliance with monitoring schedules prior to prescribing.

- Patients should be asked about the presence of sore throat, rash or abnormal bruising at each visit.

- Pneumococcal polysaccharide vaccine (PPV), COVID-19 vaccine and annual influenza vaccine should be given as per Joint Committee of Vaccination and Immunisation (JCVI)/The Green Book recommendations. Shingles vaccine should be given to those individuals who are severely immunocompromised, or anticipating immunosuppressive therapy, and eligible in line with JCVI/The Green Book recommendations and Scottish Government vaccination programme. Patients should be referred by specialist services to receive these vaccines in accordance with local protocol.

RESPONSIBILITIES OF PRIMARY CARE/PRESCRIBING CLINICIAN

To preserve vital venous access, blood monitoring for RENAL TRANSPLANT patients will be done by the renal specialist service 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 for **RENAL TRANSPLANT** should:

- Prescribe medication (**by brand name**) under the guidance of the Renal Consultant. Checking before prescribing each instalment of medication that the monitoring is up to date and that results are within a satisfactory range.
- Ensure that the relevant monitoring requirements have been undertaken at the correct frequency (see information under responsibility of Acute care/specialist service).
- Only continue to prescribe medication if it is being satisfactorily monitored. Noting medication should not be stopped without first discussing with the Renal Consultant, specialist service.
- 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
- Patients should be asked about the presence of sore throat, rash or abnormal bruising at each visit.
- Ensure when the patient has an intercurrent illness FBC, U+E and LFTs are done and make sure abnormal results are acted upon promptly. If an intercurrent illness occurs, when completing laboratory request always include details of the patient's medication.
- If bloods are taken due to intercurrent illness, ensure they are monitored and contact Renal Consultant to advise if results are out with range (see Abnormal Monitoring section).
- 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.
- Be alert for any of the known adverse reactions.
- Ensure no interacting medications are prescribed in primary care.
- Monitor for concordance with therapy.
- The patient should be encouraged to ensure blood tests are undertaken at the correct intervals (see information under responsibility of Acute care/specialist service).
- It is responsibility of primary care to ensure that the medication is recorded on the patient's clinical medication record. This will facilitate central searches for vaccinations in order to ensure patients receiving DMARDs are called by the HSCP teams for required vaccinations, e.g. influenza and covid programmes.
- Report any adverse events to consultant and the MHRA using the Yellow Card System.
- Post exposure prophylaxis (PEP) should be considered in non-immune individuals if exposed to shingles or chickenpox as per The Green Book.
- If something unexpected occurs contact on call renal registrar or consultant.

MONITORING

To preserve vital venous access, blood monitoring for **RENAL TRANSPLANT** patients will be done by the renal specialist service unless otherwise notified OR the patient develops an intercurrent illness which would require bloods to be taken in primary care.

Results should be reviewed and action taken as per Abnormal Monitoring Section below.

For **RENAL TRANSPLANT** the renal specialist service will review results, for monitoring they have undertaken.

All results should also be reviewed by Primary Care routinely prior to prescribing, and if additional monitoring due to an intercurrent illness.

Note: 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.

RESPONSIBILITY OF THE PATIENT

- Take medication regularly as directed by the specialist/doctor.
- Patients are instructed to take the drug at the same times each day. This is necessary to facilitate interpretation of blood levels.
- Attend hospital and GP clinic appointments as requested by specialist/GP practice. Failure to attend appointments may result in medication being reviewed/stopped.
- The patient should ensure all blood tests are taken at the correct intervals.
- Report any adverse effects to the specialist/GP and present rapidly to specialist/GP should their condition 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 (minimum SPF 30).
- Be aware of need to use contraception where appropriate.

PRESCRIBING INFORMATION

For specific product information consult the current summary of product characteristics (http://emc.medicines.org.uk/) and the BNF BNF (British National Formulary) | NICE

CONTRAINDICATIONS

For full details please refer to the current Summary of Product Characteristics (SPC) available at www.medicines.org.uk.

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

PREGNANCY RENAL TRANSPLANT

Discuss with Renal Consultant. Tacrolimus should not be used during pregnancy unless there is no suitable alternative to prevent transplant rejection.

Women on tacrolimus should be advised to seek specialist advice prior to conception.

It is recommended that maternal blood pressure, renal function, blood glucose and drug levels are monitored throughout pregnancy.

BREAST-FEEDING RENAL TRANSPLANT

Discuss with Renal Consultant. Manufacturer advises avoid.

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, gastrointestinal signs and symptoms and ascites
Cardiac Disorders and Vascular Disorders	Ischaemic coronary artery disorders, tachycardia, hypertension - assess and manage accordingly. Patients on tacrolimus who develop hypertension (140/90mmHg) which cannot be controlled with antihypertensives, should be discussed with Renal Consultant Haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
Renal and urinary disorders	Renal impairment, renal failure, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms
Metabolism and Nutrition Disorders	Hyperglycaemia, hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, metabolic acidosis, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia - slight, reversible increase possible. If increase meets standard NHS Grampian thresholds for treatment (e.g. consider NHS Grampian Lipid Lowering flowcharts for primary or secondary prevention, as indicated), then discuss with specialist team Other electrolyte abnormalities, diabetes mellitus and hyperkalaemia
Respiratory Disorders, thoracic and mediastinal 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 and insomnia

Nervous System Disorders	Seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders, tremor and headache
Blood and Lymphatic system disorders	Anaemia, leucopenia, thrombocytopenia, leucocytosis, abnormal red blood cell analyses
Eye Disorders	Blurred vision, photophobia and other eye disorders
Ear and Labyrinth Disorders	Tinnitus
Skin and subcutaneous tissue disorders	Pruritus, rash, alopecia, acne, increased sweating
Musculoskeletal and connective tissue disorders	Arthralgia, muscle spasms, pain in limb and back pain
Hepatobiliary Disorders	Cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
General disorders and administration site conditions	Asthenic conditions, febrile disorders, oedema, pain and discomfort, distorted body temperature perception and weight increased
Infection	Increased susceptibility to viral, fungal, bacterial and protozoal infections. In the event of infection please do not discontinue immunosuppression without discussion with the renal consultant. It can be considered appropriate to continue these drugs in patients with minor viral and bacterial 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** <150 x 10^9/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

Tacrolimus is extensively metabolised in the liver via the cytochrome P-450 enzyme system and may have inducing or inhibitory effects on these enzymes. Therefore care should be taken when co-administering other drugs known to be metabolised by this system.
Advice should be obtained from the Renal specialist service if required.

Some important interactions to consider include the following:

Potassium sparing diuretics, ACE inhibitors, angiotensin-II receptor antagonists and potassium salts	Caution as co-administration may lead to hyperkalaemia.
Grapefruit, grapefruit juice	Increase tacrolimus levels.
Lansoprazole and ciclosporin	May potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.
High dose prednisolone or methylprednisolone	May be administered for the treatment of acute rejection but has the potential to increase or decrease tacrolimus blood levels.
Ketoconazole, fluconazole, itraconazole, voriconazole, and isavuconazole, erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g. telaprevir, boceprevir) and the combination of ombitasvir and paritaprevir with ritonavir, when used with and without dasabuvir) or the CMV antiviral letermovir, 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.
Cannabidiol	Reports of increased blood levels during concomitant use with cannabidiol. Tacrolimus and cannabidiol should therefore be co-administered with caution, closely monitoring for side-effects.
Aminoglycosides, amphotericin B, ciprofloxacin. Vancomycin, trimethoprim (+sulfamethoxazole), fibric acid derivatives (e.g. bezafibrate and fenofibrate), NSAIDS,	Combinations with increased risk of nephrotoxicity. Close monitoring of renal function required. If a significant impairment of renal function occurs, the dosage of the co-administered medicinal product should be reduced or an alternative considered.
Live attenuated vaccines	Avoid. Immunosuppressants may affect the response to vaccination and vaccination during treatment may be less effective.

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.

This information is not intended to be a complete list of interactions. For further information consider appropriate reference sources such as SmPC/Vision system.

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

www.medicines.org.uk/emc/product/4743/smpc
www.medicines.org.uk/emc/product/4743/safetyalert
www.medicines.org.uk/emc/product/6720/smpc
www.medicines.org.uk/emc/product/6720/safetyalert

ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION

In the event of a 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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