SHARED CARE ARRANGEMENT AND PRESCRIBING INFORMATION FOR ORAL TACROLIMUS (ADULTS) EXCLUDING RENAL TRANSPLANT

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

This SCA is applicable for ALL conditions/specialities EXCLUDING RENAL 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
Brands - 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 Specialist 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 transplant recipients)

Formulary status: Formulary

Black triangle medicine: NO

Risk minimisation materials: NO

CONDITION(S) TO BE TREATED UNDER THIS SCA

- Prophylaxis of transplant rejection (excluding renal transplant), treatment of steroid resistant rejection.
- It may also be used in patients with intolerable side effects to ciclosporin.
- Nephrotic Syndrome.

TYPICAL DOSAGE REGIME	
Licensed dose	See Specialist service/SmPC for advice – variable according to condition being treated
Route of administration	Oral
Recommended starting dose	See Specialist service for advice – variable according to condition being treated
Titration dose/increment	See Specialist service for advice
Maximum dose	See Specialist service for advice
Situations requiring dose adjustment	See Specialist service for advice and Monitoring Schedule for DMARDs
Duration of treatment	See Specialist service for advice

RESPONSIBILITY OF ACUTE CARE/SPECIALIST SERVICE

- Baseline as per Monitoring Schedule for DMARDs:
  - 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 patient to contact their physician immediately should pregnancy occur.
- Request for initiation of therapy and recommendations for dose increments to Primary Care.
- Advise Primary Care on requirements for trough level monitoring and target levels as necessary for condition
- Monitoring clinical response to treatment and advising on final dose required for the patient. Clinical decision regarding final dose required for patient.
- 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.

RESPONSIBILITY OF PRIMARY CARE/PRESCRIBING CLINICIAN

A Practice agreeing to prescribe tacrolimus should:

- Prescribe medication (**by brand name**) under the guidance of the Consultant from the relevant specialist service.
- Checking before prescribing each instalment of medication that the monitoring is up to date and that results are within a satisfactory range.
- Note: for individuals referred for vaccinations by the specialist service it is ideal to wait for vaccinations before starting immunosuppressive treatments. However this risks not controlling the autoimmune condition quickly which can negatively affect long term prognosis. Therefore specialties do not insist on a delay in starting immunosuppressive treatment to allow for vaccinations and recommend vaccinations happen as soon as possible after starting immunosuppressive treatment.
- Ensure that the relevant monitoring requirements have been undertaken at the correct frequency.
- The General Practitioner (GP) has primary responsibility for monitoring according to the Monitoring Schedule for DMARDs and review of results.
- Only continue to prescribe medication if it is being satisfactorily monitored.
- For transplant (excluding renal transplant not covered under this SCA) and nephrotic syndrome tacrolimus whole blood 12-hour trough blood concentrations are require to be monitored 7 to 14 days after each dose change. The target blood level for an individual patient will depend on the condition, time since transplant, history of rejection and side effects and will be advised by the relevant 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, abnormal bruising or bleeding 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 action taken as per the Monitoring Schedule for DMARDs.
- Infection - During a serious infection tacrolimus should be temporarily discontinued until the patient has recovered from the infection and is off antibiotics for 2 weeks with no recurrence of infection. (This excludes any transplant patients who should be discussed with specialist service).
  It can be considered appropriate to continue these drugs in patients with minor or uncomplicated viral infections or, if deemed clinically appropriate by the Specialist, in patients requiring long term antibiotic prophylaxis e.g. for prevention of recurrent UTIs.
- Contact the relevant specialist service 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.

- 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 immunosuppressants 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 Consultant of specialist service.

MONITORING

Refer to the NHSG Guidelines For The Monitoring of Disease Modifying Anti-Rheumatic Drugs (DMARDs) For Healthcare Professionals.

Primary Care are responsible to ensure results are reviewed and action taken as per monitoring guidance.

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/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 (minimum SPF 30).

PRESCRIBING INFORMATION

For specific product information consult the current summary of product characteristics (http://emc.medicines.org.uk/), the BNF/BNF for Children 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).
- Severe infections - during a serious infection tacrolimus should be temporarily discontinued until the patient has recovered from the infection and is off antibiotics for 2 weeks with no recurrence of infection. (This excludes any transplant patients who should be discussed with specialist service).

PREGNANCY

Women on tacrolimus should be advised to seek specialist advice prior to conception as it is recommended that maternal blood pressure, renal function, blood glucose and drug levels are monitored throughout pregnancy, however switching to alternative therapy is not required.
British Society for Rheumatology Guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids from April 2023 states that tacrolimus is safe in pregnancy and can be continued.

BREAST-FEEDING

British Society for Rheumatology Guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids from April 2023 states that tacrolimus is safe in breastfeeding (in a healthy, full term infant). This is outwith the product license which states patients should avoid breastfeeding while taking this medicine, but supported by specialist services.

COMMON SIDE EFFECTS

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, 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, renal failure acute, 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 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
Neoplasms (benign and malignant)	Benign and malignant neoplasms and skin malignancies

Action abnormal monitoring results are per NHSG Disease Modifying Anti-Rheumatic Drugs (DMARDs) Monitoring Guidance.

The specialist service should be contacted if there are any patient specific issues or concerns regarding side effects or abnormal results.

COMMON DRUG INTERACTIONS (for a full list see SmPC)

Tacrolimus is extensively metabolised in the liver via the cytochrome P-450 enzyme system and may have an inducing or inhibitory effect 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 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/cotrimoxazole (+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

- Adoport 0.5mg Hard Capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- British Society for Rheumatology Guideline

ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION

In the event of a concern being raised, the primary care practitioner should contact the referring consultant for the appropriate specialist service via the hospital switchboard, via their secretary, by email or letter, whichever is more appropriate. If the concern is urgent, and out of hours advice is required, the on call Registrar for the speciality may be contacted via the switchboard.

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