RENAL TRANSPLANT PATIENTS ONLY

SHARED CARE ARRANGEMENT AND PRESCRIBING INFORMATION FOR CICLOSPORIN (ADULT) RENAL TRANSPLANT

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: Ciclosporin (Neoral®). Within NHS Grampian, the brand in use for renal organ transplantation is Neoral®.

Formulation: Capsule/Oral Solution

Strength: (10mg, 25mg, 50mg, 100mg Capsule), 100mg/mL Oral Solution

Note: Prescribing and dispensing should be by brand name only as advised by the Renal Consultant. This is in order to minimise the risk of inadvertent switching between products, which has been associated with reports of toxicity and graft rejection (MHRA Drug Safety Update June 2012).

Neoral® soft gelatin capsules and Neoral® oral solution are bioequivalent and can be used interchangeably.

STATUS OF MEDICINE

Licence status: Licensed

Formulary status: Formulary

Black triangle medicine: No

Risk minimisation materials (RMM): No

CONDITION(S) TO BE TREATED UNDER THIS SCA

RENAL TRANSPLANT: For prevention of kidney graft rejection following solid organ transplantation.

TYPICAL DOSAGE REGIME	
Licensed dose	See Renal Specialist for advice
Route of administration	Oral
Recommended starting dose	See Renal Specialist for advice

TYPICAL DOSAGE REGIME	
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.
- Request initiation of therapy 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** patents blood monitoring and review of results.

  This will follow a normal schedule, at initiation post transplant of:
  - full blood counts, U+E (including creatinine, urea and potassium), blood pressure and LFT (including ALT and Alk Phos) three times per 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 three to six monthly during year two and beyond if stable with satisfactory graft function,
  - lipids monitored week 4 then every 12 months,
  - whole blood 12-hour trough ciclosporin A level 7 to 14 days after each dose change.

  For individuals transferred from an alternative immunosuppressant monitoring would begin at alternate weeks for 4 weeks, then monthly following the schedule above from this point.

  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.
- Provide counselling, as appropriate, regarding pregnancy and breastfeeding.

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 Ciclosporin 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
  - Increased risk of malignancy – benign, malignant neoplasms, skin and other tumours.
- Patients should be asked about the presence of sore throat, abnormal bruising or bleeding at each visit.
- Ensure when the patient has an inter-current illness FBC, U+Es and LFTs are done, results reviewed, and 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 Consultant 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 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 undertaken 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).

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 the active substance or to any of the excipients.
- Combination with products containing Hypericum perforatum (St John's Wort).
- Combination with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) and for which elevated plasma concentrations are associated with serious and/or life threatening events, e.g. bosentan, dabigatran etexilate and aliskiren.
- Do not give with tacrolimus due to increased risk of nephrotoxicity.
- Some statins are specifically contra-indicated with ciclosporin and many may require a reduced dose if concomitantly administered. Ensure the SmPC for the individual statin is checked before prescribing.

PREGNANCY RENAL TRANSPLANT

Discuss with Renal Consultant. Experience with ciclosporin in pregnant women is limited. Ciclosporin should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risk versus benefit.

Women on ciclosporin 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.

BREAST-FEEDING RENAL TRANSPLANT

Discuss with Renal Consultant.

COMMON SIDE EFFECTS

Blood and lymphatic system disorders	Leucopenia
Metabolism and nutrition disorders	Hyperlipidemia - 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 Hyperglycaemia, anorexia, hyperuricaemia, hyperkalaemia and hypomagnesaemia
Nervous System Disorders	Tremor, headache, convulsions and paraesthesia
Vascular Disorders	Hypertension -assess and manage accordingly. Patients on ciclosporin who develop hypertension (140/90mmHg) which cannot be controlled with antihypertensives, should be discussed with Renal Consultant. Flushing
Gastro-intestinal disorders	Nausea, vomiting, abdominal discomfort/pain, diarrhoea, gingival hyperplasia and peptic ulcer
Hepatobiliary disorders	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Hirsutism, acne and hypertrichosis
Musculoskeletal and connective disorders	Myalgia and muscle cramps
Renal and urinary disorders	Renal dysfunction
General side effects	Pyrexia, infection and fatigue – 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.

Abnormal Monitoring Results	**Action To Be Taken**
• WBC <4 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
• >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
• MCV>105fL	Discuss with Renal Unit/Registrar on call or Consultant
• Abnormal bruising, sore throat, rash, oral ulceration	Check FBC. Discuss with Renal Unit/Registrar on call or Consultant
• Unexplained fever	Discuss with Renal Unit/Registrar on call or Consultant
• Suspicion of or newly diagnosed malignancies	Discuss with Renal Unit/Registrar on call or Consultant

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

COMMON DRUG INTERACTIONS

Ciclosporin is extensively metabolised in the liver via the cytochrome P450 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 sought 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.
Barbiturates, antiepileptics, St John's Wort, octreotide and rifampicin	Decrease ciclosporin levels.
Grapefruit, macrolide antibiotics (mainly erythromycin and clarithromycin), azole antifungals (ketoconazole, fluconazole, itraconazole and voriconazole), verapamil, telaprevir, amiodarone, danazol, diltiazem and imatinib	Increase ciclosporin levels.
Amiodarone	Substantially increases the plasma ciclosporin concentration with an increase in serum creatinine. This interaction can occur for a long time after withdrawal of amiodarone, due to its very long half-life (about 50 days).
Dabigatran	Not recommended due to P-gp inhibitory activity of ciclosporin
Statins, simvastatin and rosuvastatin are contra-indicated with ciclosporin	Risk of myopathy increased with concurrent administration of HMG-CoA reductase inhibitors (statins). Consult SmPC for dosage adjustment information.
Nifedipine	Increased rate of gingival hyperplasia.
Cannabidiol	Reports of increased blood levels during concomitant use with cannabidiol. Ciclosporin 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, H2-receptor antagonist (e.g. cimetidine), methotrexate	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.

Digoxin, colchicine	Ciclosporin may increase plasma levels of co-medications that are substrates of this enzyme and/or transporter, e.g. need to monitor carefully these medicines.
Live attenuated vaccines	Avoid live vaccines. Immunosuppressants may affect the response to vaccination and vaccination during treatment may be less effective.

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/1034/smpc

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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