SHARED CARE ARRANGEMENT AND PRESCRIBING INFORMATION FOR CICLOSPORIN (NEORAL®) (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: Ciclosporin (Neoral®). Within NHS Grampian, the brand in use is Neoral®.

Formulation: Capsule/Oral Solution.

Strength: 10mg, 25mg, 50mg, 100mg Capsule and 100mg/mL Oral Solution.

Note: Prescribing and dispensing should be by brand name only. 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: Ciclosporin is licensed for prophylaxis of graft rejection in transplantation and is used in combination with other immunosuppressants. Ciclosporin is also licensed for use in other non-transplant indications within rheumatology, gastroenterology and dermatology specialties.

Formulary status: Formulary – available for restricted use under specialist supervision.

Black triangle medicine: NO

Risk minimisation materials: NO

CONDITION(S) TO BE TREATED UNDER THIS SCA

- Prophylaxis of graft rejection in liver and pancreas transplantation (excluding renal transplant).
- Used in combination with other immunosuppressants.
- It may be used in the treatment of rheumatoid arthritis and psoriasis.
- 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.
- 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.
- Advise Primary Care on requirement for trough level monitoring and target levels as necessary for condition.
- 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.

RESPONSIBILITY OF PRIMARY CARE/PRESCRIBING CLINICIAN

A Practice agreeing to prescribe ciclosporin 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 (see information under responsibility of Acute care /specialist service).
- 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 ciclosporin whole blood 12-hour trough blood concentrations are required to be monitored 7 to 14 days after each dose change, with a target range as indicated below. However, 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.
    - To obtain a trough level - take a morning blood sample when the patient has omitted the morning dose.
        - Liver transplant (first six months) 100 to 150 µg/L
        - Liver transplant (six months onwards) 70 to 100 µg/L
- Ensure the GP is aware that the drug can cause:
    - Nephrotoxicity
    - Increase in blood pressure
    - Infection
    - Increase 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 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 specialist consultant to advise if results are out with range (see Abnormal Monitoring section).
- Infection - During a serious infection ciclosporin 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. (if for transplant recipient discuss with specialist service)
- 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 the appropriate specialty.
- Notify consultant/specialist service if drug is stopped.

MONOTORING

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 undertaken 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 detail please refer to the current Summary Product Characteristic (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).
- Severe infections - during a serious infection ciclosporin 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).
- 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

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.

British Society for Rheumatology Guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids from April 2023 states that ciclosporin 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 ciclosporin 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

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 Disorders and administration site conditions	Pyrexia, infection and fatigue - discuss severe infection with specialist service

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)

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 relevant 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/co-trimoxazole (+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

- Neoral Soft Gelatin Capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- Neoral Oral Solution - 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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