NORTH AND EAST DEVON HEALTHCARE COMMUNITY SHARED CARE PRESCRIBING GUIDELINE

http://www.devonpct.nhs.uk/Treatments/NE_Devon_Shared_Care_Guidelines.aspx#C
https://nww.devonpctinfo.nhs.uk/Prescribing/SCG/

PREVENTION OF REJECTION IN RENAL TRANSPLANTATION
CICLOSPORIN (NEORAL®)

This shared care guideline sets out details for the sharing of care of patients in whom **CICLOSPORIN** is prescribed for the prevention of **REJECTION OF RENAL TRANSPLANTATION**. These guidelines provide additional limited information necessary to aid in the prevention of rejection of patients with **CICLOSPORIN**. As with all shared care guidelines they highlight significant prescribing issues but should be used in conjunction with the ABPI summary of product characteristics (SPC/Data sheet) and ***do not*** replace them.

INTRODUCTION/BACKGROUND INFORMATION

Ciclosporin has an important role in organ and tissue transplantation.
Immunosuppression is essential in preventing the rejection of allograft organs in transplantation. However the greatest risks to life after renal transplantation are the adverse effects of long-term immunosuppression.

Ciclosporin is an immunosuppressant acting as a calcineurin inhibitor. It acts by specifically and competitively inhibiting signal transduction pathways in T-lymphocytes, preventing T-cell proliferation. It is virtually non-myelotoxic but markedly nephrotoxic.

INDICATIONS FOR THE PURPOSES OF THIS GUIDELINE

Prevention of graft rejection following renal transplants.

NICE GUIDANCE

Ciclosporin is an initial drug choice when a calcineurin inhibitor is indicated as part of an initial or a maintenance immunosuppressive regimen in renal transplantation for adults. The initial choice of ciclosporin or tacrolimus should be based on the relative importance of their side-effect profiles for individual patients.

DOSAGE AND ADMINISTRATION

After post-operative titration of dose by the renal clinic, maintenance therapy is given at a dose of 2mg/kg to 6mg/kg daily, in two divided doses approximately twelve hours apart. Dose will be adjusted according to ciclosporin levels, renal function and concomitant additional immunosuppressant therapy e.g. corticosteroids.

Most patients will be prescribed the drug in the form of capsules but some, who find the larger capsules difficult to swallow, will need the oral solution.

Neoral® solution has a characteristic taste. The oral solution should be diluted immediately before being taken. For improved taste the solution can be diluted into a glass containing orange juice or squash or apple juice, but **not grapefruit juice**. However, it may also be taken in a glass of water if preferred though the taste is stronger. It should be stirred well and taken immediately. Patients should be advised to rinse their glass with the liquid used to dilute the solution and drink the mixture to ensure that the full dose is taken.

The measuring syringe should not be rinsed with water, alcohol or any other liquid, but should be wiped on the outside with a dry tissue. This prevents gel formation on standing.

CONTRAINDICATIONS

- Known hypersensitivity to ciclosporin.
- Combination with tacrolimus.
- Women should not breast-feed.

PRECAUTIONS

- Hepatic dysfunction
- Impair renal function.
- Pregnancy.
- Porphyria.
- Avoid other immunosuppressants with the exception of corticosteroids (increased risk of infection and lymphoma).
- Interactions (see below).
- High dietary intake of potassium (including salt substitutes and potassium supplements) and the use of potassium sparing diuretics should be avoided.
- Use of sunbeds and unprotected exposure to sunlight are not recommended due to potential risk of skin malignancy.

SIDE EFFECTS

Adverse effects are usually mild to moderate and usually respond to dosage reduction.

common > [1 in 10] > Common > [1 in 100] > Uncommon > [1 in 1000] > Rare > [1 in 10000] > Very rare

Very common/ common

Hypercholesterolaemia, hypertension, hyperkalaemia, hypomagnesaemia, hyperuricaemia, renal dysfunction, gout, gastrointestinal disturbances: abdominal pain, anorexia, nausea, vomiting and diarrhoea, gingival hyperplasia, hepatic dysfunction, hypertrichosis, muscle cramps, myalgia, fatigue, tremor, paraesthesia, burning sensation of hands and feet (usually first week), headache, predisposition to infection.

Uncommon / rare

Haemolytic anaemia, thrombocytopenia, haemolytic uraemic syndrome, menstrual disorders, gynaecomastia, hyperglycaemia (diabetes), pancreatitis, allergic rash, muscle weakness, myopathy, oedema, weight increase, signs of encephalopathy or demyelination (e.g. convulsion, confusion etc.), motor polyneuropathy.

Very rare

Optic disc oedema including papilloedema with possible visual impairment secondary to benign intracranial hypertension, colitis, cortical blindness.

Increased risk of malignancies including lymphoma, skin and other tumours appear to be linked to degree and duration of immunosuppression. The incidence is similar to that of other immunosuppressive agents or therapies.

MONITORING

Secondary care

- Blood urea and electrolytes and blood pressure every 2 weeks for the first 12 weeks and every 4 weeks thereafter (more frequently if dosage increased or if a known interacting drug is initiated or its dosage increased).
- Hyperuricaemia.
- Monitor serum potassium especially in renal dysfunction (risk of hyperkalaemia).
- Monitor serum magnesium if symptoms indicate hypomagnesaemia.
- Monitor kidney function – significant increases in creatinine and urea that may indicate rejection or toxicity.
- Monitor liver function (dosage adjustment based on bilirubin and liver enzymes may be needed). Test LFTs monthly for 3 months then 3 monthly thereafter.
- Ciclosporin levels as required.

Primary care

- Monitor blood pressure every 4 weeks - refer or increase antihypertensive medication if hypertension develops.
- Measure blood lipids before treatment and thereafter 6 monthly as appropriate. Consider treatment as a high-risk primary prevention unless there is co-morbidity indicating a secondary prevention approach.
- Record results in the patient held record when shared care in place.

REFER TO THE SPECIALIST TEAM IF

Side effect	Action
Increased blood pressure. The suggested treatments are made on an overall benefit assessment. The recommended monitoring of treatment diminishes risks of possible interactions.	Suggested stepwise management of hypertension using the following drug classes: 1. ACE inhibitor or Angiotensin receptor blockers (ARB) - use in glomerular disease but not with renovascular disease 2. Calcium Channel Blocker (caution there are several interactions) 3. Beta blocker 4. Diuretic 5. Others 6. Refer to specialist
Hypercholesterolaemia	Discuss with specialist
Benign Intracranial Hypertension	Discontinue drug and urgent referral to specialist
Abnormal bruising	Refer to specialist

COMMON/SIGNIFICANT DRUG INTERACTIONS

This list is **NOT exhaustive**, the data sheet and BNF must be consulted for a more comprehensive list of potential drug interactions.

Food: Grapefruit or Grapefruit juice (not to be ingested for 1 hour prior to dose of Ciclosporin)

Interference with the p450 system.

Drugs that **reduce** blood levels (Increased dosage required - danger of rejection) e.g. St. Johns Wort (*Hypericum perforatum*), carbamazepine, phenytoin.

Drugs that **increase** blood levels (Reduced dosage required - danger of toxicity) e.g. Macrolide antibiotics, Amiodarone, Conazole' antifungals

Nephrotoxic drugs e.g. Aminoglycoside antibiotics, quinolones, trimethoprim, co-trimoxazole, amphotericin, melphalan, colchicine.

Drugs that increase potassium levels e.g. ACE inhibitors

Drugs that increase ciclosporin nephrotoxicity e.g. non-steroidal anti-inflammatory drugs, allopurinol.

Drugs that increased hepatotoxicity e.g. Danazol, anabolic steroids and oral contraceptives.

Other drug interactions

- An increased risk of myopathy occurs with statins.
- Live vaccinations (Oral polio, measles, mumps, rubella, BCG, oral typhoid, yellow fever) should not be administered whilst taking ciclosporin. Attenuated vaccines may be less effective.
- Nifedipine - avoid in patients who develop gingival hyperplasia with ciclosporin. May also occur with other dihydropyridine calcium channel blockers.

NOTES

- Patients require counselling on the potential skin malignancy risks of exposure to UV light including not using sunbeds and covering exposed skin with clothes or sunscreen SPF of at least 25.

PRODUCT INFORMATION

- Prescribing of ciclosporin must be **BY BRAND** as Neoral®.
- Sandimmun® is not bioequivalent and is available on named-patient basis only for patients who fail to transfer to Neoral® for a clinical reason. Any conversion between brands must be undertaken very carefully. The renal unit would undertake this conversion.
- Neoral® is available as 25mg capsules, 50mg capsules, 100mg capsules and as a solution, 100mg/ml.
- Capsules should be left in the blister pack until required for use.
- Solution should be stored between 20°C and 30°C.

REFERENCES:

- Summary of Product Characteristics: Neoral®, - accessed on electronics medicines compendium www.emc.medicines.org.uk January 2008.
- BNF 55 March 2008.
- NICE guidance 85 - Immunosuppressive therapy for renal transplantation in adults September 2004 http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11544

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AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

These are suggested ways in which the responsibilities for the management of patients with Prevention of **rejection of renal transplantation** who are prescribed **ciclosporin** can be shared between the specialist and the general practitioners. GPs are **invited** to participate. If the GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event the total clinical responsibility for the patient for the diagnosed condition remains with the specialist**. If a specialist asks the GP to prescribe this drug the GP should reply to this request as soon as practical.**

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and be accepted by them.

The doctor who prescribes the medication has the clinical and legal responsibility for the drug and the consequences of its use.

Specialist responsibilities:

- ❑ Initiation of **ciclosporin** and stabilisation of patient's condition. Responsibility for prescribing is retained for 3 months, or longer if the patient's condition or drug dosing is not stabilised.
- ❑ Provide the patient or patient's parents/guardians/carers with suitable written and verbal information about the drug and preparation prior to starting medication and discuss the benefits and side effects of treatment.
- ❑ Carry out initial monitoring requirements as per Shared Care Guideline.
- ❑ As appropriate, liaison with other members of the multidisciplinary team e.g. renal pharmacist, transplant nurse.
- ❑ Ask the GP whether they are willing to participate in shared care.
- ❑ Prescribing the drug for the initial term and/ or until the patient's condition/dose is stabilised and the GP agrees to take over responsibility for prescribing.
- ❑ Specify review dates at clinically relevant time intervals for both the GP and the consultant.
- ❑ Prompt communication with GP of any changes in treatment, results of monitoring undertaken and assessment of adverse events.
- ❑ Provide the GP with relevant contact information with clear arrangements for back-up advice and support should further assistance be required relating to this drug.
- ❑ Reporting adverse events to the CSM.

General Practitioner responsibilities:

- ❑ Reply to request for shared care as soon as practical.
- ❑ Prescribing of **ciclosporin** after communication with the specialist regarding the need for treatment.
- ❑ Undertake monitoring as outlined in the shared care guideline. Blood pressure 4 weekly and lipid level 6 monthly (unless carried out in the renal clinic).
- ❑ Prompt referral to a specialist if there is a change in the patient's status.
- ❑ Report to and seek advice from a specialist on any aspect of patient care that is of concern to the GP and may affect treatment.
- ❑ Report adverse events to specialist and CSM.
- ❑ Stop treatment in the case of a severe adverse event or as per shared care guideline.

Patient responsibilities:

- ❑ Take the **ciclosporin** as prescribed.
- ❑ Report any adverse effects to their GP and/or specialist regarding their treatment.
- ❑ Ensure that they have a clear understanding of their treatment.
- ❑ Ensure they attend for monitoring requirements as per shared care guideline.
- ❑ Aware that treatment will be stopped if patient does not attend for monitoring.
- ❑ Dispose of unused or unwanted **ciclosporin** appropriately.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No:	E-mail address
Dr R D'Souza	(01392) 402587	Richard.DSouza@rdeft.nhs.uk
Dr C Bingham	(01392) 406366	Coralie.Bingham@rdeft.nhs.uk
Dr. H. Clarke	(01392) 406367	Helen.Clarke@rdeft.nhs.uk
Dr.M.Bello-Villalba	(01392) 402191	Maria.Bello@rdeft.nhs.uk
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Dr. C Mulgrew	(01392) 403535	Chris.Mulgrew@rdeft.nhs.uk

Shared Care Agreement Letter - Consultant Request

To: Dr.....

Practice Address: .....

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Patient Name:
Hospital number:
Date of birth:
Address:

DIAGNOSED CONDITION:
.....

I recommend treatment with the following drug:
.....

I am requesting your agreement to sharing the care of this patient according to the Devon Primary Care Trust North and East Devon Health Community Shared Care Prescribing Guidelines for this drug.

Signed:	
Consultant name:	
Department:	
Contact telephone number:	
Date:	

GP RESPONSE

I agree/ do not agree* to share the care of this patient in accordance with the Shared Care Guideline.

Signed: ..... Date: .....

GP name: ..... *Delete as appropriate