### DRUG: Ciclosporin (Neoral®) for Renal Transplant (Adults)

#### Indication:
Prophylaxis of transplant rejection in kidney recipients

Ciclosporin is an immunosuppressant drug with a narrow therapeutic index. It was used in patients who were prescribed it as an initial immunosuppression drug, combined with azathioprine and prednisolone before guidelines changed in 2004. It is now more commonly prescribed for patients who do not tolerate tacrolimus.

Ciclosporin is never used in combination with tacrolimus.

#### Licensing Information:
Prophylaxis of transplant rejection in kidney recipients is one of the licensed indications of ciclosporin.

#### Formulations:
- Neoral® brand of ciclosporin
  - Capsules – 25mg, 50mg, 100mg
  - Oral solution - 100mg/mL

#### Prescribing notes
- When prescribing ciclosporin, all prescribers should state the trade name, formulation (i.e. capsule or oral solution), the dose and the frequency (once daily or twice daily).

- Formulations and brands are NOT interchangeable. Any changes in formulation or brand must be supervised closely by the Consultant nephrologist. The patient must be closely monitored for changes in blood-ciclosporin concentration, serum creatinine, blood pressure and transplant function.
  - The original brand of ciclosporin, Sandimmun® is also listed in the BNF and is available on a patient-named basis. There are still some patients on Sandimmun®.
  - Capimune, Capsorin and Deximune ciclosporin formulations are also listed in the BNF but not routinely prescribed for the renal transplant patients. Because of differences in bioavailability, ciclosporin must be prescribed by brand.

#### Dosage & administration:

### Dosage

Detailed information is available in the product data sheet (SPC).

- Doses of ciclosporin are titrated to a desired trough monoclonal ciclosporin blood level. As a general guide, the levels will reduce over the first months post-transplant. At 3-12 months the levels aimed for...
are usually 100microgram/L to 300microgram/L.

- Doses required to achieve this vary between patients, though they are usually in the range of 100mg to 250mg twice daily at three months post-transplant.

Administration
- Neoral® should be taken twice daily, every twelve hours. On blood monitoring days, the morning dose should be omitted until after the blood is sampled. The 100mg capsule is large and often patients will prefer to take the 50mg strength. 10mg and 25mg strength capsules and 100mg/mL liquid are also available.

- The oral solution can be mixed with orange juice (or squash) or apple juice to improve taste, or mixed with water immediately before taking. Rinse the container with juice or water to ensure the total dose is taken. Do not mix with grapefruit juice.

- The measuring syringe should not be rinsed with water, alcohol or any other liquid. If it is necessary to clean the measuring device, the outside should be wiped with a dry tissue.

Contraindications & Warnings:

**Contraindications :**

- Hypersensitivity to ciclosporin or to any of the other excipients of NEORAL.
- Concomitant use of tacrolimus
- Concomitant use of rosuvastatin (SPC recommendation) or simvastatin (MHRA recommendation Aug 2012)

**Warnings :**

- Suspected non-compliance with immunosuppression therapy is serious and can lead to loss of the graft function. The patient should be referred to the renal physician urgently.

- Pregnancy – patients discovered or planning to become pregnant should be started on folic acid 400micrograms daily and referred to the renal physician at the earliest opportunity. Ciclosporin should be continued.

- The combined oral contraceptive is a suitable option for renal transplant recipients.

**Interactions:**

The patient’s renal function should be taken into consideration when co-prescribing for renal transplant patients. Ciclosporin is metabolised by cytochrome P450 and therefore interacts with many drugs that are also metabolised by this group of liver enzymes.

The following drugs should not be initiated by a GP unless discussed with the renal physician:
### Interacting drugs

<table>
<thead>
<tr>
<th>Interacting drugs</th>
<th>Effects on ciclosporin blood levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin, clarithromycin, azithromycin</td>
<td>Increased</td>
</tr>
<tr>
<td>Diltiazem, nicardipine, lercanidipine, verapamil</td>
<td>Increased</td>
</tr>
<tr>
<td>Fluconazole, itraconazole, ketoconazole</td>
<td>Increased</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Decreased</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Decreased</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Decreased</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Decreased</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Decreased</td>
</tr>
<tr>
<td>St John's Wort</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

### Other interacting agents:

- Simvastatin and rosuvastatin are contra-indicated with ciclosporin
- Atorvastatin should be used at a maximum dose of 10mg daily in combination with ciclosporin
- Pravastatin can be used to a maximum dose of 40mg daily in combination with ciclosporin
- Patients should not drink or eat grapefruit juice or fruit because it can cause increases in ciclosporin levels.
- NSAIDs (and other nephrotoxic drugs) should be used with extreme caution.
- Potassium-sparing medicines may exacerbate ciclosporin-induced hyperkalaemia and should only be initiated with regular monitoring of U&Es.
- Avoid the use of live vaccines

Appendix 1 of the BNF is a useful guide to whether any medicine is likely to cause a problem. If there is a clinical need to use such medicines then this is best undertaken in the renal clinic with careful monitoring of ciclosporin levels.

For full list see SPC at [www.medicines.org.uk/EMC](http://www.medicines.org.uk/EMC)

### Adverse Effects:

The monitoring of adverse effects will not usually require additional routine appointments unless a problem is anticipated:

- **Hypertension**
  
  Hypertension (BP >130/>80mmHg) is a commonly encountered adverse effect which the GP will be best placed to monitor and treat. NICE hypertension guidance for drug selection is suitable for renal transplant recipients.
  
  Patients started on ACE inhibitors or Angiotensin II receptor antagonists (and for subsequent dose increases) should have U&Es checked 14 days later. Creatinine rising by >20% or eGFR falling >15mL/min is not an absolute contra-indication, but this scenario is best managed under
specialist supervision and referral to the renal physician is recommended. A dihydropyridine calcium channel blocker such as nifedipine may be used but diltiazem, nicardipine, felodipine and verapamil should not be used as they may increase plasma ciclosporin levels.

- **Benign gingival hyperplasia**  
  This is relatively common with ciclosporin especially when nifedipine is co-prescribed. Transplant recipients are advised to brush their teeth twice daily.

- **Hirsutism**  
  Hirsutism may be a problem, particularly to dark skinned females. Facial hair bleaches and depilatory creams are safe and often effective but electrolysis should be avoided because of infection risk.

- **Headache, tremor, and paraesthesiae**  
  These adverse effects are frequently seen. If persistent or severe, they may reflect toxic levels of ciclosporin. In this case, the patient should be referred back to the renal physician.

- **Hepatic dysfunction and hyperlipidaemia**  
  Hepatic dysfunction and hyperlipidaemia are screened at outpatient appointments. Hyperlipidaemia patients are prescribed statins (the monitoring of efficacy and adverse effects is then undertaken in the renal clinic as ciclosporin may enhance statin myopathy). Simvastatin is now contra-indicated with ciclosporin. Atorvastatin are not recommended at doses above 10mg once daily. Pravastatin is a suitable licensed alternative and can be prescribed up to doses of 40mg daily.

- **Nephrotoxicity**  
  Can occur with ciclosporin. It can be acute, blood level related nephrotoxicity identified primarily by serum creatinine monitoring which will be undertaken at the hospital. This toxicity may be difficult to distinguish from acute rejection but is reversible by dose reduction. A chronic nephrotoxicity may also occur necessitating withdrawal of this drug.

- **Cancer risk**  
  Like all immunosuppressants, ciclosporin increases the risk of developing lymphomas and other malignancies, particularly those of the skin. The increased risk appears to be related to the degree and duration of the immunosuppression rather than to the use of specific agents.

### Responsibilities of the specialist initiating treatment:

<table>
<thead>
<tr>
<th>General:</th>
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<tbody>
<tr>
<td>- To assess the suitability of the patient for treatment.</td>
</tr>
<tr>
<td>- To ensure that the patient/carer has received counselling and understands the therapy, its benefits, limitations, continued monitoring (where applicable), adverse effects, and is aware of actions to take if</td>
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</tbody>
</table>
adverse effects are suspected.
• Inform the GP of the information provided to the patient.
• To review the patient at agreed intervals and copy any relevant results to the GP
• Carry out disease and drug monitoring as listed below
• Formally hand over to GP by letter and patient informed - send a copy (either electronically or paper copy) of the Shared Care Guideline to the GP and ask whether they are willing to participate in shared care.
• Monitor the patient for adverse events and report to the GP and, where appropriate, the Commission on Human Medicines/MHRA using the Yellow Card scheme

**Prescribing:**
• Secondary care will prescribe ciclosporin for the first 3 months post transplant or until the immunosuppression regimen is stable

**Disease & drug monitoring:**
• Monitor bloods at each hospital appointment, the frequency of which is determined by clinical need.

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea &amp; electrolytes (including calcium &amp; phosphate)</td>
<td>At each hospital appointment</td>
</tr>
<tr>
<td>Full blood count</td>
<td></td>
</tr>
<tr>
<td>Mid-stream urine (for culture &amp; sensitivities)</td>
<td></td>
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<tr>
<td>Whole blood, trough, monoclonal ciclosporin level</td>
<td></td>
</tr>
<tr>
<td>Liver function tests</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td>Lipid screening for total cholesterol</td>
<td>Every 6 months</td>
</tr>
</tbody>
</table>

• Discuss shared care arrangement with patient.
• Support and advise GPs as required.
• Assess response to treatment and initiate any dose changes as clinically appropriate including discontinuation of treatment.

**General and Prescribing:**
• To reply to the request for shared care within 2 weeks of receipt of the Consultant letter.
• Monitor* and prescribe as recommended by the specialist. The GPs will be typically asked to take up the monitoring and prescribing of ciclosporin approximately 3 months after transplantation, or until the patient is on a stable immunosuppressant regimen.
• Ensure the correct brand of ciclosporin is used
• Alert the hospital consultant of any suspected non-compliance with immunosuppressants
• Ensure there are no drug interactions with any other medications initiated in primary care, including avoiding the use of live vaccines

*GP to monitor for side effects, drug interactions etc. Consultant will however do all routine blood monitoring.

**Disease & drug monitoring:**
• Drug monitoring will normally be carried out by secondary care unless
otherwise requested. GP must however ensure smear tests are up to
date for female patients (3 yearly for females aged 25 to 49 and 5
yearly for females aged 50 to 65).

- Urgent referral to specialist as clinically appropriate
- To stop treatment on the advice of the specialist.
- To refer back to the Specialist if the patient’s condition deteriorates.
- To identify adverse effects if the patient presents with any signs and
liase with the hospital Specialist where necessary. To report adverse
effects to the Specialist and where appropriate to the Commission on
Human Medicines/MHRA (Yellow Card scheme).

Responsibilities of the Patient / Carer:

**General :**
- Report any possible side effects to the hospital/GP.
- Ensure they have an adequate supply of medication.
- Attend appointments.
- To report to the hospital or GP if there any questions regarding their
treatment
- To notify the hospital or GP if starting new medicines (including herbal
remedies) and of the purchase of medication over the counter
- To dispose of unused or expired medication appropriately at a
community or hospital pharmacy

**Disease & drug monitoring:**
As above –contact GP or initiating team if side effects develop (see adverse
effects) and attend appointments including those for routine blood
tests/investigations

**Specialist to GP:**
- The specialist will inform the GP when they have initiated ciclosporin,
stating the brand the patient is taking and when there are any
subsequent changes in treatment – standard clinic letter.
- When the patient is near completing a satisfactory initiation period, the
renal physician will send a copy (either electronically or paper copy) of
the Shared Care Guideline to the GP and ask whether they are willing
to participate in shared care and take over prescribing.
- Inform the GP of the information provided to the patient

**GP to Specialist:**
- To reply to the request for shared care within 2 weeks of receipt of the
Consultant letter.
- Irrespective of whether you accept prescribing responsibility or not,
you should inform the consultant of relevant medical information
regarding the patient and changes to the patient’s medication regime
irrespective of indication.
- Notify Consultant immediately if treatment with ciclosporin is
discontinued is if non compliance is suspected.

**Contact names & details:**
If you have any concerns regarding individual patients, see consultant letter
for medical contact details or contact one of the following:
<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Location</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr D Border</td>
<td>Consultant Nephrologist, York &amp; Harrogate</td>
<td>01904 725813 (Sec.)</td>
</tr>
<tr>
<td>Dr C Jones</td>
<td>Consultant Nephrologist, York &amp; Malton</td>
<td>01904 725374 (Sec.)</td>
</tr>
<tr>
<td>Dr P Laboi</td>
<td>Consultant Nephrologist, York &amp; Selby</td>
<td>01904 725813 (Sec.)</td>
</tr>
<tr>
<td>Dr K McCullough</td>
<td>Consultant Nephrologist, York</td>
<td>01904 725393 (Sec.)</td>
</tr>
<tr>
<td>Dr Richardson</td>
<td>Consultant Nephrologist, York</td>
<td>01904 725393 (Sec.)</td>
</tr>
<tr>
<td></td>
<td>Or via switchboard on 01904 631313</td>
<td></td>
</tr>
<tr>
<td>Dr Than</td>
<td>Consultant Nephrologist, Harrogate &amp; York</td>
<td>01904 725393 (Sec.)</td>
</tr>
<tr>
<td>Hazel Wootton or Gillian Taylor</td>
<td>Specialist Transplant Nurses</td>
<td>01904 726617</td>
</tr>
</tbody>
</table>

Other members of the renal team may also be able to offer advice with questions or problems and can be contacted through the hospital switchboard 01904 631313 or the renal unit on 01904 725370.

**Cost:**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoral 25mg capsules</td>
<td>£18.59 for 30</td>
</tr>
<tr>
<td>Neoral 50mg capsules</td>
<td>£36.41 for 30</td>
</tr>
<tr>
<td>Neoral 100mg capsules</td>
<td>£69.11 for 30</td>
</tr>
<tr>
<td>Neoral Oral solution 100mg/mL</td>
<td>£103.55 for 50mL</td>
</tr>
</tbody>
</table>

**References:**

- Leeds Teaching Hospital NHS Trust shared care guidelines for ciclosporin (Neoral®) post adult renal transplant 2008
- British National Formulary 64 (September 2012)

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC (data sheet) or BNF for further prescribing information.

The original Microsoft Word file of this document is located on:
York Teaching Hospital NHS Foundation Trust Pharmacy Department X:\MEDICINES INFORMATION\Shared Care Guidelines\Approved Shared Care Guidelines\CICLOSPORIN (Renal Transplant) Shared Care Guideline V1.0

Shared Care Guidelines also available electronically via [http://www.yorkandscarboroughformulary.nhs.uk/](http://www.yorkandscarboroughformulary.nhs.uk/)

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