

Ciclosporin (Neoral®)

SCG: For Transplant patients

The following guidelines are designed to provide information relating to ciclosporin and to outline the responsibilities of the primary and secondary care teams and patients in the prescribing of ciclosporin.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

Introduction:

Early attempts at organ transplantation without utilising immunosuppressive therapy proved unsuccessful and chemical immunosuppressive agents came into use in the early 1960's, increasing one year survival rates. The discovery of ciclosporin, introduced in 1978, was a major advance in immunosuppressive therapy, and by the mid 1980's most immunosuppressive therapy regimens were ciclosporin based. A further advance in ciclosporin was the development of Neoral®, a pre-concentrated formulation of ciclosporin which undergoes microemulsification in the presence of water, thus giving more consistent absorption allowing greater predictability and consistency of plasma levels than with the Sandimmun® formulation.

RESPONSIBILITIES and ROLES

Specialist responsibilities (Transplant team):

- Initially prescribe and stabilise the patient on the treatment regimen and monitor transplant graft function
- Measure ciclosporin blood levels and advise changes of dose to patient and GP
- Provide patients with a current medication record book ("blue book")
- Monitor efficacy of the treatment and side effects.
- Provide access to back up and support facilities.
- Evaluate any adverse events reported by the patient or GP (all potential adverse events should be reported to the CHM (MHRA)).
- Educate patients in knowledge of drug therapy to maximise compliance and be aware of when to seek medical attention.

General Practitioner's responsibilities:

- Prescribe ciclosporin maintenance therapy once the patient is stabilised on therapy and side effects have been excluded as far as possible by the hospital. Dosage instructions will be provided by the Transplant Unit.
- Encourage patients to complete their daily medication record and document any changes to therapy in the "blue book".
- Check for possible drug interactions when newly prescribing or stopping concurrent medication.
- Report any suspected adverse events to the Transplant Unit (all potential adverse events need to be reported).
- Monitor blood counts and discuss any abnormalities with the Transplant Unit.

Patient's role:

1. Take the ciclosporin (Neoral[®]) as prescribed and complete daily medication record in their "blue book".
2. Notify any adverse events to GP and Transplant Unit.
3. Notify use or intended use of over the counter (OTC) and herbal medications.
4. Ensure they attend for monitoring as per shared care guideline.

BACK-UP ADVICE AND SUPPORT

Papworth Hospital Main Switchboard	01480 830541
Transplant Unit Reception	01480 364455
Transplant Co-ordinator	page via switchboard 01480 830541
Pharmacy Medicines Information Service	01480 364179 Mon-Fri 9 am – 5 pm
Transplant Pharmacist	01480 364179 (Bleep 931)
Consultant Transplant Cardiologist:	Dr Jayan Parameshwar
Consultant Transplant Cardiologist:	Dr Clive Lewis
Consultant Transplant Pulmonary Physician:	Dr Jas Parmar

Out of hours, contact the on-call pharmacist via switchboard.
Consultant and medical staff are always available to give advice and can be contacted through the main hospital switchboard on: 01480 830541

SUPPORTING INFORMATION

Licensed Indications:^{1,2}

Ciclosporin is licensed for the prevention of graft rejection following kidney, liver, heart, combined heart-lung, lung, bone marrow or pancreas transplants and in a variety of other disorders (GVHD, psoriasis, atopic dermatitis and rheumatoid arthritis).

Dosage and Administration:

Ciclosporin is usually given twice a day, the dose given is adjusted to maintain whole blood trough levels within the target range. The dose is adjusted based on renal function and trough concentrations, which vary depending on the organ involved and time from transplant. With time the risk of rejection decreases and the dose can be reduced to give lower maintenance blood levels.

Some of our patients, especially those with cystic fibrosis may require three times daily doses to maintain adequate ciclosporin levels.^{3,4} To further improve absorption pancreatic insufficient patients with cystic fibrosis are advised to take pancreatic enzyme supplements at the same time as their immunosuppression.

It is important for patients to be instructed to take ciclosporin at the same times each day so that trough levels are representative of the true value when they return to hospital for monitoring blood levels. Patients are instructed not to take their ciclosporin on the morning of their clinic visit until after their blood test so that blood levels taken represent trough concentrations.

Contraindications - in transplantation:

Known hypersensitivity to ciclosporin. Concomitant use of tacrolimus.

Therapeutic Use:

All new patients and almost all existing patients have been stabilised on the Neoral[®] brand. Ciclosporin is a critical dose drug, due to the different absorption profiles of the different ciclosporin preparations it is necessary to specify the brand (i.e. Neoral[®] or Sandimmun[®]) to be dispensed when prescribing. It is advised that patients are maintained on the brand of ciclosporin which they have been stabilised on by the Transplant Unit.

The BNF now contains the statement "Patients should be stabilised on a single brand of oral ciclosporin because switching between formulations without close monitoring may lead to clinically important changes in blood-ciclosporin concentration. Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching. If it is necessary to switch a patient stabilised on one brand of ciclosporin to another brand, the patient should be monitored closely for changes in blood-ciclosporin concentration, serum creatinine, blood pressure, and transplant function".¹

Side Effects:

All immunosuppressive agents are powerful and potentially toxic drugs, and therefore adverse events may be observed. Any adverse effects detected should be reported directly to the Transplant Unit - **it is vital that drug doses are not changed without first consulting the Transplant Unit.**

The following are adverse events which may be observed in patients taking ciclosporin:

- Nephrotoxicity
- Hyperkalaemia
- Hyperlipidaemia
- Hypertension
- Hyperuricaemia
- Hepatic dysfunction
- Hypertrichosis
- Gingival Hypertrophy
- Susceptibility to **infection** (bacterial, viral, fungal and protozoal is increased in patients receiving immunosuppressive therapy)
- **Tremor, burning sensation** in the hands and feet and **headache** are common side effects. Only occasionally severe enough to warrant dose reduction.

Malignancy, especially lymphomas caused by oncogenic viruses and skin tumours are more common in immunosuppressed patients.

The list is not exhaustive and the summary of product characteristics and BNF should be consulted for a comprehensive list of adverse events.

Monitoring:

Secondary Care (at each Outpatient Clinic appointment):

- Trough levels are usually taken to monitor levels. A C2 level (level taken 2 hours after a dose) is also analysed for some patients. Patients are instructed not to take their ciclosporin on the morning of their clinic visit so that blood levels taken represent trough concentrations. If levels are required in addition to this, the transplant unit will give written notification.

- Blood creatinine, urea and electrolytes to monitor renal function
- Liver function
- Blood pressure
- Compliance with medication regime
- Monitor for drug interactions.

Primary Care:

- Blood creatinine, urea and electrolytes to monitor renal function every 6 months after year 2 post transplant between Outpatient Clinic appointments
- Liver function
- Blood pressure
- Monitor for drug interactions
- Take blood sample for ciclosporin level (trough) on written request of the Transplant Unit.

Drug Interactions:^{1,2,5.}

Many drugs, including ciclosporin, are metabolised via the microsomal cytochrome P-450 enzyme system in the liver. Some drugs have the effect of inhibiting P-450 thereby increasing available ciclosporin in the blood to potentially toxic levels. Others induce the enzyme promoting the degradation of ciclosporin to sub therapeutic levels. Herbal medicines can also affect ciclosporin efficacy either by direct effect on the P-450 system (eg St John's Wort) or indirectly by antagonising the immunosuppressant effect of ciclosporin (eg echinacea).

For advice on ciclosporin interactions please do not hesitate to contact the pharmacy Medicines Information Department. The following list is **not** exhaustive and the summary of product characteristics and BNF should be consulted for a comprehensive list of drug interactions. These drugs are not contraindicated in patients receiving ciclosporin but dose adjustment of the latter may be required.

1. **Drugs which may decrease ciclosporin levels:**

Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, sulfadimidine i.v.; rifampicin, rifabutin, octreotide, probucol, orlistat, St John's Wort, ticlopidine, sulfapyrazone, terbinafine, bosentan griseofulvin.

2. **Drugs which may increase ciclosporin levels:**

Acetazolamide, allopurinol, amiodarone, azithromycin carvedilol, chloroquine, cimetidine, clarithromycin, colchicines danazol, diltiazem, doxycycline, erythromycin, fluconazole, fluoxetine, fluvoxamine, glibenclamide, hydroxychloroquine, itraconazole, ketoconazole, lercandipine, metoclopramide, methylprednisolone (high dose), metronidazole, nefazodone, nicardipine, norfloxacin, oral contraceptives, posaconazole, protease inhibitors (imatinib) propafenone, ursodeoxycholic acid, verapamil, vitamin E, voriconazole.

3. **Drugs which may potentiate the risk of muscle toxicity:**

Colchicine, lipid lowering drugs ("statins" and "fibrates", particularly when used in combination).

4. **Drugs which may potentiate hyperkalaemia:**

ACE inhibitors, potassium sparing diuretics, potassium supplements.

5. **Drugs which may potentiate ciclosporin nephrotoxicity:**

Aminoglycosides, amphotericin B, ciprofloxacin, colchicine, NSAID's, thiazide diuretics, trimethoprim, ACE inhibitors.

6. **Drugs which may potentiate gingival hypertrophy:**
Nifedipine, phenytoin.

NB

- Vaccines may be less effective in immunocompromised patients.
- Live vaccines should be avoided.
- Grapefruit juice increases plasma ciclosporin concentration. Where possible it's use should be avoided or a consistent intake advised (but not within the hour preceding a dose of ciclosporin).

Cost:

Funding of medicines for cardiothoracic transplantation outside the hospital setting, whether pre or post transplant is the responsibility of the patient's Primary Care Trust. As directed by the Department of Health National Specialist Commissioning Advisory Group (NSCAG) in August 2002, PCTs need to ensure that funding for post transplant drug treatment is made available for patients. **As soon as a GP is made aware of a patient requiring an expensive medicine, they are advised to discuss the funding mechanisms for it with their PCT prescribing manager.**

Availability:

Ciclosporin (Neoral®) is available from Novartis to be prescribed in packs of 60 capsules of 10 mg, 30 capsules of 25mg, 50mg and 100mg and as a 50ml bottle of oral solution 100 mg / ml. Community pharmacies can obtain Neoral® from local wholesalers within 24 hours. If wholesalers are unable to supply then Novartis Customer Care Hotline tel: 08457419442 should be contacted to arrange a supply direct from the manufacturer.

Ciclosporin (Sandimmun®) is only available on a named patient basis from Novartis for patients unable to convert to the Neoral® preparation.

Other preparations of ciclosporin have not been used by Papworth Hospital.

References:

1. BNF. Number 63. March 2012.
2. Summary of Product Characteristics - Neoral®. Accessed via emc.medicines.org on 06/06/2012. Last updated 24/02/2012.
3. Deierhoi MH *et al.* Review of select transplant subpopulations at high risk of failure from standard immunosuppressive therapy. *Clinical Transplantation*. 2000; 14(5): 439-448.
4. Knoop C *et al.* Ciclosporin pharmacokinetics and dose monitoring after lung transplantation: comparison between cystic fibrosis and other conditions. *Transplantation*. 2003; 76(4): 683-688.
5. Stockleys Drug Interactions. Accessed via medicinescomplete.com on 06/06/2012.

Guidelines::

Reviewed by: KV 2006 Approved by: Drugs and Therapeutics Committee November 2006.

Reviewed by: LP, Transplant Directorate Pharmacist

Approved by: Transplant Steering Group 07/2010

Approved by: Drugs and Therapeutics Committee 07/2010

Reviewed by: HC, Transplant Directorate Pharmacist 06/2012

Approved by: Transplant Steering Group 06/2012

Approved by: Drugs and Therapeutics Committee Chairman's action 09/2012