Cambridgeshire and Peterborough
Clinical Commissioning Group

Shared Care Guideline

Ciclosporin (Neoral®) – in inflammatory bowel disease

Executive Summary

- Unlicensed indication, but widely established use of ciclosporin.
- Starting dose of 5-8mg/kg (in twice daily divided doses).
- Further dosing will be altered to maintain whole blood trough levels between 150-250mcg/L.
- Prescribing must be brand specific to avoid clinically significant changes in whole blood levels.
- Patients should take doses 12 hours apart.
- Patients should not take dose of ciclosporin the morning of trough levels until blood has been taken.
- Treatment will continue for approximately 3 months before weaning during initiation of thiopurines.
- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope

Trust and general practice in adult patients.

2. Aim

To induce a sustained period of remission of symptoms for patients with inflammatory bowel disease.

3. Introduction

Ciclosporin is used as a disease modifying agent to manage severe ulcerative colitis or steroid refractory disease not requiring immediate surgery. Although unlicensed to treat these indications, its use is established in the management of inflammatory bowel disease. Its use requires close monitoring. This shared care guideline outlines the responsibility of primary and secondary care clinicians using ciclosporin in inflammatory bowel disease.

4. Abbreviations

- BP- blood pressure
- FBC- full blood count
- GP- general practitioner
- LFTs- liver function tests
- U&Es- urea and electrolytes
- NSAIDs- non-steroidal anti-inflammatory drug
- IBD- inflammatory bowel disease
- mg- milligram
- kg- kilogram
- mcg- microgram
- L- litre
- SPC- summary of product characteristics
- BNF- British National Formulary
- OATP- organic anion transporter proteins
- CYP- cytochrome
- ALT- Alanine transaminase
- AST- Aspartate transaminase

5. Dose and Administration

Specific to IBD – other conditions may be prescribed alternative doses

Note: Patients should be stabilised on Neoral® brand of ciclosporin and should not be switched. This could lead to clinically important changes in blood ciclosporin levels. Prescribing should be done by brand name to avoid inadvertent switching.

- Starting dose of 5-8 mg/kg/day (in twice daily divided doses).
- Doses are subsequently altered according to ciclosporin whole blood trough levels to maintain between 150-250mcg/L
- Advise patients to take ciclosporin at the same time each day with doses 12 hours apart so that trough levels are representative.
- Advise patients not to take ciclosporin on the morning of blood level monitoring until after their blood test so that the level taken represents true trough levels.
- Treatment would continue for approximately 3 months, if effective, before weaning in conjunction with introduction of thiopurines.
    - Thiopurines would be initiated once dose of prednisolone is 15mg.
    - Weaning of ciclosporin would not commence until thiopurine metabolite levels had been taken & therapy optimised.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/1307

6. Adverse Effects

Side effect	What to do
Very common (≥1/10): hyperlipidaemia, tremor, headache, hypertension, hirsutism, renal dysfunction	See hypertension and hyperlipidaemia guidance below. If efficacy has been established, it is preferable to treat the hirsutism with depilatories. If mild tremor or headache, most of these subside as treatment becomes established. Consider dose reduction or stop and contact hospital specialist or IBD nurses if continues.
Common (≥1/100, <1/10): nausea, vomiting, diarrhoea, peptic ulcer, hepatic function abnormal, hypertrichosis, myalgia, muscle cramps, pyrexia, paraesthesia, abdominal discomfort, leucopenia, hyperglycaemia, anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia, convulsions, flushing, gum hyperplasia, acne, fatigue	If mild, most of these subside as treatment becomes established. Consider dose reduction or stop and contact hospital specialist or IBD nurses if continues. If efficacy has been established, it is preferable to treat gum hyperplasia with oral hygiene, rather than stopping ciclosporin
Rare (≥1/10,000, <1/1,000): haemolytic uraemic syndrome, microangiopathic haemolytic anaemia, motor polyneuropathy, pancreatitis, muscle weakness, myopathy, menstrual disturbances, gynaecomastia	Thought to occur with a similar frequency as in patients on other immunosuppressives. Contact Hospital specialist immediately if suspected.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/1307

7. Cautions

See BNF (8.2.2) or SPC for Neoral for full list.

- **Potential nephrotoxicity**: see monitoring section below
- **Potential hepatotoxicity**: see monitoring section below
- Caution with concomitant non-steroidal anti-inflammatory drug (NSAIDs), in particular diclofenac which increases plasma concentration of ciclosporin. The dose of diclofenac should be halved, if used concomitantly. See drug interactions below.
- Patients should avoid 'live' vaccines, for further details see below.
- Patients should try and avoid contact with people that have active chicken pox or shingles and should report any such contact urgently to their GP or specialist.
- Switching between brands should be avoided due to differences in bioavailability.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/1307

8. Contraindications

See BNF (8.2.2) or SPC for Neoral for full list.

- Known hypersensitivity to ciclosporin
- Uncontrolled hypertension
- Uncontrolled infections
- Malignancy
- Abnormal baseline renal function
- Patients taking 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.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/1307

9. Interactions

See Appendix 1 for a list of common drug interactions

- **Drug interactions with ciclosporin are common** so check BNF appendix 1 and www.medicines.org.uk for significant interactions before prescribing.
- If in doubt of how to manage drug interactions contact hospital specialist or IBD nurses.
- Ciclosporin is an inhibitor of CYP3A4 & P-glycoprotein

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/1307

10. Pregnancy and breast feeding

Ciclosporin is in general contraindicated during pregnancy. In exceptional cases the decision may be taken by the specialist that the benefits of continuing treatment outweigh the risks. There is limited human data.

Ciclosporin is contraindicated in breastfeeding.

Men and women planning pregnancy should stop the drug three months before conception. There is limited data on the effect of Ciclosporin on fertility.

11. Immunisations

Avoid live vaccines. Annual influenza vaccine recommended.

12. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

	Whose responsibility	Monitoring to be done	Frequency to be done
Pre-treatment	Hospital gastroenterology team	Renal function LFTs U&Es FBC Magnesium BP	• BP and renal function to check at least twice before starting
Initiation to stabilisation	Hospital gastroenterology team	Renal function LFTs U&Es FBC BP	• Weekly for 2-3 weeks • Monthly thereafter
		Ciclosporin levels (Whole blood trough levels. Target 150-250mcg/L)	• Weekly for 2-3 weeks • Monthly thereafter Dependant on individual response and assessment
Ongoing monitoring once stable (as assessed by IBD nurses)	GP	Renal function LFTs U&Es FBC BP	Monthly
		Ciclosporin levels (Whole blood trough levels. Target 150-250mcg/L)	Monthly

Blood test results	
eGFR< 25% from baseline	Monitor closely and reduce the dose of ciclosporin by 25% to 50%. If fails to normalise within one month, contact hospital specialist or IBD nurse and consider stopping the drug.

<35% from baseline	Further reductions should be considered. If dose reductions are not successful in improving eGFR within one month, contact hospital specialist or IBD nurses and consider stopping the drug.
Potassium rises to above reference range	Withold ciclosporin until discussed with the gastroenterology team.
Platelets <150 x 10^9 /l	
Significant rise in fasting lipids	
High BP: >140/90 on two consecutive readings two weeks apart	Treat BP before stopping ciclosporin (note interactions with several antihypertensives). If BP cannot be controlled, stop ciclosporin and achieve BP control before restarting ciclosporin. Discuss with the gastroenterology team.
Alanine transaminase (ALT), aspartate transaminase (AST) or alkaline phosphatase more than two x upper limit of normal	Withold until discussed with the gastroenterology team. Check any other reason such as alcohol and drug interactions, including over-the–counter medication
Abnormal bruising/ bleeding	Check FBC immediately and withold ciclosporin until discussed with the gastroenterology team

13. Shared Care Responsibilities

a. Hospital specialist:

- Send a letter to the GP requesting shared care for the patient.
- Inform GP of patients who do not attend clinic appointments.
- To provide any advice to the patient/carer when requested.
- Initiate treatment and prescribe the first month of treatment.
- Routine clinic follow-up on a regular basis.
- Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
- Evaluation of any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment where necessary.
- Ensure that backup advice is available at all times.

b. General Practitioner:

- Agreement to shared care guideline by the GP.
- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.
- Monitor patient's overall health and well-being.
- Prescribe the drug treatment as described.
- Monitor blood results in line with recommendations from hospital specialist.
- Help in monitoring the progression of disease.
- Complete blood monitoring details in Patient Held Record Book.

c. Patient or parent/carer:

- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant).
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or GP.

14. Contact numbers for advice and support

GPs to contact the gastroenterologist registrar on call via Addenbrookes switchboard in the first instance via 01223 245151

Cambridge University Hospital NHS Foundation Trust		
Specialist	**Post**	**Telephone**
Inflammatory Bowel Disease Helpline for Patients		01223 257212 (voice mail)
Dr Miles Parkes	Consultant Gastroenterologist	01223 216389
Dr Jeremy Woodward	Consultant Gastroenterologist	01223 596231
Dr GD Corbett	Consultant Gastroenterologist	01223 256887
Dr Dunecan Massey	Consultant Gastroenterologist	01223 256983
Dr Stephen Middleton	Consultant Gastroenterologist	01223 217467
Dr Ewen Cameron	Consultant Gastroenterologist	01223 348718
Dr Tim Raine	Consultant Gastroenterologist	01223 216389
Prof Arthur Kaser	Consultant Gastroenterologist	Ext 768308
Sr Allison Nightingale	Inflammatory Bowel Disease Nurse Specialist	01223 217990 **(for GPs to contact for advice)**

15. Monitoring compliance with and the effectiveness of this document

Gastroenterology will regularly review their incidents and feedback from GPs with regard to the use of this drug and update the guideline accordingly.

16. Equality and Diversity Statement

This document complies with the Cambridge University Hospital NHS Foundation Trust service Equality and Diversity statement.

17. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

18. Document management

Document ratification and history	
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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/1307

Appendix 1: Common drug interactions

^ = may increase ciclosporin levels; **v** = may decrease ciclosporin levels

ACE inhibitors			**May potentiate hyperkalaemia**
Aldosterone antagonists			**May potentiate hyperkalaemia**
Amiodarone	**^**		
Aminoglycosides			**Increased risk of nephrotoxicity**
Angiotensin-II Receptor antagonists			**May potentiate hyperkalaemia**
Barbituates		**v**	
Calcium-channel blockers	**^**		
Carbamazepine		**v**	
Carvedilol	**^**		
Colchicine			**May increase exposure to colchicine, resulting in an increased risk of myotoxicity**
Diclofenac			**Use half dose (see NSAIDs)**
Digoxin			**Increased plasma concentration of digoxin**
Ezetimibe	**^**		
Fibrates			**May increase risk of renal impairment**
Grapefruit juice	**^**		
Hydroxychloroquine	**^**		
Macrolides	**^**		
Methylprednisolone (high dose)	**^**		
Metoclopramide	**^**		
Metronidazole	**^**		
Non-steroidal anti-inflammatory drugs (NSAIDS)			**May potentiate nephrotoxicity**
Phenytoin		**v**	
Potassium sparing diuretics			**May potentiate hyperkalaemia**
Potassium supplements			**May potentiate hyperkalaemia**
Quinolones			**Increased risk of nephrotoxicity**
Rifampicin		**v**	
St John's Wort		**v**	
Statins			**Increased risk of myopathy**
Triazole antifungals	**^**		**Dose reductions may be required. Contact specialist prior to initiation. Ciclosporin dose should be reduced by 70-80% when used with ketoconazole.**
Trimethoprim			**Increased risk of nephrotoxicity**