Cambridge University Hospitals NHS
NHS Foundation Trust

NHS
Cambridgeshire and Peterborough
Clinical Commissioning Group

Shared Care Guideline

Ciclosporin for inflammatory dermatoses

Executive Summary

- Ciclosporin is currently licensed to treat psoriasis and atopic eczema; however is also used to treat other skin conditions such as bullous pemphigoid, hidradenitis suppurativa, lichen planus, pyoderma gangrenosum, urticaria and vasculitis.
- **Starting dose of 2.5- 5mg/kg/day (in two divided doses 12 hours apart)**
- Ciclosporin trough levels are generally not checked when prescribing for dermatological indications, but regular monitoring of renal function is required.
- Whole grapefruit or grapefruit juice should be avoided whilst on ciclosporin.

  Switching between brands of ciclosporin should be avoided due to differences in bioavailability.
- Ciclosporin has many drug-disease, drug-food and drug-drug interactions including with over-the-counter drugs. In particular, NSAID co-administration should be used with caution.
- The prescriber must check for drug interactions whenever a new medication is started and/or a new disease state is identified in the patient.
- Ciclosporin must not be taken by women who are pregnant or breast feeding, nor by the male partner of a woman trying to conceive.
- Ciclosporin is generally not a cure, but is used to induce a period of remission. A course of treatment is usually 3-6 months to minimise long-term risk, but can be repeated.
- 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

Prescribing and Monitoring by General Practitioners for adults and children.

2. Aim

Ciclosporin is not a cure. It is used to induce a reduction in symptoms, and possibly a period of remission in patients with inflammatory skin conditions. Its initiation and use require close monitoring.

3. Introduction

Ciclosporin is used as an immunosuppressant in the treatment of several skin diseases. It is licensed to treat psoriasis and atopic eczema, however can also be used in the treatment of bullous pemphigoid, hidradenitis suppurativa, lichen planus, pyoderma gangrenosum, urticariaurticarial, vasculitis and other conditions.

Systemic immunosuppressants such as ciclosporin are generally considered where topical therapy and/or phototherapy have been ineffective, or where it is necessary to get the skin under control quickly.

Ciclosporin is generally not a cure, but is used to induce a period of remission. A course of treatment is usually 3 – 6 months to minimise long-term risk, but can be repeated.

This shared care guideline outlines the responsibility of primary and secondary care clinicians using ciclosporin in inflammatory dermatoses.

4. Abbreviations

- AIIRA angiotensin-II-receptor antagonist
- ACE inhibitor angiotensin-converting enzyme inhibitor
- ALT alanine transaminase
- BAD British Association of Dermatologists
- BNF British National Formulary
- BP blood pressure
- CK creatinine kinase
- FBC full blood count
- GP general practitioner
- kg kilogram
- LFTs liver function tests
- mg milligram
- NSAID non-steroidal anti-inflammatory drug
- PUVA psoralen ultra-violet A
- RA rheumatoid arthritis
- RFTs renal function tests
- SPC summary of product characteristics
- U&Es urea and electrolytes (including creatinine)
- UV ultra violet light

5. Dose and Administration

Patients should be stabilised on a licensed brand of ciclosporin and patients should not be switched to other brands.

- Starting dose of 2.5- 5mg/kg/day (in two divided doses)
- May be increased until clinically effective to a maximum dose of 5mg/kg/day.
- One treatment course is normally between 3 – 6 months
- A lower 'maintenance' dose may be used, again in two divided doses.
- Patients with atopic eczema may flare quickly on withdrawal of ciclosporin, so may benefit from tapered reduction / initiation of further concurrent therapy such as azathioprine or methotrexate.

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.	If efficacy has been established the hirsutism can be treated with depilatories. If mild tremor or headache, these generally subside as treatment becomes established. If problems continue, then consider dose reduction or stop and contact hospital specialist or dermatology nurses.
Common (≥1/100 to <1/10): nausea, vomiting, diarrhoea, peptic ulcer, hepatic dysfunction, hypertrichosis, myalgia, muscle cramps, pyrexia, paraesthesia, abdominal discomfort, leucopenia, hyperglycaemia, anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia, gum hyperplasia, acne, fatigue.	If mild, most of these subside as treatment becomes established. Consider dose reduction or stop and contact hospital specialist or dermatology nurses if continues. Gum hyperplasia may be prevented / treated with good oral hygiene.
Rare (≥1/10,000 to <1/1,000): lymphoproliferative disorders and other malignancies, haemolytic uraemic syndrome, microangiopathic haemolytic anaemia, 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 (SPC):
http://www.medicines.org.uk/emc/medicine/1307

7. Contraindications

- Known hypersensitivity to ciclosporin
- Uncontrolled hypertension
- Uncontrolled infections, especially herpes simplex virus
- Malignancy- patients should be up to date with recommended screening, e.g. cervical smear
- Abnormal baseline renal function
- Avoid concurrent UV therapy
- 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 concentrations are associated with serious and/or life threatening events e.g. bosentan, dabigatran etexilate and aliskiren.
- Other drugs contraindicated with ciclosporin – see drug interactions below
- Pregnancy – see section 10 below
- Breast feeding – see section 10 below

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

8. Cautions

See BNF (chapter 8) or SPC for Neoral® for full list.

- **Potential nephrotoxicity**: 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.
- Patients should avoid 'live' vaccines, for further details see below.
- Grapefruit juice should be avoided as this increases the plasma concentration of ciclosporin.
- 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.
- Patients should be advised to avoid exposure of unprotected skin to the sun.
- Patients should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy
- Drugs that must always be avoided if ciclosporin is prescribed include:

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

9. Interactions

Ciclosporin is an inhibitor of CYP3A4 & P-glycoprotein.

Drug interactions with ciclosporin are common. A wide range of drugs may interact leading to clinically significant drug interaction, therefore for each patient check the BNF and www.medicines.org.uk for significant interactions before prescribing. A direct link to the Summary of Product Characteristics for Neoral® (ciclosporin) is http://www.medicines.org.uk/emc/medicine/1307

See also appendix 1.

If in doubt of how to manage drug interactions, contact hospital specialist.

10. Pregnancy and breast feeding

- Ciclosporin is generally contraindicated in 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 breast feeding as it is present in breast milk.
- Men and women planning pregnancy should stop ciclosporin three months before conception. There is limited data on the effect of ciclosporin on fertility.

10. Immunisations

- Avoid live vaccines (although shingles vaccine – Zostavax is not contraindicated with oral DMARDS).
- Annual influenza vaccine recommended

11. Monitoring standards & actions to take in the event of abnormal test results/symptoms

Pre treatment, by hospital team:

- Varicella status. Consider immunisation in non-immune patients.
- Quantiferon (TB)
- HIV testing
- Hepatitis virology screen
- Baseline creatinine: 2 levels and mean value calculated
- U&Es
- CK
- Uric acid
- FBC
- LFT
- Lipid profile
- Blood pressure (at least twice before starting treatment). Check BP≤140/09mmHg, treat hypertension before commending ciclosporin.
- Blood glucose
- Urinalysis
- Consider contraception requirement
- In adult patients, check up to date with recommended screening
- In paediatric patients, ensure childhood vaccinations are up to date (further information available in 'The Green Book: Immunisation against Infectious Disease')

During therapy, by GP (or hospital team if attending hospital):

All results to be recorded in patient held monitoring booklet

- Creatinine, electrolytes and BP fortnightly until dose stable for 3 months, then monthly
- FBC and LFT monthly
- Fasting lipid profile 1 month after starting treatment

Blood test results:

Result	Action
Creatinine: **>30% above baseline** **>50% above baseline**	Repeat creatinine in one week, and if still >30% above baseline contact dermatology team. **Stop** drug and contact dermatology team immediately.
Potassium rises to above reference range (>5.2mmol/L)	Withhold ciclosporin until discussed with dermatology team.

Platelets < 150 x 10^9/L	Withhold ciclosporin until discussed with dermatology team.
Significant rise in fasting cholesterol and/or triglycerides	In the event of raised lipids discuss with dermatology team. Consider restriction of dietary fat/lifestyle factors/dose reduction.
High BP: >140/90mmHg on two consecutive readings two weeks apart	Discuss with dermatology team- consider treating BP (e.g. with amlodipine) before stopping ciclosporin (note interactions with several antihypertensives).
Alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase or serum bilirubin more than two times upper limit of normal	Withhold until discussed with dermatology team. Check any other reason such as alcohol, drug interactions, including over-the-counter medication, viral infection
Abnormal bruising/bleeding	Check FBC immediately and withhold ciclosporin until discussed with dermatology team

Symptoms / side effects and actions to take

Symptoms/side effects	Action
• Nausea, tremor, paraesthesia, headache or abdominal discomfort.	Occur commonly but most subside as treatment becomes established if mild. If symptoms are severe, not tolerated or do not resolve after ongoing treatment, discuss with the hospital dermatology team.
• Hyperuricaemia, hirsutism, gum hyperplasia.	Occur less commonly. If efficacy with ciclosporin is established, treat hirsutism with depilatories and gum hyperplasia with oral hygiene. If symptoms are severe, not tolerated or not controlled, discuss with the hospital dermatology team.
• Lymphoproliferative disorders and other malignancies.	Occur rarely and are thought to occur with a similar frequency to or immunosuppressant drugs. **Stop treatment with ciclosporin** and contact hospital dermatology team immediately.
• Abnormal bruising and/or bleeding	Check FBC immediately and withhold ciclosporin until discussed with the hospital dermatology team.

12. Shared Care Responsibilities

a. Hospital specialist:

b. Carry out pre-treatment monitoring, confirm suitability of ciclosporin therapy and gain patient's informed consent to treatment.

c.

- 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.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring ensuring this states the current dose most recent blood results and frequency of monitoring.
- Evaluation of any reported adverse effects reported by the GP or patient.
- Advise the GP on review, duration or discontinuation of treatment where necessary

d. 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 the disease.
- Complete blood monitoring details in Patient Held Record Book.

e. 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.

13. Contact numbers for advice and support

Cambridge University Hospital NHS Foundation Trust		
Specialist	**Post**	**Telephone**
Dr NP Burrows	Consultant Dermatologist	01223 216459
Dr SK Chan	Consultant Dermatologist	01223 216501
Dr JK Gass	Consultant Dermatologist	01223 216501
Dr N Flanagan	Consultant Dermatologist	01223 586678
Dr TKK Ha	Consultant Dermatologist	01223 216459
Dr SS Haque Hussain	Consultant Dermatologist	01223 216501
Dr PG Norris	Consultant Dermatologist	01223 216459
Dr JC Sterling	Consultant Dermatologist	01223 216501
Dr JM Thomas	Consultant Dermatologist	01223 216459
Dr PM Todd	Consultant Dermatologist	01223 216459
Dr MP Wallace	Specialist Sister	01223 217391
CNS Jane Day	Specialist Sister	01223 217391
CNS Fiona Toh	Specialist Sister	01223 217391
CNS Jacqueline Tomlinson	Specialist Sister	01223 217391
On-call Dermatology Registrar available from 8am – 8pm Monday to Friday via switchboard		

14. Monitoring compliance with and the effectiveness of this document

Dermatology will regularly review their incidents and feedback from GPs with regard to the use of this drug and update the guideline accordingly. The patient held results booklet will be inspected at each outpatient attendance.

Equality and Diversity Statement

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

Disclaimer

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Document Management

Document ratification and history	
Approved by:	Cambridge University Hospitals NHS Foundation Trust Joint Drug and Therapeutics Committee (JDTC)
Date approved:	19 March 2019
Submitted for ratification by:	Cambridgeshire and Peterborough Joint Prescribing Group (CPJPG)
Date ratified:	17 January 2019
Date placed on CPJPG website:	03 May 2019
Review date:	January 2021
Obsolete date:	April 2021
Supersedes which document?	Version 1, June 2016
Authors:	Dr SS Haque Hussain, Consultant Dermatologist Dr PG Norris, Consultant Dermatologist Narinder Bhalla, Consultant Pharmacist
Owning Provider Trust:	Cambridge University Hospitals NHS Foundation Trust
File name:	SCG Ciclosporin for inflammatory dermatoses Version2 January 2019.doc
Version number:	2
CUH document ID:	100004

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

Drug	Increased ciclosporin levels	Decreased ciclosporin levels	Other effects
ACE Inhibitors			May potentiate hyperkalaemia
Aldosterone antagonists			May potentiate hyperkalaemia
Amiodarone	^		
Aminoglycosides			Increased risk of nephrotoxicity
Angiotensin II Receptor antagonists			May potentiate hyperkalaemia
Barbiturates		v	
Calcium channel blockers	^		
Carbamazepine		v	
Carvedilol	^		
Colchicine			My increase exposure to colchicine, resulting in an increased risk of myotoxicity
Diclofenac			Use half dose (see NSAIDs)
Digoxin			Increased plasma concentration of digoxin
Ezetimebe	^		
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