Ciclosporin

Referral Criteria

- These guidelines are for patients over 16 years of age.
- Shared Care is only appropriate if it provides the optimum solution for the patient.
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patients' GP
- Safe prescribing must be accompanied by effective monitoring
- When transfer is agreed, the patient will be given a supply of ciclosporin sufficient for 4 week maintenance therapy
- **The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.**

SHARED CARE RESPONSIBILITIES

Consultant

- Undertake the necessary testing to confirm a diagnosis for which ciclopsorin treatment is recommended.
- Ensure the patient's concurrent drug therapy is stabilised and there are no contra-indications to treatment with ciclopsorin
- Discussion with the patient regarding benefits and side effects of treatment. Ensure patient understands their treatment regime, monitoring and follow up. Provide appropriate patient information leaflet.
- Ensure the patient understands the shared care agreement and has signed the Patient Agreement Letter (page 7-8)
- Perform pre-treatment screening (see Monitoring section) and provide results to GP.
- Ensure documented normal cervical smear within recommendations of the national programme.
- Check skin for pre-existing skin malignancy
- Initiate treatment and prescribe until the patient has been on a stable dose for minimum of SIX weeks
- To send a letter to the GP requesting shared care and enclose shared care agreement
- Review the patient in outpatients as clinically appropriate and advise the GP promptly after these reviews on when to adjust the dose, stop treatment or consult with the specialist.
- To send a letter/ result notification after each clinic attendance including current dose, most recent blood results and frequency of monitoring or advise GP of non-attendance.
- To evaluate any reported adverse effects by GP or patient. To report any adverse events to the CHM and GP. https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
- Ensure that backup advice is available at all times. (see Contacts section) and respond to any GP queries as soon as practicable.

General Practitioner

- Consider request to prescribe under shared care arrangements and reply only if you do not agree to share care, in a timely manner within 14 days as outlined on page 6 with clinical reasons and return to Consultant and Pharmacy department.
- Monitor patient's overall health and well-being.
- Ensure compatibility with other concomitant medication
- Prescribe ciclosporin, by brand, at the dose recommended.
- Monitor U&E, creatinine, blood pressure, FBC and LFTs at recommended frequencies (see Monitoring section) and refer if abnormal.
- Adjust the dose as advised by the specialist
- Stop treatment on advice of specialist or immediately if any urgent need to stop treatment arises (see monitoring section)
- Report any adverse events to the specialist and CHM.
- https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
- Inform specialist of any change in the medical condition of patient which may have effect on disease / medications.
- Ensure patient is offered an annual flu vaccination and a one off pneumococcal vaccination

Patient

- Report to specialist or GP if there is not a clear understanding of their treatment and discuss any concerns in relation to treatment.
- Report any adverse effects to their Specialist whilst taking ciclosporin, especially unexplained bruising/bleeding, unexplained rash which should be reported immediately.
- Report any changes in disease symptoms to Specialist whilst taking ciclosporin.
- Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy whilst taking ciclosporin.
- Try to avoid contact with chickenpox and shingles if no definite history of chickenpox, and report any such contact to urgently to their GP and/or consultant
- Inform GP or specialist of any other medicines being taken including over-the-counter products.
- Attend for regular reviews and blood monitoring tests.

CONTACT NUMBERS FOR ADVICE AND SUPPORT

Princess Alexandra Hospital NHS Trust - Rheumatology	
Consultant via switchboard: Nicola McCutcheon Specialist Rheumatology Pharmacist Rheumatology specialist nurse	01279 444455 ext 7434 / 7420 Ext 7819 Direct dial 01279 827819 (voicemail) 01279 444455 Ext 7434

Princess Alexandra Hospital NHS Trust - Dermatology	
Consultants: Medicines Information Clinical Nurse Specialist Dermatology	01279 444455 ext 7431 / 7421 01279 827054 07920139253 or ext 7431 / 7421

Princess Alexandra Hospital NHS Trust - Gastroenterology	
Consultant via switchboard: Clare Macpherson Specialist Gastroenterology Pharmacist IBD specialist nurse	01279 444455 ext 7424 / 7821 Bleep 272 Direct dial: 01279 278224 (voicemail if not answered) Direct dial:01279 278223 (voice mail only)

Licensed indications	Unlicensed Indications
Rheumatoid arthritis	Psoriatic arthritis [1]
Psoriasis	Bullous pemphigoid [2]
Atopic dermatitis	Pyoderma gangrenosum [3]
	Connective tissue disorders [4]
	Chronic actinic dermatitis [5]
	Cutaneous vasculitis [6]
	Systemic lupus erythematosus [5]
	Scleroderma [7]
	Ulcerative Colitis [8]

Therapeutic Summary

Ciclosporin, a calcineurin inhibitor, is a potent immunosuppressant which is virtually non-myelotoxic but markedly nephrotoxic. Ciclosporin blocks the amplification of certain T cell immune responses and suppresses IL-2 synthesis and release. The time to response is usually 3 months
See SPC for full details http://www.medicines.org.uk/emc/medicine/1307

Dose and Route of Administration

Rheumatology
Starting dose: 2.5 mg/kg/day in two divided doses for 6 weeks, and then may be increased every 2-4 weeks by incremental dose of 25 mg until clinically effective or the maximum dose of 4mg/kg is reached. Maintenance Dose: Often effective between 2.5 – 3.2 mg/kg/day. Adjust to patients' tolerance and benefit. Constantly evaluate *before increasing* to the maximum dose which may be 4mg/kg/day

Dermatology
2.5 mg/kg/day in two divided doses if good response is not seen within 2 weeks then increase to 5mg/kg is reached. A starting dose of 5mg/kg may be used if rapid control is required.

Gastroenterology
Ulcerative Colitis - ciclosporin is only for those steroid refractory UC who are Azathioprine or 6MP naïve. Ciclosporin is given orally in a microemusion formula (Neoral) in doses starting at 2-4mg/kg/day administered every 12 hours. Treatment is usually for 3 - 6 months only. Dose adjustments are made during therapy based on clinical response and blood levels. Dose is reduced by half every month, starting from 3 months from discharge

Adverse Effects and Management

Benign Gingival hyperplasia: not uncommonly seen and patients are advised on good oral hygiene. If hyperplasia persists it is advisable to consider stopping but discuss with the specialist team.

Hirsuitism: may be a cause for stopping therapy in some. May try bleaches and depilatory creams that are often safe.

Tremor, headache & paraesthesia: are common and if persistent or severe, discuss with the specialist team.

Hypertension: B.P (Diastolic) over 95 mm of Hg – Consider reducing the dose of Ciclosporin by 25-50%. If the BP still remains elevated, may like to follow the British Hypertension Society treatment regimen. Usually a beta-blocker or calcium channel blocker is used but Diltiazem, Nicardipine and Verapamil should NOT be used as they may increase the plasma ciclosporin levels. STOP Ciclosporin if BP remains uncontrolled. Diuretics frequently increase serum creatinine and best avoided, if possible.

Hyperlipidaemia: Statin therapy can be used if necessary but the dose should not exceed 10mg/day.

Nephrotoxicity: Increases in serum creatinine and urea during first few weeks of treatment are generally dose dependent and reversible on dose reduction.

Electrolyte Disturbances: hyperkalaemia (may occur by concurrent use of potassium sparing diuretics), hyperuricaemia, hypomagnesaemia.

Commonly: hepatotoxicity- bilirubinaemia, elevation of liver enzymes nausea, vomiting, diarrhoea, abdominal pain,

pancreatitis muscle cramp, myalgia, fatigue
Lymphadenopathy – if patient develops a single swollen lymph node (not related to inflamed skin in dermatology patients) fast track referral of patient to specialist for review.
Less Commonly: Anaemia, thrombocytopenia, Allergic rash, Increased risk of benign intracranial hypertension

Cautions

- **Vaccination:** Avoid use of all LIVE vaccines – administration should be postponed until at least 6 months after stopping ciclosporin
- **Cancer risk:** Due to increased risk of lymphomas and malignancies of the skin, patients should be advised to avoid excessive exposure to the sun and to use high factor sunscreens.
- **Immunosuppression:** Patients who have not had chicken pox and are in contact with anyone with the virus are advised to contact either their own GP or the specialist department to have VZ antibody status checked. If antibodies are negative it is recommended for these patients to have VZ immunoglobulin. Please see Human Varicella-Zoster Immunoglobulin (VZIG) Doc for further information and contact details.
- **Prescribing: Important** Patients should be stabilised on a particular 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 to a different brand of ciclosporin, the patient should be monitored closely for changes in blood-ciclosporin concentration, serum creatinine and blood pressure.

Contraindications

Renal and liver failure (unless advised otherwise by a specialist)
Uncontrolled hypertension
Suspected systemic infection or sepsis
Severe electrolyte imbalance i.e. hyperkalaemia
Malignancy
Known hypersensitivity to Ciclosporin
Concomitant use of rosuvastatin, dagbigtran or oral tacrolimus

Pregnancy and Lactation

Careful assessment of risks vs benefit to be considered before use in women of childbearing potential, during pregnancy and breast-feeding. Patients discovered or planning to become pregnant should be referred to the initiating specialist at the earliest opportunity without stopping ciclosporin.

The drug may be excreted in milk and patients should be advised against breast-feeding.

Monitoring Standards for Ciclosporin based on BSR BHPR Standards 2017

The following standards have been agreed for the monitoring of ciclosporin in all patients at Princess Alexandra Hospital NHS Trust.

Pre-treatment by Specialist	Height, weight, blood pressure, FBC, U&Es, LFTs, calculated GFR and albumin	
Initial monitoring by Specialist	FBC Creatinine / calculated GFR ALT +/- AST Albumin	Every 2 weeks until on stable dose for 6 weeks.
Ongoing monitoring by GP	FBC Creatinine / calculated GFR ALT +/- AST Albumin	Then once on stable dose monitor monthly.
	FBC Creatinine / calculated GFR ALT +/- AST Albumin	Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis, Specialist to advise.
Dose increase	FBC Creatinine / calculated GFR ALT +/- AST Albumin	Every 2 weeks until on stable dose for 6 weeks, then revert to previous schedule
Specialist and GP	BP and Glucose	At every visit

Ciclosporin levels	**Gastroenterology Patients only:** **In hospital** during initiation to avoid a colectomy- first drug level should be send on Day 2 (before the 3rd dose) and then biweekly until the level is therapeutic (if not increase the dose by 25%) and stable (in two consecutive levels). Then check the level weekly for the first month before patient can be transferred to shared care. **In community:** Once a month, take 12 hour trough ciclosporin levels prior to administration of morning dose (aim for 150-250ng/ml). **Ensure patient is advised to withhold ciclosporin until blood taken.**

Action and Advice

If a GP has taken blood tests for the general medical management of a patient and blood test results fall into the categories below or the patient reports one of the adverse events below, these are recommendations for considering the withdrawal of Ciclosporin therapy:

Blood Test Results	
Creatinine increased by >30% of baseline in two consecutive readings one week apart (even if creatinine values still lies within laboratory's' normal range)	Withhold until discussed with specialist team
eGFR ≤ 55ml/min	Withhold until discussed with specialist team
Potassium rises above reference range	Withhold until discussed with specialist team
Platelets < 150 x 10^9/l	Withhold until discussed with specialist team
> 2-fold rise in AST, ALT, alkaline phosphatase (from upper limit of reference	Withhold until discussed with specialist team
Blood pressure > 140/90 on two consecutive readings to weeks apart	Treat blood pressure before stopping the ciclosporin (note interactions with several anti- hypertensives). If BP cannot be controlled, stop ciclosporin and obtain BP control before restarting ciclosporin. Discuss with the specialist team.
Unexplained reduction in albumin <30 g/l	Discuss with specialist team
Ciclosporin levels (Gastroenterology patients only)	Ciclosporin levels of 500ng/ml then stop for 2 consecutive days and discuss with specialist team Ciclosporin levels between 300-500ng/ml, reduce dose by 25% and discuss with specialist team.
Symptoms	
Unexplained Rash	Withhold until FBC results available & discuss with specialist team
Abnormal bruising or bleeding	Withhold until FBC results available & discuss with specialist team

Clinically relevant Drug interactions

Please note that ciclosporin interact with many drugs and prescribers should refer to the BNF and SPC for full information. This list is not comprehensive.

Drugs that decrease ciclosporin levels: barbiturates, carbamazepine, phenytoin, orlistat, terbinafine and rifampicin
Drugs that increase ciclosporin levels: azole anti-fungals, diltiazem, nicardipine, verapamil, amiodarone, metoclopramide, oral contraceptives, high dose methylprednisolone, allopurinol, tacrolimus, some anti- retrovirals.
Nephrotoxic Drugs: Use ciclosporin with caution with other nephrotoxic drugs. Monitor renal function closely.
NSAIDs and Diclofenac: close monitoring of renal function is essential. Reduce dose of diclofenac by 50% when given with Ciclosporin
Colchicine: ciclosporin may increase the level of colchicine – **avoid concomitant use**
Statins: use lower doses to reduce the risk of muscular toxicity. Refer to relevant statin SPC. Rosuvastatin is specifically contraindicated.
Nifedipine: use with caution due to increased risk of gingival hypertrophy.
Digoxin: Ciclosporin may increase serum levels of digoxin
St John's Wort: decreases level and clinical effect of ciclosporin – **avoid concomitant use**.
Potassium sparing drugs: (potassium sparing diuretics, ACE inhibitors, Angiotensin II antagonists) use with **extreme caution** as may lead to significant increase in potassium.
Grapefruit or grapefruit juice: grapefruit increases the bio-availability of ciclosporin and should be avoided.
Macrolides: marked increase in ciclosporin levels. **Avoid if possible.** If use is unavoidable, monitor ciclosporin levels closely and reduce dose as necessary.
Quinolones and Trimethoprim: increased risk of nephrotoxicity
Cimetidine: increased risk of nephrotoxicity

Herbal / Complimentary medications are not recommended when taking this medication as interactions may occur.

Further Information and references

1). Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis NICE TA 199
https://www.nice.org.uk/guidance/ta199/resources/etanercept-infliximab-and-adalimumab-for-the-treatment-of-psoriatic-arthritis-pdf-82598565006277

2). British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012
http://www.bad.org.uk/shared/get-file.ashx?id=47&itemtype=document

3). Ciclosporin compared with prednisolone therapy for patients with pyoderma gangrenosum: cost-effectiveness analysis of the STOP GAP trial. https://www.ncbi.nlm.nih.gov/pubmed/28391619 Br J Dermatol. 2017 Apr 9

4). An audit of cyclosporin for systemic lupus erythematosus and related overlap syndromes: limitations of its use
http://ard.bmj.com/content/59/6/487 Annals of the Rheumatic Disease Volume 59 Issue 6

5). Long-term Follow-up of Eczema Patients Treated with Cyclosporine Acta Derm Venereol (Stockh) 1998; 78: 40–43

Chronic actinic dermatitis.pdf

6). Cyclosporin A in the treatment of cutaneous vasculitis. Clinical and cellular effects Journal of the European Academy of Dermatology and Venereology Volume 6, Issue 2, March 1996, Pages 135-141
http://www.sciencedirect.com/science/article/pii/092699599400000X

7). Cyclosporin and tacrolimus: their use in a routine clinical setting for scleroderma Rheumatology, Volume 39, Issue 8, 1 August 2000, Pages 865–869 https://academic.oup.com/rheumatology/article/39/8/865/1784039/Cyclosporin-and-tacrolimus-their-use-in-a-routine

8). Ulcerative colitis: management CG 166 https://www.nice.org.uk/guidance/cg166/resources/ulcerative-colitis-management-pdf-35109695126725

This document does not replace the SPC and BNF and should be read in conjunction with it.

BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs 2017
https://academic.oup.com/rheumatology/article/3053478/BSR-and-BHPR-guideline-for-the-prescription-and?searchresult=1

BSG guidelines for management of inflammatory bowel disease in adults:
https://www.bsg.org.uk/clinical/bsg-guidelines.html?section=inflammatory-bowel-disease

CKS
http://cks.nice.org.uk/dmards#!scenario:3

Arthritis Research UK
http://www.arthritisresearchuk.org/arthritis-information/drugs/ciclosporin.aspx

West Essex Shared Care Guidelines
Shared Care Letter - West Essex CCG

GMC Prescribing Guidance: Shared Care
https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/shared-care

GP response to Shared Care Agreement

(only complete & send if NOT participating in shared care)

This shared care agreement has been approved by the Medicines Management Optimisation Programme Board

Patient Name:	NHS No:
Consultant:	Medicine requested for shared care: **Ciclosporin**

I will **NOT** be undertaking the GP responsibilities as described in the agreed shared care agreement. My clinical reasons for declining shared care for this patient are listed in the box below:

Yours sincerely

{GP name}

{Surgery}

Please send a copy of this response to:

1. The Specialist/consultant requesting shared care
2. **ANONYMISED COPY OF THIS FORM ONLY** to the E-MAIL: **tpa-tr.ClinicalPharmacy@nhs.net**

(sending a copy of this form to the PAH pharmacy will help to identify any inappropriate requests for shared care e.g. indication not covered, hospital monitoring requirements not fulfilled. It will also help to inform the CCG Medicines Optimisation Team of the reasons shared care is not being undertaken by GPs allowing for changes to be made in future updates to improve patient safety)

P14064

The Princess Alexandra Hospital NHS
NHS Trust

Hamstel Road
Harlow, Essex
CM20 1QX

Tel: 01279 444455

Information for patients:

SHARED CARE: Agreement information and confirmation

Patient name:

.....

Medicine:

.....

We would be grateful if you would take time to read this information as it will help us work with you to manage your condition and ensure safe prescribing of the specific medicine listed above.

What is a Shared Care Agreement (SCA)?

A Shared Care Agreement (SCA) enables the care you have for a specific condition to be shared between the hospital and your GP.

The agreement means that the medicine the hospital has started, can be continued by your GP, so you won't have to visit the hospital to collect your medicine.

The SCA gives information on your medicine, guidance on the prescribing and monitoring responsibilities for your consultant (in the hospital), your GP and you. For an SCA, to work everyone involved must understand it and communicate effectively.

Your consultant and your GP will need to sign the agreement and if you agree to this approach, we would ask you to sign this letter, to indicate your agreement to have your care managed in this way.

How does shared care work?

Your consultant and GP share responsibility for your care.

The consultant is a specialist in your condition and will start prescribing your medicine, making sure it is suitable for you. There will come a point in your treatment when you may not need to be monitored by the consultant as often and this monitoring can be done by your GP.

Once your GP has agreed to the SCA, they will be able to prescribe the same medicine for you at the dose recommended by the consultant.

The organisation which regulates GPs, the General Medical Council, says that 'when a GP prescribes a medicine, the GP needs to satisfy themselves that the prescription is needed, appropriate for the patient and within the limits of their competence'.

So, your GP can only issue a prescription if the consultant and you keep to the responsibilities you have agreed (see below). If responsibilities are not kept or if the GP no longer feels it is safe to prescribe the medicine, he/she will explain the reasons to you and your consultant, then prescribing responsibilities will be transferred back to the hospital.

What do I need to do to ensure the SCA can continue?

- **Attend hospital outpatients**
  You must still attend the hospital for regular reviews as directed by your consultant (these may be less frequent than before). If you do not attend your hospital appointments, your GP will not be able to continue issuing prescriptions for this medication.
- **Attend GP appointments**
  You must attend any appointments you have with your GP in relation to this medicine, so they can look after you effectively.
- **Have blood tests as you have been advised to**
  Your consultant should have informed you

continued overleaf

if and how often you need to have blood monitoring tests. You can usually have your blood taken at an appropriate clinic and not need to go to the hospital.

- If you do not have the blood monitoring tests as advised by your consultant, your GP will no longer be able to issue you with prescriptions as it would not be safe to do so.

What do I do if I am having side-effects to the medicine?

Your consultant should have informed you of the common side-effects to expect and what to do if you experience them. If you think you may be having side-effects from a medicine report these directly to your consultant. Your GP may need to seek advice from your consultant before issuing you with another prescription; this is to ensure it is safe for you to continue on the medication.

What if my disease symptoms change or get worse?

Report any changes in disease symptoms or circumstances that could affect management of your disease to your consultant.

What about the other medicines I take?

Inform your GP and the consultant of all other medicines you are taking, including those you may have bought yourself. Do not take new medicines (including those you could buy) until you have discussed this with your pharmacist, GP or consultant.

If you would like to go ahead with a shared care agreement for the specific medication identified on page 1, please sign below to confirm that you:

- Understand the shared care agreement.
- Are happy to have your care for this aspect of your health managed by a shared care agreement.
- You agree to attend regular review appointments as requested.
- You agree to have blood tests as required.

Patient's signature .....

Date .....

Print name .....

If at any point in time you would like this shared care agreement to stop, please talk to your GP.