

OPT-OUT SHARED CARE GUIDELINE

It is assumed that shared care **will** be accepted unless the specialist is informed otherwise within 28 days of receipt of the request at the end of this document.

MEDICATION NAME: CICLOSPORIN CAPSULES

INDICATIONS COVERED: Rheumatoid Arthritis, Psoriatic Arthritis and other inflammatory conditions in Adults

NHS Brighton and Hove CCG, Crawley CCG, Horsham and Mid-Sussex CCG
Traffic Light System Classification: Amber

NOTES to the general practitioner (GP) or primary care prescriber

For medicines which require specialist initiation and/or dose titration and specific ongoing monitoring. For initiation, dose stabilisation and prescribing (including monitoring) by a specialist until the patient is stabilised (usually for 3 months) after which the GP may be asked to work under shared care through the use of approved shared care guidelines.

The expectation is that these guidelines should provide sufficient information to enable GPs or primary care prescribers to be confident to take clinical and legal responsibility for prescribing these medicines.

The questions below will help you confirm this:

- Is the patient currently under your care (e.g. shared care should not be agreed if the patient is currently in intermediate care following hospital discharge)?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this effective shared care guideline?
- Have you been provided with relevant clinical details including monitoring data?

If you can answer YES to all these questions (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility. It is assumed that shared care will be accepted unless the specialist is informed otherwise with 28 days of receipt of this request.

If the answer is NO to any of these questions, you should not accept prescribing responsibility. You should inform the consultant or specialist within 28 days, outlining your reasons for NOT prescribing. If you do not have the confidence to prescribe, we suggest you discuss this with your local Trust or specialist service, who will be willing to provide training and support. If you still lack the confidence to accept clinical responsibility, you still have the right to decline. Your CCG medicines management pharmacist will assist you in making decisions about shared care if you are unsure.

Prescribing unlicensed medicines or medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber's professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.

The GP or primary care prescriber has the right to refuse to agree to shared care, in such an event the total clinical responsibility will remain with the consultant or specialist.

Reason for update: New	Prepared by: Dr.U.Davies, D.Finney, Dr.S.Griffith, Dr.K.Jordan, Dr.R.Makadsi, Dr.G.Papasavvas, Dr.W.Shattles, SCT Medicines Management Team	Updated by: N/A
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Approved by NHS Brighton and Hove CCG on: 22.09.2015 / 01.12.2015		
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Information

This information sheet does not replace the Summary of Product Characteristics (SPC), which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF.

1. Link to the relevant SPC website: <http://www.medicines.org.uk/emc/>

2. Background to use for the indications, including licence status:

Ciclosporin is a disease modifying anti rheumatic drug and potent immunosuppressant used in rheumatoid arthritis, psoriatic arthritis and other inflammatory conditions.

Ciclosporin should only be initiated on the recommendation of a specialist. It can be used in combination with other DMARDs such as methotrexate with careful monitoring.

This guideline covers the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PA) and other inflammatory conditions.

Ciclosporin has a marketing authorisation that includes severe, active rheumatoid arthritis and the treatment of severe psoriasis in patients in whom conventional therapy is inappropriate or ineffective.

3. Dose & administration:

Doses are initiated at 2.5 mg per kg per day in two divided doses for 6 weeks then may be increased at 2 to 4 week intervals by 25 mg until clinically effective or a maximum dose of 4mg per kg per day is reached.

Ciclosporin may need to be given for up to 3 months before therapeutic benefit is seen. Withdraw if no benefit after 3 months at maximum tolerated dose.

Doses should be equally distributed throughout the day (i.e. 12 hours apart) and a consistent schedule should be maintained with regard to time of day and in relation to meals.

4. Cautions:

- Patients with nephrotic syndrome.
- Patients with impaired hepatic function – dose reduction may be necessary in patients with severe hepatic impairment.
- Elderly (65 years or older) – Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range. Renal function should be monitored with particular care.
- Patients receiving multiple immunosuppressive agents.
- Patients with hyperuricaemia.
- Patients with epilepsy or liver disease – A 500mg dose of Neoral® contains 500mg ethanol, equivalent to 15ml beer / 5ml wine, other brands of ciclosporin may also have ingredients that are metabolised to alcohol.
- Varicella Zoster Virus Infection – in patients with close contact to chickenpox or shingles consider passive immunization with varicella zoster immunoglobulin (VZIG). Contact specialist and see Green Book Chapter 34 for further details.
- Avoid excessive unprotected sun exposure – advise high factor sun protection.

This list is not exhaustive; refer to the Summary of Product Characteristics (SPC) or BNF for further guidance.

5. Contraindications:

- Known hypersensitivity to ciclosporin or any of its excipients.
- Abnormal renal function.
- Liver failure.
- Uncontrolled hypertension.
- Uncontrolled infections or suspected systemic infection or sepsis.
- Any kind of malignancy.
- Severe electrolyte imbalance i.e. hyperkalemia.
- Pregnancy. Any patient contemplating becoming pregnant must be seen by the specialist at the earliest opportunity to discuss the complex issues surrounding therapy with ciclosporin.
- Breastfeeding mothers. Any patient contemplating breast feeding must be seen by the specialist at the earliest opportunity to discuss the complex issues surrounding therapy with ciclosporin.
- Live vaccines (see drug interaction section).
- Concomitant use with products containing Hypericum perforatum (St John's Wort).
- Concomitant use 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.
- Patients on Neoral® should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

This list is not exhaustive; refer to the Summary of Product Characteristics (SPC) or BNF for further guidance.

6. Side effects:

The principal adverse reactions associated with the administration of ciclosporin include:

Renal dysfunction, increased infections, hyperlipidaemia, hypercholesterolaemia, headache, hepatotoxicity, tremor, hirsutism, hypertension.

Other common side effects include: Gastrointestinal disturbances, anorexia, electrolyte disturbances, myalgia, convulsions, paraesthesia, flushing, abdominal discomfort/pain, gingival hyperplasia, peptic ulcer, hepatic function abnormalities, and liver injury including cholestasis, jaundice, hepatitis and liver failure with some fatal outcome, acne, hypertrichosis, myalgia, muscle cramps, pyrexia and fatigue - this list is not exhaustive, refer to the Summary of Product Characteristics or BNF for further guidance.

Many side effects associated with ciclosporin therapy are dose-dependent and responsive to dose reduction.

This list is not exhaustive; refer to the Summary of Product Characteristics (SPC) or BNF for further guidance.

Table 1. Side effects and actions to take for abnormal results:

SIDE EFFECT	ACTIONS
Platelets $<150 \times 10^9/l$	Withhold and discuss with specialist.
Liver Function: AST/ALT/ ALP $>$ twice upper limit of reference range	Withhold and discuss with specialist. Investigate alternative cause (i.e. alcohol, drug interactions including over the counter medication).
Renal Function If creatinine increases by more than 25% from baseline at more than one measurement (even if creatinine still within normal range).	Repeat U&Es in 1 week and if still increased \geq 25% from baseline, withhold and discuss with specialist.
Potassium rises above reference range.	Withhold and discuss with specialist.
Significant rise in fasting lipids.	Withhold and discuss with specialist.
High BP: $\geq 140/90$ on two consecutive readings 2 weeks apart.	Treat BP - note interactions with several anti-hypertensives. If BP cannot be controlled, withhold ciclosporin and discuss with specialist.
Abnormal Bruising.	Check FBC immediately. Withhold and discuss with specialist.

Please note that in addition to absolute values, a rapid fall/rise or consistent downward/upward trend in haematological or biochemical index should prompt caution and extra vigilance.

7. Notable drug interactions:

Drugs that decrease ciclosporin levels:

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

Drugs that increase ciclosporin levels:

Macrolide antibiotics (e.g. erythromycin, azithromycin and clarithromycin); ketoconazole, fluconazole, itraconazole, voriconazole; diltiazem, nifedipine, verapamil; metoclopramide; oral contraceptives; danazol; methylprednisolone (high dose); allopurinol; amiodarone; cholic acid and derivatives; protease inhibitors, imatinib; colchicines; nefazodone.

Other relevant drug interactions

- Care should be taken when using ciclosporin together with other nephrotoxic drugs.
- Concomitant use with tacrolimus should be avoided due to increased potential for nephrotoxicity.
- The concurrent administration of nifedipine with ciclosporin may result in an increased rate of gingival hyperplasia compared with that observed when ciclosporin is given alone.
- Increased plasma levels of both lercanidipine and ciclosporin have been observed following concomitant administration. Therefore caution is recommended when co-administering ciclosporin together with lercanidipine.
- NSAIDs: Close monitoring of renal function is essential, doses may need to be reduced, seek specialist advice. Examples of NSAIDs that exhibit nephrotoxic synergy include diclofenac, naproxen and sulindac. The concomitant use of diclofenac and ciclosporin has been found to result in a significant increase in the bioavailability of diclofenac (avoid diclofenac).
- Severe digitalis toxicity has been seen within days of starting ciclosporin in several patients taking digoxin.
- When statins are concurrently administered with ciclosporin, their dosage should be reduced according to their SPC. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of

myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis. Rosuvastatin is specifically contraindicated with ciclosporin.

- Caution is required for concomitant use of potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) or potassium containing drugs since they may lead to significant increases in serum potassium.
- Ciclosporin may increase the plasma concentrations of repaglinide and thereby increase the risk of hypoglycaemia.

Vaccines

- Severe or fatal infections may occur if a live vaccine is given concurrently. **AVOID LIVE VACCINES.** Herpes zoster vaccine is not contraindicated in these patients. Please see <http://tinyurl.com/nvdeqp2>.
- Inactivated vaccines such as influenza vaccine are safe to use although they may elicit a lower response.

Non Drug interactions

Grapefruit and grapefruit juice – concomitant intake of grapefruit juice has been reported to increase the bioavailability of ciclosporin. Patients should be told to avoid.

This list of interactions is not exhaustive; refer to the Summary of Product Characteristics (SPC) or BNF for further guidance.

8. Criteria for use:

Chronic inflammatory conditions as determined by the appropriate specialist according to this shared care guideline. Specialist has initiated and dose stabilised (usually for a minimum 3 months).
GP or Primary Care Prescriber confident to take clinical and legal responsibility for prescribing this drug.

9. Any further information (e.g. supporting therapies):

Prescribing and dispensing of ciclosporin should be by **brand** to avoid any inadvertent switching. If it is necessary to switch brand this should be done under specialist supervision with close monitoring of ciclosporin levels and renal function.

Patient should avoid excessive exposure to UV light, including sunlight.

Oral formulations contain around 12% vol. ethanol, with a 500mg dose equivalent to 500mg ethanol (15mL beer or 5mL wine).

10. References:

- Brighton and Hove CCG, *Effective Shared Care Agreement (ESCA): Ciclosporin*. December 2012. Available at: http://www.brightonandhoveccg.nhs.uk/sites/default/files/resources/ch_10_musculoskeletal_cp.pdf (accessed 09.04.15).
- British Society for Rheumatology, Immunisation against shingles in people with inflammatory rheumatic disease. Available at http://www.rheumatology.org.uk/includes/documents/cm_docs/2013/i/immunisation_with_zostavax_for_people_with_inflammatory_rheumatic_disease.pdf (access 11.08.15).
- Chakravarty, K. et al, *BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists, British Society for Rheumatology*, Oxford University Press, 2008. Available at: http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmar_d_therapy.pdf (accessed 09.04.15).
- Immunisations against infectious diseases (Green Book online), *Chapter 34: Varicella*. Updated April 2013. Available at [Varicella: the green book, chapter 34 - Publications - GOV.UK](http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/263842/Varicella_the_green_book_chapter_34_-_Publications_-_GOV.UK) (accessed 26.03.15).
- Joint Formulary Committee. *British National Formulary; Ciclosporin*, April 2015, British Medical Association and Royal Pharmaceutical Society. London. Available at: <https://www.medicinescomplete.com/mc/bnf/current/index.htm> (accessed 20.04.15).
- Summary of Product Characteristics, *Neoral® Soft Gelatin Capsules*. Novartis Pharmaceuticals. Last update 06.03.14. Available at: <http://www.medicines.org.uk/emc/medicine/1307> (accessed 09.04.15).
- UKMI. *Suggestions for Drug Monitoring in Adults in Primary Care*. February 2014. Available at <http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Drug%20monitoring%20document%20Feb%202014.pdf> (accessed 20.04.15).

RESPONSIBILITIES and ROLES

Consultant or Specialist responsibilities

- 1 Confirm diagnosis and indication for treatment with ciclosporin.
- 2 To discuss fully the aims, benefits, risks and side effects of treatment and a treatment plan with the patient and/or carer and for written information to be supplied to the patient and/or carer. Inform patient to report immediately any exposure to Varicella Zoster Virus.
- 3 Exclude existing pregnancy in women with child bearing potential.
- 4 Prior to treatment ask GP whether patient has had pneumococcal vaccination and flu vaccination and, if not, immunise (unless contra-indicated). Inform patient not to start medication until after immunisation.
- 5 Inform GP when initiating treatment so the GP is aware what is being prescribed and can add to GP clinical record.
- 6 Undertake baseline monitoring as required and record varicella status.
- 7 Record other medications and address potential drug interactions before starting therapy.
- 8 To discuss the potential implications of pregnancy and breastfeeding in women of child bearing potential and agree a risk minimisation strategy where appropriate.
- 9 To initiate treatment by prescribing and monitoring usually for a minimum of 3 months.
- 10 Undertake monitoring if dose changed.
- 11 Monitor and prescribe according to guidelines until handover is appropriate (including when dose changes are made).
- 12 Discuss the possibility of shared care with the patient and/or carer and ensure that they understand the plan for their subsequent treatment.
- 13 Supply GP with a summary of the patient's review (including anticipated length of treatment) and a link to, or a copy of, the shared care guideline when requesting transfer of prescribing to GP or primary care prescribers.
- 14 Advise GP if treatment dose changes or treatment is discontinued.
- 15 Inform GP if patient does not attend planned follow-up.

GP or Primary Care Prescriber responsibilities

- 1 Continue prescribing of ciclosporin with **the specific brand** at the dose recommended and undertake monitoring requirements.
- 2 Undertake all relevant monitoring as outlined in the monitoring requirements section below, and take appropriate action as set out in this shared care guideline
- 3 Monitor for adverse effects throughout treatment and check for drug interactions on initiating new treatments.
- 4 Add information about the medicine to patient record, initially as "hospital prescribed", and highlight the importance that this medicine is only to be prescribed under a shared care guideline in primary care.
- 5 Inform patient to report immediately of any issues that may arise.
- 6 Inform patients to report immediately any exposure to Varicella Zoster Virus.
- 7 Refer patient back to the Consultant/Specialist if any concerns.
- 8 Ensure that if care of the patient is transferred to another prescriber, that the new prescriber is made aware of the shared care guideline (e.g. ensuring the patient record is correct in the event of a patient moving surgery).

Monitoring requirements and appropriate dose adjustments

- 1 **Pre-treatment:**
 - FBCs, ESR and / or CRP.
 - U&Es, check creatinine twice, 2 weeks apart to obtain a mean value for baseline.
 - LFTs (including bilirubin, fasting lipids).
 - Blood pressure: must be $\leq 140/90$ on two occasions 2 weeks apart. If greater than 140/90 treat hypertension before starting ciclosporin.
 - In patients with psoriatic arthritis: Assess whether patient has received PUVA before commencing ciclosporin. If total dose exceeds 1000 J discuss with dermatologists.
- 2 **Initiation:**
 - **Weeks 2,4,6,8,10,12:** FBC, LFTs, U&Es, creatinine, ESR and / or CRP.
 - Fasting lipids: after 1st month of therapy, then periodically.
 - Blood Pressure: Check at each appointment and maintain $\leq 140/90$.
 - **Weeks 18, 24:** FBC, LFTs, U&Es, creatinine, ESR and / or CRP and blood pressure.
3. **Maintenance:** Every three months thereafter: FBC, U&Es, creatinine, LFTs, ESR and / or CRP.
 - Fasting lipids every 6 months.
 - Blood Pressure: Check each time patient attends monitoring clinic and maintain $\leq 140/90$.
4. **Dose change when on maintenance:** Recheck U&Es, creatinine, ESR and / or CRP after dosage increase (as above).
5. **Concomitant treatment with an NSAID initiated or NSAID dosage increased:** Recheck U&Es
6. Monitor for adverse drug reactions throughout treatment.
7. Check for drug interactions on initiating new treatments.
8. Provide patient with pneumococcal vaccination and flu vaccination unless contra-indication.
9. Ensure that if care of the patient is transferred to another prescriber that the new prescriber is made aware of the shared care agreement and guidelines.
10. Whilst absolute values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance.

Continued

Patient's or Carer's role	
1	Make sure that you understand the treatment and ask for more information, if needed.
2	Share any concerns in relation to treatment with whoever is prescribing this medicine for you.
3	Tell the prescriber of this medication about any other medication being taken, including over-the-counter products.
4	Read the patient information leaflet included with your medication and report any side effects or concerns you have to whoever is prescribing this medicine for you.
5	Report immediately any exposure to Varicella Zoster Virus.
6	Attend the follow up appointments with the consultant or specialist.
7	Attend any monitoring appointments (e.g. blood tests). Undertake required monitoring.

SHARED CARE GUIDELINE

MEDICATION NAME: Ciclosporin

INDICATION: Rheumatoid Arthritis, Psoriatic Arthritis and other inflammatory conditions in Adults

DATE OF REQUEST:

Agreement to transfer prescribing to general practice or primary care prescriber:

Patient details:

Name:
Address:
DoB:
NHS No:
Hospital No:

Medication name, form and strength: Ciclosporin capsules

The following tests and investigations have been carried out:

Date treatment initiated:

At the last patient review the medication appeared to be effectively controlling symptoms or providing benefit:
Yes/No

The patients has now been stabilised on a dose of:

The patient has been given written information about their medication:
Yes/No

The patient understands that this medication is being prescribed under a shared care agreement between their GP and specialist and that they have responsibilities under the agreement to ensure they attend their GP to be regularly monitored.
Yes/No

The patient has been informed that the GP can opt-out of taking on prescribing responsibility if they do not feel clinically able to prescribe or if the patient persistently does not attend for monitoring:
Yes/No

Date of next clinic appointment:

If the practice declines shared care, then the named consultant or specialist should be informed within 28 days of receipt of this request. Forms used to decline prescribing can be found here:
Brighton and Hove CCG: <http://www.gp.brightonandhoveccg.nhs.uk/prescribing/joint-formulary-supporting-information>
Crawley CCG, Horsham and Mid Sussex CCG:
<http://www.horshamandmidsussexccg.nhs.uk/EasySiteWeb/GatewayLink.aspx?allid=415216>

BACK-UP ADVICE AND SUPPORT

	Name and position	Telephone	Email
Specialist or Consultant			
Alternative specialist (e.g. departmental contact)			
Specialist pharmacist			
Out of hours (e.g. medical team on call)			

Link to full SCG: [http:// www.sussexmskpartnershipcentral.co.uk/](http://www.sussexmskpartnershipcentral.co.uk/)