PATHWAYS AND GUIDELINES DEVELOPMENT SUBGROUP

Shared Care Protocol

GMMMG NHS

Shared Care Guideline Ciclosporin for use in childhood nephrotic syndrome		**Reference Number**
Version: 1	**Replaces:** n/a	**Issue date:** dd/mm/yyyy
Author(s)/Originator(s): (please state author name and department) Professor Nicholas Webb (Paediatric Nephrology Department, RMCH) Dr Helen Stannard (Paediatric Nephrology Department, RMCH) Ms Hong Thoong (Pharmacy Department, RMCH/CMFT)		**To be read in conjunction with the following documents:** Current Summary of Product characteristics (http://www.medicines.org.uk) BNFC

Date approved by Interface Prescribing Group: *dd/mm/yyyy*	**Date approved by Greater Manchester Medicines Management Group:** *dd/mm/yyyy*
Date approved by Commissioners: *dd/mm/yyyy*	**Review Date:** *dd/mm/yyyy*

Please complete all sections

1. Name of Drug, Brand Name, Form and Strength	Ciclosporin (Neoral®) 100mg/ml Oral Solution 10 mg, 25 mg, 50 mg or 100 mg soft gelatin capsules
2. Licensed Indications	Ciclosporin is licensed for: The treatment of steroid dependent or steroid resistant nephrotic syndrome (associated with adverse prognostic features) due to minimal change glomerulonephritis, focal segmental glomerulosclerosis or membranous glomerulonephritis in both adults and children. Prevention of graft rejection following kidney, liver, heart, combined heart-lung, lung or pancreas transplants. Treatment of transplant rejection in patients previously receiving other immunosuppressive agents. It is also licensed for Bone Marrow Transplantation, psoriasis, atopic dermatitis and rheumatoid arthritis. Not licensed in children <3 months old.
3. Criteria for shared care	Prescribing responsibility will only be transferred when: ▪ Treatment is for a specified indication and duration. ▪ Treatment has been initiated and established by the secondary care specialist. ▪ The patient's initial reaction to and progress on the drug is satisfactory. ▪ The GP has agreed in writing in each individual case that shared care is

	appropriate. ▪ The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements
4. Therapeutic use & background	For use in nephrotic syndrome where the disease is frequently relapsing and standard first line therapy has been unsuccessful/inadequate. It can be used in both the steroid-sensitive and steroid-resistant subtypes.
5. Contraindications (please note this does not replace the SPC or BNF and should be read in conjunction with it).	Do not administer in conjunction with other calcineurin inhibitors. Ciclosporin is contraindicated in uncontrolled hypertension, uncontrolled infections and malignancy
6. Prescribing in pregnancy and lactation	This drug cannot be prescribed in the pregnant or breast-feeding patient. Treatment should be discontinued.
7. Dosage regimen for continuing care	***Route of administration*** Oral
	Preparations available: 100mg/ml Oral Solution 10 mg, 25 mg, 50 mg or 100 mg soft gelatin capsules
	Please prescribe: In children aged 1 month to 18 years old the dose is 3mg/kg twice daily (rounded to the nearest measurable dose or capsule where appropriate) and treatment is initiated by the specialist team following discussion with the patient and family. Note: this dose may be increased, if necessary, in corticosteroid-resistant disease. To guide treatment, a blood test is performed to measure a trough level, 12 hours after the previous dose. This will be done at an Outpatient attendance. Currently there are no evidence-based guidelines for trough levels but the range 50-125 micrograms/l is used in clinical practice.
	Is titration required: No
	There is no maximum dosage of ciclosporin. The dose may be increased by the specialist according to what is required to generate acceptable trough levels. Note: if capsules are required, the dose may be rounded up or down to the nearest capsule
	Adjunctive treatment regime: Patients may also be taking prednisolone – in high doses if their nephrotic syndrome has relapsed or in lower dose(s) for maintenance therapy. A small number may also be receiving additional immunosuppressant therapy such as mycophenolate or azathioprine. If the patient is suffering a relapse during which they are clinically oedematous then they may also be receiving other treatment such as oral diuretics, penicillin V and omeprazole.
	Conditions requiring dose reduction: High blood trough levels as previously discussed. Evolving renal impairment felt to be due to ciclosporin with reduction of GFR to less than 30 Hypertension – although treatment with antihypertensive agents may also be commenced. Hepatic impairment. All dose changes will be undertaken by the specialist team and will be communicated to the GP in writing.

Usual response time:
A trial of ciclosporin is usually continued for six months, with three months of acceptable trough levels, to properly assess response.

Duration of treatment:
This is generally up to two years, but it can be continued longer by the specialist team if felt to be beneficial. A renal biopsy will be performed after two years of treatment because of the potential risk of nephrotoxicity (tubulointerstitial lesions). If treatment continues beyond two years then patients will need a biopsy annually.

Treatment to be terminated by:
The Specialist Paediatric Nephrology team.
This will be communicated to the GP in writing.

NB. All dose adjustments will be the responsibility of the initiating specialist care unless directions have been specified in the medical letter to the GP.

8.Drug Interactions

For a comprehensive list consult the BNF or Summary of Product Characteristics

The following drugs must <u>not</u> be prescribed without consultation with the specialist:
Note: This information should be read in conjunction with the company's summary of product literature and the current BNFC.
There are a significant number of drug interactions with ciclosporin.

Several agents are contraindicated:

- Tacrolimus
- St John's Wort
- Bosentan
- Lercanidipine

The following drugs may be prescribed with caution:
Drugs and other agents may affect plasma concentrations of ciclosporin. These are detailed below.

Drugs that increase ciclosporin levels	Drugs that decrease ciclosporin levels
Allopurinol	Rifampicin
Amiodarone	St John's Wort
Macrolide antibiotics – azithromycin, clarithromycin, erythromycin	Antiepileptics – carbamazepine, Phenobarbital and phenytoin
Chloramphenicol	Sevelamer
Antifungals – fluconazole, itraconazole, ketoconazole, posaconazole, miconazole voraconazole	
Chloroquine and hydroxychloroquine	
Carvedilol	
Calcium-channel blockers – diltiazem, nicardipine and verapamil	
Grapefruit juice	

Ciclosporin can increase the plasma concentration of prednisolone.

Care should also be taken for other types of drug interactions involving ciclosporin, including:

- Increased risk of hyperkalaemia with ACE inhibitors and potassium-sparing diuretics and aldosterone antagonists
- Increased risk of nephrotoxicity when given with other potentially nephrotoxic agents, such as NSAIDs, aminoglycosides, quinolones and amphotericin
- Live vaccinations

9. Adverse drug reactions

For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult Summary of Product Characteristics or BNF

Specialist to detail below the action to be taken upon occurrence of a particular adverse event as appropriate. Most serious toxicity is seen with long-term use and may therefore present first to GPs.

Adverse event System – symptom/sign	**Action to be taken** Include whether drug should be stopped prior to contacting secondary care specialist	**By whom**
Visual disturbance	Refer to secondary care same day. Stop the ciclosporin (concern re possible Benign Intracranial Hypertension).	GP
Headache	Check blood pressure. If normal, treat with appropriate analgesia (paracetamol). If hypertension please refer to patients' named Consultant – may need treatment with antihypertensive agents. Significantly elevated blood pressure associated with headache requires emergency referral to named Consultant's hospital.	GP
Nausea and vomiting, diarrhoea	If possible then continue with the medication. If necessary then refer to the patient's named Consultant	GP
Hypertrichosis	Continue, provide reassurance that this is cosmetic and will settle off treatment. Refer to specialist team if significant problem.	GP
Gingival overgrowth	Continue and provide reassurance that this will stop with the discontinuation of ciclosporin Advise good dental hygiene. Refer to specialist if significant concerns	GP
Creatinine rises >30% from baseline	Repeat in 1 week and if still >30% above baseline withhold until discussed with the Consultant	GP

	Potassium rises to above the reference range	Withhold until discussed with the Consultant as risk of hyperkalaemia	GP
	Platelets <150 x 10^9/l	Withhold until discussed with the Consultant	GP
	'Significant' rise in fasting lipids	Discuss with the Consultant and consider starting a statin.	GP
	High BP ≥ 140/90 on two consecutive readings 2 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 Consultant.	GP
	AST, ALT or ALP more than 2 x upper limit of reference range	Withhold until discussed with the Consultant. Check any other reason such as drug interaction including over the counter medication as risk of hepatic dysfunction	GP
	The patient should be advised to report any of the following signs or symptoms to their GP without delay: Visual disturbance Significant headache		
	Other important co morbidities (e.g. Chickenpox exposure): Varicella status should be checked in all patients at diagnosis and vaccinate as soon as possible when the patient is off steroids and other immunosuppressant therapy. It is for the specialist to make the recommendation for vaccination at the appropriate time. Individuals who are non-immune and are exposed to chicken pox should be referred to the specialist centre by the GP on the same day for treatment. Live vaccinations should not be given while patients are on ciclosporin or other immunosuppressive agents.		
	Any adverse reaction to a black triangle drug or serious reaction to an established drug should be reported to the MHRA via the "Yellow Card" scheme.		
10.Baseline investigations	*List of investigations / monitoring undertaken by secondary care* Prior to commencing therapy the specialist team will check the child's blood pressure. Blood will be taken to check: urea and electrolytes, liver function and varicella status. Trough ciclosporin levels will be measured at Outpatient visits. Blood pressure will be monitored as ciclosporin can cause hypertension. Non-attendance for these appointments will be followed-up by the specialist Paediatric staff.		

<table>
<tr><td rowspan="3">11. Ongoing monitoring requirements to be undertaken by GP</td><td colspan="2">Is monitoring required?</td><td colspan="3">Yes</td></tr>
<tr><td>Monitoring</td><td>Frequency</td><td>Results</td><td>Action</td><td>By whom</td></tr>
<tr><td>Early morning urine dipsticks for protein</td><td>Daily</td><td>Three + positive proteinuria for three consecutive days</td><td>As per child's individual plan - contact specialist for advice or commence high-dose prednisolone course and consider a proton pump inhibitor to cover gastric side effects.</td><td>Patient / Parent / carer</td></tr>
<tr><td></td><td>FBC, U&E, LFT, BP, fasting lipids</td><td>In accordance with clinic appointments (usually 4-5 monthly), but a minimum of twice a year</td><td colspan="2">See Section 9: Adverse drug reactions above</td><td>Hospital</td></tr>
<tr><td>12. Pharmaceutical aspects</td><td colspan="5">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</td></tr>
<tr><td>13. Patients excluded from shared care</td><td colspan="5">• Unstable disease state
• Pregnant and breast feeding patients as ciclosporin should be discontinued.
• Patient does not consent to shared care.
• Patient does not meet criteria for shared care specified in section 3.</td></tr>
<tr><td>14. Responsibilities of initiating specialist</td><td colspan="5">• Initiate treatment and prescribe until dose is stable
• Undertake baseline monitoring.
• Dose adjustments.
• Monitor patient's initial reaction to and progress on the drug.
• Ensure that the patient has an adequate supply of medication until GP supply can be arranged.
• Patients will be considered suitable for transfer to GP prescribing ONLY when they meet the criteria listed in section 12 above.
• The consultant team will write formally to the GP to request shared care using the Shared Care Agreement Form (Appendix 2) which must be fully completed. Failure to supply all the required information will result in the refusal of the request until all information has been supplied.
• Patients will only be transferred to the GP once the GP has agreed via signing copies of the Shared Care Agreement Form (Appendix 2).
• Continue to monitor and supervise the patient according to this protocol, while the patient remains on this drug, and agree to review the patient promptly if contacted by the GP
• Provide GP with diagnosis, relevant clinical information and baseline results,</td></tr>
</table>

	treatment to date and treatment plan, duration of treatment before consultant review. • Provide GP with details of outpatient consultations, ideally within 14 days of seeing the patient or inform GP if the patient does not attend appointment. • Provide GP with advice on when to stop this drug. • Act upon communication from the GP in a timely manner. • Provide patient with relevant drug information to enable Informed consent to therapy. • Provide patient with relevant drug information to enable understanding of potential side effects and appropriate action. • Provide patient with relevant drug information to enable understanding of the role of monitoring. • Provide patient with monitoring booklet where appropriate. • Be available to provide patient specific advice and support to GPs as necessary.
15. Responsibilities of the GP	• Continue treatment as directed by the specialist. • Act upon communication from the specialist in a timely manner. • To formally reply to the request for shared care from the specialist. • Ensure no drug interactions with concomitant medicines. • To monitor and prescribe in collaboration with the specialist according to this protocol. • To ensure that the monitoring and dosage record is kept up to date (if applicable). • To undertake vaccination as directed by the initiating consultant, the BNF or Green Book. • Symptoms or results are appropriately actioned, recorded and communicated to secondary care when necessary. • Formally reply to the consultant's request to shared care within 14 days of receipt, using the shared care agreement forms (Appendix 2). NB the GP should only agree to the transfer of prescribing if all details of the form have been completed. • If the GP does not feel it is appropriate to take on the prescribing then the prescribing responsibilities will remain with the specialist. The GP should indicate the reason for declining. • Enter a READ code on to the patient record to highlight the existence of shared care for the patient. • Undertake more frequent tests if there is evidence of clinical deterioration, abnormal results, or symptoms suggesting abnormal hepatic function or other risk factors. Contact consultant team for advice on monitoring in these circumstances if required. • Check all monitoring results prior to issuing a repeat prescription to ensure it is safe to do so. • Monitor the patient's general wellbeing. • Seek urgent advice from secondary care if: o Visual disturbance and/or significant headache o Non-compliance is suspected o The GP feels a dose change is required o There is a deterioration renal function and/or hepatic function o The GP feels the patient is not benefiting from the treatment • The shared care agreement will cease to exist, and prescribing responsibility will return to secondary care, where: o The clinical situation deteriorates such that the shared care criterion of stability is not achieved. o The clinical situation requires a major change in therapy. o GP feels it to be in the best stated clinical interest of the patient for prescribing responsibility to transfer back to the consultant team. The

	consultant team will accept such a transfer within a timeframe appropriate to the clinical circumstances. There must be discussion between the consultant team and GP on this matter and agreement from the consultant team to take back full prescribing responsibility for the treatment of the patient. The consultant team should be given 14 days' notice in which to take back prescribing responsibilities from primary care.			
16. Responsibilities of the patient	• To take medication as directed by the prescriber, or to contact the GP if not taking medication • To attend hospital and GP clinic appointments, bring monitoring booklet (if issued) • Failure to attend will result in medication being stopped (on specialist advice). • To report adverse effects to their Specialist or GP.			
17.Additional Responsibilities e.g. Failure of patient to attend for monitoring, Intolerance of drugs, Monitoring parameters outside acceptable range, Treatment failure, Communication failure	**List any special considerations**	**Action required**	**By whom**	**Date**
	Nil	Nil		
18. Supporting documentation	The SCG must be accompanied by a patient information leaflet. http://www.medicinesforchildren.org.uk/search-for-a-leaflet/ciclosporin-for-nephrotic-syndrome/ Royal Manchester Children's Hospital patient information leaflet – Childhood Nephrotic Syndrome (see appendix).			
19. Patient monitoring booklet (may not be applicable for all drugs)	Patient monitoring booklet is not applicable in this case.			
20. Shared care agreement form	Attached below			
21. Contact details	See Appendix 1			

Appendix 1 – Local Contact Details

Lead author contact information	**Name:** Professor Nicholas Webb
	Email: Nicholas.Webb@cmft.nhs.uk
	Contact number: Professor Webb's secretary number is 0161 701 2961
	Organisation: Royal Manchester Children's Hospital

Commissioner contact information	**Name:** Roz Jones
	Email: roz.jones2@nhs.net
	Contact number: 01138252815
	Organisation: North of England Specialised Commissioning Team (North West Hub) NHS England

Secondary care contact information	**If stopping medication or needing advice please contact:** patient's name consultant
	Doctor: Professor N Webb, M Shenoy, R Lennon, A Kaur, D Wallace or N Plant
	Contact number: Their secretaries on 0161 701 2161
	Fax: N/A
	Hospital: Royal Manchester Children's Hospital Central Manchester Foundation Trust

Shared Care Agreement Form

Specialist request

***IMPORTANT: ACTION NEEDED**

Dear Dr *[insert Doctors name here]*

Patient name: *[insert Patients name here]*
Date of birth: *[insert date of birth]*
NHS Number: [insert NHS Number]
Diagnosis: *[insert diagnosis here]*

This patient is suitable for treatment with Ciclosporin (Neoral) for the treatment of Nephrotic Syndrome

This drug has been accepted for Shared Care according to the enclosed protocol (as agreed by Trust / CCG / GMMMG). I am therefore requesting your agreement to share the care of this patient.

The patient has been fully counselled on the medication.

Treatment was started on *[insert date started]* *[insert dose].*

If you are in agreement, please undertake monitoring and treatment from *[insert date]*
NB: date must be at least 1 month from initiation of treatment.

Baseline tests: *[insert information]*

Next review with this department: *[insert date]*

You will be sent a written summary within 14 days. The medical staff of the department are available at all times to give you advice. The patient will not be discharged from out-patient follow-up while taking *[insert text here]*.

Please use the reply slip overleaf and return it as soon as possible.

Thank you.

Yours

[insert Specialist name]

Shared Care Agreement Form

GP Response

Dear Dr *[insert Doctors name]*

Patient *[insert Patients name]*

NHS Number *[insert NHS Number]*

Identifier *[insert patient date of birth/address]*

I have received your request for shared care of this patient who has been advised to start *[insert text here]*

A I am willing to undertake shared care for this patient as set out in the protocol

B I wish to discuss this request with you

C I am unable to undertake shared care of this patient.

My reasons for not accepting are: *(Please complete this section)*

GP signature Date

GP address/practice stamp

Appendix – Patient Information Leaflet – RMCH – Childhood Nephrotic Syndrome

Central Manchester University Hospitals NHS

Royal Manchester Children's Hospital

Childhood nephrotic syndrome

Information for families

Shared Care Guideline Summary:
Ciclosporin for the treatment of *childhood nephrotic syndrome*

Drug	Ciclosporin (Neora®l) 100mg/ml Oral Solution 10 mg, 25 mg, 50 mg or 100 mg soft gelatin capsules
Indication	For use in nephrotic syndrome where the disease is frequently relapsing and standard first line therapy has been unsuccessful/inadequate. It can be used in both the steroid-sensitive and steroid-resistant subtypes.
Overview	The treatment of steroid dependent or steroid resistant nephrotic syndrome (associated with adverse prognostic features) due to minimal change glomerulonephritis, focal segmental glomerulosclerosis or membranous glomerulonephritis in both adults and children.
Specialist's Responsibilities	**Initial investigations:** Prior to commencing therapy the specialist team will check the child's blood pressure. Blood will be taken to check: urea and electrolytes, liver function and varicella status. Trough ciclosporin levels will be measured at outpatient visits. Blood pressure will be monitored as ciclosporin can cause hypertension. Non-attendance for these appointments will be followed-up by the specialist Paediatric staff. **Initial regimen:** In children aged 1 month to 18 years old the dose is 3mg/kg twice daily (rounded to the nearest measurable dose or capsule where appropriate) and treatment is initiated by the specialist team following discussion with the patient and family. Note: this dose may be increased, if necessary, in corticosteroid-resistant disease. To guide treatment, a blood test is performed to measure a trough level, 12 hours after the previous dose. This will be done at an Outpatient attendance. Currently there are no evidence-based guidelines for trough levels but the range 50-125 micrograms/l is used in clinical practice. **Clinical & Safety monitoring:** FBC, U&E, LFT, BP, fasting lipids in accordance with clinic appointments (every 4-5 months) but a minimum of twice a year. **Prescribing duration:** This is generally up to two years, but it can be continued longer by the specialist team if felt to be beneficial. A renal biopsy will be performed after two years of treatment because of the potential risk of nephrotoxicity (tubulointerstitial lesions). If treatment continues beyond two years then patients will need a biopsy annually. **Prescribing details:** Specialist initiated. Transferred to GP once stabilised. **Documentation:** Patients will only be transferred to the GP once the GP has agreed by signing copies of the Shared Care Agreement Form.
GP's Responsibilities	**Maintenance prescription:** Prescribe ciclosporin in accordance with the specialist's recommendations. **Clinical monitoring:** To report to and seek advice from the specialist on any aspect of patient care which is of concern to the GP and may affect treatment. **Safety monitoring:** None to be carried out by GP **Duration of treatment:** Stop treatment on advice of specialist, generally after 2 years. **Re-referral criteria:** Seek urgent advice from secondary care if:

	➢ Visual disturbance and/or significant headache ➢ Non-compliance is suspected ➢ The GP feels a dose change is required ➢ There is a deterioration renal function and/or hepatic function ➢ The GP feels the patient is not benefiting from the treatment **Documentation:** Formally reply to the consultant's request to shared care within 14 days of receipt, using the shared care agreement forms.

Adverse Events

Adverse events	Action
Visual disturbance	Refer to secondary care same day. Stop the ciclosporin (concern re possible Benign Intracranial Hypertension).
Headache	Check blood pressure. If normal, treat with appropriate analgesia (paracetamol). If hypertension please refer to patients' named Consultant – may need treatment with antihypertensive agents. Significantly elevated blood pressure associated with headache requires emergency referral to named Consultant's hospital.
Nausea and vomiting, diarrhoea	If possible then continue with the medication. If necessary then refer to the patient's named Consultant
Hypertrichosis	Continue, provide reassurance that this is cosmetic and will settle off treatment. Refer to specialist team if significant problem.
Gingival overgrowth	Continue and provide reassurance that this will stop with the discontinuation of ciclosporin Advise good dental hygiene. Refer to specialist if significant concerns
Creatinine rises >30% from baseline	Repeat in 1 week and if still >30% above baseline withhold until discussed with the Consultant
Potassium rises to above the reference range	Withhold until discussed with the Consultant as risk of hyperkalaemia
Platelets <150 x 10^9/l	Withhold until discussed with the Consultant
'Significant' rise in fasting lipids	Discuss with the Consultant and consider starting a statin.
High BP ≥ 140/90 on two consecutive readings 2 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 Consultant.
AST, ALT or ALP more than 2 x upper limit of reference range	Withhold until discussed with the Consultant. Check any other reason such as drug interaction including over the counter medication as risk of hepatic dysfunction

Contra-indications Cautions Drug Interactions	Please refer to the BNF and/or SPC for information
Other Information	There is no maximum dosage of ciclosporin. The dose may be increased by the specialist according to what is required to generate acceptable trough levels. Note: if capsules are required, the dose may be rounded up or down to the nearest capsule
Contact Details	**Name:** **Address:** **Telephone:**