HSC Health and Social Care

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

Interface Pharmacist Network Specialist Medicines

Ciclosporin (non-transplant indications)

Shared Care Guideline

Specialist details	Patient identifier
Name: _____	
Location: _____	
Tel: _____	**Date:** _____

Introduction

Licensed indications include: rheumatoid arthritis, atopic dermatitis, severe psoriasis, uveitis, nephrotic syndrome.

Unlicensed indications include: pyoderma gangrenosum, blistering conditions, connective tissue disorders, severe ulcerative colitis, aplastic anaemia, chronic refractory idiopathic thrombocytopenic purpura (ITP), neurosarcoidosis, vasculitis of any aetiology, myasthenia and inflammatory neuropathies, refractory asthma, inflammatory eye disease, chronic urticarial angiodoema.

Adult dosage and administration

Indication	Initial dose	Dosing schedule (notes)
Atopic dermatitis	2.5 - 5mg/kg daily in two divided doses	Increased to a maximum 5mg/kg daily if no improvement within 2 weeks. Initial dose of 5mg/kg daily is justified if condition requires rapid improvement
Severe psoriasis	2.5 - 5mg/kg daily in two divided doses	Increased to a maximum 5mg/kg daily if no improvement within 1 month. Initial dose of 5mg/kg daily is justified if condition requires rapid improvement
Rheumatoid arthritis	3mg/kg daily in two divided doses	After 6 weeks, may be increased at 2 - 4 week intervals by 25mg until clinically effective or the maximum dose of 5mg/kg is reached
Uveitis	5mg/kg daily in two divided doses	May be increased to 7mg/kg daily in refractory cases. Once remission is achieved, maintenance doses should not exceed 5mg/kg daily
Other inflammatory eye diseases	2mg/kg daily in two divided doses	Titrate upward using ciclosporin levels. Usual maximum 4mg/kg daily
Nephrotic syndrome	5mg/kg daily in two divided doses (In impaired renal function, the initial dose should not exceed 2.5mg/kg/day)	The dose should not exceed 5mg/kg/day. For maintenance treatment, the dose should be slowly reduced to the lowest effective level
ITP	100mg daily in two divided doses	Dose may be titrated according to clinical response and WCC
Ulcerative colitis	The total oral dose is up to 5 mg/kg per day in two divided doses	
Neurology (inflammatory myopathies)	4 - 6mg/kg daily in two divided doses	May be increased to max 10mg/kg daily if necessary to achieve required therapeutic levels
Respiratory (refractory asthma)	1.5mg/kg daily in two divided doses	Titrate upwards using ciclosporin levels. Usual maintenance dose 100 - 150mg twice daily

Dose adjustments are made during therapy based on clinical response and in some cases ciclosporin levels.

Available as:

Neoral® 10mg, 25mg, 50mg and 100mg capsules and 100mg/ml solution (note small volumes required for dosing).

Deximune®, Capimune®, Capsorin® 25mg, 50mg and 100mg capsules.

Ciclosporin must be prescribed by brand name only and should not be prescribed generically.

Hospital specialist responsibilities

- Assess if the patient is suitable for treatment with ciclosporin.
- Agree shared care with the patient's GP.
- Varicella Zoster immune status: if non-immune, consider immunisation prior to starting treatment.
- Advise the GP on the dose of ciclosporin to be prescribed. If already initiated in secondary care, specify brand.
- Provide patient/carer with relevant (preferably written) information on use, side-effects and need for monitoring of medication.
- Undertake baseline tests as indicated in the monitoring table.
- Review results of safety monitoring and request additional tests as required.
- Perform trough drug levels and adjust dose if required (ensure time of last dose is written on request form).
- Monitor disease response to treatment and need to continue therapy.
- Continue to review the patient at agreed specified intervals, sending a written summary to the GP whenever the patient is reviewed.
- Provide any other information for the GP including ciclosporin dose adjustments.

<table>
<tr><th colspan="2">Monitoring table</th><th>Hospital specialist</th><th colspan="3">GP</th><th>Hospital specialist</th></tr>
<tr><th rowspan="2">Test</th><th rowspan="2">Indication</th><th rowspan="2">Pre-treatment baseline</th><th colspan="3">During treatment</th><th rowspan="2">At review</th></tr>
<tr><th>Until on stable dose for 6 weeks</th><th>Thereafter</th><th>Only where indicated by specialist **</th></tr>
<tr><td>FBC</td><td rowspan="5">Baseline assessment, dose adjustment</td><td rowspan="5">✓</td><td rowspan="5">Every 2 weeks</td><td rowspan="5">Every month</td><td rowspan="5">Every 3 months **</td><td rowspan="6">As part of the review or as clinically indicated</td></tr>
<tr><td>LFTs</td></tr>
<tr><td>U&Es, eGFR*</td></tr>
<tr><td>Blood pressure*</td></tr>
<tr><td>Blood glucose</td></tr>
<tr><td>ESR/CRP
(Rheumatology and Gastroenterology only)</td><td>Disease activity scoring</td><td>✓</td><td colspan="3">Every 3 months</td></tr>
<tr><td>Height & weight</td><td>Baseline assessment</td><td>✓</td><td colspan="3" rowspan="3">Not routinely required</td><td rowspan="5">If clinically indicated</td></tr>
<tr><td>Chest x-ray</td><td rowspan="2">Baseline respiratory assessment and TB screening</td><td rowspan="2">If clinically indicated</td></tr>
<tr><td>PFTs, TB screening if indicated</td></tr>
<tr><td>Urinalysis</td><td>To assess for renal disease (proteinuria) or infection</td><td>✓</td></tr>
<tr><td>Lipids</td><td>To detect increase in blood lipids</td><td>✓</td><td colspan="3">Every 6 months</td></tr>
<tr><td>Trough ciclosporin level</td><td>Dose adjustment</td><td>If clinically indicated</td><td colspan="3">If requested by specialist</td></tr>
<tr><td colspan="2">Ask about oral ulceration, sore throat, unexplained rash or unusual bruising/bleeding</td><td>✓</td><td colspan="3">At every consultation</td><td>✓</td></tr>
</table>

If a further DMARD /JAKis added as combination therapy, or the dose is increased, the initial starting schedule should be reinstated.
There may be clinical circumstances where the frequency of monitoring may vary and this should be specified by the initiating specialist
* Renal function and blood pressure should be checked on at least TWO occasions before commencing treatment.
** Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis as recommended by specialist at review or by specialist communication

GP responsibilities

- Prescribe ciclosporin **by brand;** a number of brands are available. If already initiated in secondary care, continue on same brand.
- Arrange and record ongoing monitoring as advised by specialist (see monitoring table), ensuring practice systems are in place to recall patients for monitoring blood tests.
- The specialist may occasionally request tests or ciclosporin levels (ensure time of last dose is written on request form) to be repeated at the GP practice but will provide specific advice on this and the process to follow.
- Follow-up any non-compliance with the monitoring schedule. The risks of cessation of therapy versus risks of toxicity should be considered. Contact the specialist if treatment is stopped or further advice required.
- Report any adverse drug reactions to the initiating specialist and the usual bodies (eg. MHRA/CHM).
- Ensure no drug interactions with other medicines.
- Administer **inactivated** influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check patient has had ONE DOSE of pneumococcal vaccine (revaccination is not recommended except every five years in patients whose antibody levels are likely to have declined more rapidly eg asplenia) see BNF or Green Book
- Provide COVID 19 and **inactivated** shingles (Shingrix®) vaccination as appropriate as per local arrangements and Green Book
- Post exposure prophylaxis (antivirals or VZIG if antivirals are contraindicated) should be considered in non-immune at risk patients if exposed to chickenpox or shingles. Contact the consultant virologists, Regional Virus Laboratory, Royal Group of Hospitals on 07889 086 946 for advice if exposure is suspected. For other queries eg. those concerning exposure, infection or any recommendations relating to healthy susceptible household contacts, consult the Green Book and/or take additional advice from Regional Virus Laboratory, Royal Group of Hospitals
- Ask about oral ulceration/sore throat; unexplained rash or unusual bruising at every consultation.

Withhold ciclosporin and contact specialist if:

- WCC < 3.5 x 10^9/L
- Neutrophils < 1.6 x 10^9/L
- **Unexplained** eosinophilia > 0.5 x 10^9/L
- Platelets < 120 x 10^9/L (except ITP)
- Potassium > 5.5mmol/L
- MCV > 105fL, (check B12 & folate & TFT)
- AST/ALT > 3 times the upper limit of normal (for results between 2 - 3 x ULN, continue ciclosporin, repeat bloods and seek specialist advice). Minor elevations of AST/ALT are common
- If renal impairment develops (not always appropriate to stop but may need dose adjustment)
- Unexplained fall in serum albumin
- Oral ulceration / sore throat
- Unexplained rash / abnormal bruising
- New or increasing dyspnoea or dry cough.

Normal reference range may vary slightly between labs.
Please note an unusual fall or rise or a consistent downward or upward trend in any value should prompt review of the patient and extra vigilance. Some patients may have abnormal baseline values, specialist will advise.

Adverse effects, precautions and contraindications

Hypertension is common. If treatment is required, follow standard antihypertensive therapy guidelines but do not use diltiazem, nicardipine, lercandipine or verapamil as they may increase plasma ciclosporin levels. Nifedipine levels may be increased by ciclosporin. Refer if hypertension remains uncontrolled.
Nephrotoxicity. If a significant sustained reduction in GFR occurs, refer to specialist. Caution is advised if used concomitantly with NSAIDs, ACE inhibitors or angiotensin II antagonists, to minimise risk of acute kidney injury.
Infection: immunosuppressants can increase susceptibility to infection.
Benign gingival hyperplasia is relatively common. Patients should be advised on good oral hygiene.
Blood Disorders: leucopenia, thrombocytopenia and anaemia. GPs should be alert to any unexplained bruising or bleeding.
Hypertrichosis: discuss management with specialist.
Headache, tremor and parathesia are frequently seen. If persistent or severe they may reflect toxic levels of ciclosporin - refer to initiating specialist.
Hyperlipidaemia. Ciclosporin can induce a reversible increase in blood lipids. It is therefore advisable to perform lipid determinations before treatment and thereafter as appropriate. Refer to initiating specialist if uncontrolled.
Cancer risk. Patients receiving long-term immunosuppressive drugs are at increased risk of developing a malignancy. The most frequently occurring types are lymphoma and skin malignancy. The avoidance of excessive exposure to the sun, and the use of high factor sunscreen and protective clothing are advised. Adherence to population screening programmes is particularly important in this population.
Ultraviolet B irradiation/PUVA photochemotherapy must not be given to psoriatic arthritis patients on ciclosporin.
Caution is required for patients with previous PUVA exposure.
Pregnancy / contraception. Women of childbearing potential receiving ciclosporin should be advised to use effective contraception. Patients discovered or planning to become pregnant should be referred to the initiating specialist at the earliest opportunity without stopping ciclosporin.
Breastfeeding. Women being treated with ciclosporin should seek specialist advice.
Live vaccines. Consult the Green Book and take additional advice from initiating specialist if required.

Common drug interactions

Ciclosporin is metabolised by cytochrome P450 and interacts with many drugs that are metabolised by this group of liver enzymes. **Ciclosporin is particularly noted for numerous significant drug interactions**. The following drugs should not be initiated by GP unless discussed with specialist.
Antibiotics: erythromycin, clarithromycin and azithromycin increase ciclosporin levels. Rifampicin decreases ciclosporin levels.
Anti-epileptics: carbamazepine, phenobarbital, primadone and phenytoin decrease ciclosporin levels.
Antifungals: fluconazole, itraconazole, posaconazole, voriconazole, isavuconazole and ketoconazole increase ciclosporin levels.
Anti-obesity drugs: orlistat decreases ciclosporin levels.
Calcium channel blockers: diltiazem, nicardipine, verapamil and lercanidipine increase ciclosporin levels. Nifedipine levels may be increased by ciclosporin.
Dabigatran: concomitant use should be avoided. **Edoxaban or apixaban** should be used with caution.
Patients should avoid taking **grapefruit juice or eating grapefruit** as this can cause an increase in ciclosporin levels.
Potassium-sparing diuretics, potassium salts, aldosterone antagonists eg. spironolactone and eplerenone may exacerbate ciclosporin induced hyperkalaemia and should only be initiated with regular monitoring of U&Es.
St John's Wort is known to decrease ciclosporin levels. Herbal medicines may have an effect on drug levels. Avoid concomitant use.
Statins increase risk of myopathy. Avoid concomitant use with rosuvastatin or simvastatin. Lower doses of other statins should be used to reduce the risk of muscular toxicity.
Fibrates: increase risk of nephrotoxicity.
Tacrolimus: avoid concomitant use.
Other interacting drugs of significance: aliskerin, ambrisentan, amiodarone, apalutamide, aprepitant, antiretrovirals, baracitinib, berotralstat, bosentan, carvedilol, ceritinib, colchicine, crizotinib, digoxin, dronedarone, enzalutamide, filgotininb, methotrexate, octreotide, pitolisant, toficitinib.

Communication

For any queries relating to this patient's treatment with ciclosporin, please contact the specialist named at the top of this document.

This information is not inclusive of all prescribing information and potential adverse effects.
Please refer to full prescribing data in the SPC at www.medicines.org.uk or the BNF

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