NHS Shropshire Clinical Commissioning Group

The Robert Jones and Agnes Hunt NHS Orthopaedic Hospital NHS Foundation Trust

Oral Ciclosporin
Rheumatology Local Safety Monitoring Schedule

This local safety monitoring schedule supports clinicians under the Local Enhanced Service for High Risk Drug Monitoring (formerly Near Patient Testing). Aligning clinical and prescribing responsibility enhances patient safety because the individual signing the prescription will also be responsible for ensuring that any necessary monitoring has been undertaken and will have access to the results of this.

The prescriber and specialist assume joint clinical responsibility for the drug and the consequences of its use.

Specialist details	GP details	Patient details
Name:	Name:	Name:
Address:	Address:	Contact number:
Email:	Email:	
Contact number:	Contact number:	

Introduction

Licensed indications: severe rheumatoid arthritis
Unlicensed indications: Other refractory inflammatory arthritis such as psoriatic arthritis

Adult dosage and administration

Dose adjustments are made during therapy based on clinical response and blood levels.

Indication	Initial Dose	Dosing Schedule
Rheumatoid arthritis	2.5mg/kg daily in two divided doses for 6 weeks	May be increased at 2-4 week intervals by 25mg until clinically effective or the maximum dose of 4mg/kg/day is reached.

Patients should be stabilised on a **single brand** of oral ciclosporin because switching between different brands/formulations without close monitoring may lead to clinically important change in bioavailability. **Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching**.

Available as:	10mg capsule	25mg mg capsule	50mg capsule	100mg capsule	100mg/ml solution (note small volumes required for dosing)
Capimune®		X	X	X	
Capsorin®		X	X	X	
Deximune®		X	X	X	
Neoral®	X	X	X	X	X

It may take up to 3 months for significant response to be achieved.

Specialist responsibilities

- Provide GP with clear written advice on required dosage and frequency of ciclosporin, written monitoring guidelines and drug information. Check for interactions with other medicines.

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- Provide patient/carer with relevant (preferably written) information on use side effects and need for monitoring of medication.
- Discuss the need for adequate contraception if appropriate.
- Provide monitoring record booklet and record baseline results if appropriate.
- Baseline tests:
    - **FBC** (including differential white cell count)
    - **U&Es + creatinine** (2 tests, 2 weeks apart for mean value AND eGFR)
    - **LFTs**
    - **Blood pressure** (2 tests, ≤ 140/90 mmHg on 2 occasions, 2 weeks apart)
    - **Fasting Lipids**
    - **ESR or CRP**
    - **Varicella zoster IgG in suspected non-immune patients** and notify general practitioner as appropriate

- In patients with psoriatic arthritis assess whether patient has received PUVA before commencing ciclosporin. If total dose > 1000J discuss with dermatologists.
- Review results of safety monitoring and request additional tests as required.
- Titrate ciclosporin to an effective dose.
- Monitor disease response to treatment and need to continue therapy.
- Identify and report adverse events to the GP and the MHRA (via yellow card).
- 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

Primary Care responsibilities

- Prescribe ciclosporin (by brand name) at the dose recommended if patient is having appropriate regular blood monitoring and monitoring results are within acceptable range.
- Repeat prescriptions should be removed from the surgery repeats pile and retained separately for prescribers to review prior to signing. Maximum 28 days supply.
- Arrange and record ongoing monitoring as agreed with specialist
    - **U&E+ creatinine, Blood pressure**: every 2 weeks until dose stable for 3 months, then monthly thereafter
    - **FBC, LFTs:** monthly until dose stable for 3 months, then three monthly thereafter
    - **Fasting Lipids**: six monthly
    - **ESR or CRP** may be required 3 monthly

- Frequency of monitoring may be increased if ciclosporin dose is adjusted.
- Patients on combination DMARD therapy may need more frequent monitoring. Please check the Local Safety Monitoring Schedule for each drug.
- Report any adverse drug reactions to the initiating specialist and the usual bodies (e.g. MHRA).
- Ensure no drug interactions with other medicines.
- Administer 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 e.g. asplenia.) - see BNF or Green Book
- Ask about oral ulceration/sore throat; unexplained rash or unusual bruising at every consultation.

Varicella zoster

- *Non-immune patients* should avoid contact with people with chicken pox or shingles; consider passive immunisation using varicella immunoglobulin (VZIG) if exposure is suspected (contact Public Health England/Blood Transfusion Service for advice). Consider immunisation of non- immune patients before starting immunosuppression (if recommended by specialist)
- Varicella infection can be severe in immunosuppressed patients, and early systemic anti-viral and supportive therapy may be required. Suspend ciclosporin until recovered.

- If patient develops symptoms/signs of systemic infection, this should be treated promptly and ciclosporin withheld until the infection has cleared.
- Ensure a clinician updates the patient's record following specialist review.

Withhold Ciclosporin and contact specialist if:

- Creatinine — Increase by > 30% of baseline value
- Potassium — > 5.3 mmol/L
- Platelets — < 150 x 10^9/L (except BMT and ITP)
- AST / ALT / ALK PHOS — > 2 times the upper limit of normal
- Blood Pressure — >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 specialist team
- Lipids — Significant rise in lipids
- Oral Ulceration / sore throat
- Unexplained rash / abnormal bruising

Please note: A rapidly increasing or decreasing trend in any values should prompt caution and extra vigilance. Some patients may have abnormal baseline values, specialist will advise.

Results should be recorded in the patient's shared care monitoring booklet, if issued

Adverse effects, Precautions and Contra-indications

General: Tremor, hirsutism, diarrhoea, anorexia, nausea and vomiting.

Hypertension is common. Standard antihypertensive therapy can be used. Refer if hypertension remains uncontrolled.

Nephrotoxicity: can be acute. If serum creatinine consistently >30% above patients baseline, decrease ciclosporin dose by 25-50%.

Benign gingival hyperplasia is relatively common. Patients should be advised on good oral hygiene.

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.

Cancer risk: Patients receiving ciclosporin are at increased risk of lymphomas and malignancies of the skin: avoiding excessive exposure to the sun and use of high factor sunscreens are advised.

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. Patients should not breastfeed whilst receiving ciclosporin.

Vaccines. Live vaccines should be avoided, except on the advice of initiating specialist (See Green Book re zoster vaccine).

Contraindications

- Known hypersensitivity to ciclosporin
- Concomitant administration with *Hypericum perforatum* (St John's Wort)
- Uncontrolled hypertension
- Renal failure and liver failure
- Hyperkalaemia
- Suspected systemic infection or sepsis
- < 18 years or age

Common Drug Interactions

There are numerous drug interactions with ciclosporin. Please refer to the latest BNF/SPC before starting any new drugs. Common examples are shown below.

Antibiotics: erythromycin and clarithromycin increase ciclosporin levels; rifampicin decreases ciclosporin level.

Antifungals: fluconazole; itraconazole and ketoconazole increase ciclosporin levels.

Calcium-channel blockers: diltiazem; nicardipine and verapamil increase ciclosporin levels. Ciclosporin increases concentration of lercanidipine and felodipine. Concurrent use of calcium channel blockers and ciclosporin increases risk of gingival overgrowth

Anti-epileptics: carbamazepine; phenobarbital and phenytoin decrease ciclosporin levels.

Anti-obesity drugs: orlistat decreases ciclosporin levels.

Colchicine: Avoid due to risk of serious muscle disorders.

Digoxin: Ciclosporin causes a large rise in digoxin levels in some patients.

NSAIDs (and other nephrotoxic drugs) should be used with caution. Close monitoring of renal function is essential. Lower doses of NSAIDs may be necessary if given concomitantly. Halve the dose of **diclofenac** if co-prescribed with ciclosporin

Statins: Atorvastatin – do not exceed 10mg daily when given with ciclosporin

Fluvastatin -Starting and maintenance dose of fluvastatin should be as low as possible when combined with ciclosporin

Pravastatin - concomitant administration of pravastatin and ciclosporin leads to an approximately 4-fold increase in pravastatin systemic exposure - lower doses should be used to reduce the risk of muscular toxicity;

Simvastatin and Rosuvastatin contra-indicated with ciclosporin

Potassium-sparing diuretics may exacerbate ciclosporin-induced hyperkalaemia and should only be initiated with regular monitoring of U&E.

ACE Inhibitors and Angiotension II Receptor Antagonists – increased risk of hyperkalaemia when given with ciclosporin

St John's Wort. Avoid concomitant use.

Patients should avoid taking **grapefruit juice** or eating grapefruit as this can cause an increase in ciclosporin levels.

Tacrolimus is contra-indicated

Communication

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

This information is not inclusive of all prescribing information, potential adverse effects and drug interactions

Please refer to full prescribing data in the SPC or the BNF

References

GMC: Prescribing guidance: Shared care www.gmc-uk.org/guidance/ethical_guidance/14321.asp(accessed 20/10/2014)

NMC : Standards of proficiency for nurse and midwife prescribers http://www.nmc-uk.org/Documents/NMC-Publications/NMC-Standards-proficiency-nurse-and-midwife-prescribers.pdf (accessed 3/11/2014)

SPC Neoral : http://www.medicines.org.uk/emc/medicine/1307

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Chakravarty, K., McDonald, H., Pullar, T. et al. (2008) BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology* **47**(6), 924-925.