SHARED CARE GUIDELINE

Drug: Ciclosporin

Introduction	**Indications**: Licensed: Treatment of psoriasis and atopic dermatitis; rheumatoid arthritis and nephrotic syndrome Unlicensed: Severe ulcerative colitis – cited in NICE guidelines however use is declining **Background:** Ciclosporin is a cyclic polypeptide with immunosuppressive properties. Studies suggest that ciclosporin inhibits the development of cell-mediated reactions. It appears to block the resting lymphocytes in the G_0 to G_1 phase of the cell cycle, and also inhibits lymphokine production and release, including interleukin 2 (T-cell growth factor). The available evidence suggests that ciclosporin acts specifically and reversibly on lymphocytes. It does not depress haemopoeisis and has no effect on the function of phagocytic cells. Response to treatment may take up to 3 months. **Definitions:** Stable dose – the dose will be titrated to achieve efficacy at the lowest dose. Once efficacy achieved and provided the patient can tolerate the dose, this will be termed "stable dose" Stable bloods – results of blood tests remain below the "alert" thresholds as set by national guidelines and have stayed at similar levels for at least two consecutive tests. N.B. The patient can continue to have active disease despite being on a stable dose or having stable bloods, so the "patient" is not referred to as "stable"
Form	Oral Solution; 100mg/ml[2] 10mg, 25mg, 50mg, 100mg[3]
Dose & Administration	Starting dose 2.5-5mg/kg/day (can be lower i.e. 50mg/day) in two divided doses depending on disease severity and then treated according to response; maximum dose 5mg/kg/day. Dose titration will vary depending on indication (see BNF for further details)

Secondary Care Responsibilities	• Confirm the diagnosis.
	• Check for absence of pregnancy in women of child-bearing age and ensure the patient understands the importance of contraception.
	• Discuss the benefits and side effects of treatment with the patient. Ensure that the patient understands which warning symptoms to report.
	• Perform pre-treatment screening:
	  ○ FBC, LFTs, U&Es, creatinine/ eGFR, K^+, Mg^{++}, uric acid and fasting lipids.
	  ○ Blood pressure measured on two occasions 2 weeks apart. Treat any hypertension > 140/90
	• Ensure that the patient understands not to expect improvement from the treatment straight away.
	• Provide the patient with a monitoring and dosage record booklet and ensure that the patient knows when and where to attend for monitoring. Encourage the patient to take responsibility for ensuring that results of tests are entered in the monitoring booklet.
	• Make arrangements for shared care with the patient's GP
	• Review the patient regularly to monitor the patient's response to therapy.
	• Advise the GP on frequency of monitoring, management of any dose adjustments and when to stop treatment.
	• Ensure that clear backup arrangements exist for GPs to obtain advice.

Primary Care Responsibilities	• Provide the patient with prescriptions for Ciclosporin • Ensure that the patient understands their treatment and which warning symptoms to report (see adverse reactions below). • Monitor at the recommended frequencies (see MONITORING below) and ensure that test results are recorded in the monitoring booklet. • Report any adverse events to the consultant or specialist nurse and stop treatment on their advice or immediately if an urgent need arises (see MONITORING below). • Report any worsening of control of the condition to the consultant or the specialist nurse. • Refer immediately if a female patient discovers she is pregnant whilst taking Ciclosporin. • Follow recommended immunisation programme.
Immunisation	• Annual flu vaccination is recommended. • Pneumococcal vaccination is recommended • In patients exposed to chicken pox or shingles, if required, passive immunisation should be considered for varicella. Refer to Green book: Varicella: the green book, chapter 34 - Publications - GOV.UK • Live vaccines should be avoided, including shingles, and for up to three months following treatment.

Common Drug Interactions	There are numerous drug interactions with ciclosporin; please refer to the SPC and BNF for a detailed description before starting any new drugs. • Some antibiotics and antifungals eg. Clarithromycin, erythromycin, itraconazole, Miconazole, macrolides, sulphonamides (increased plasma concentration of ciclosporin) • Diclofenac: Reduce the dose of diclofenac by 50% • Tacrolimus should be avoided • Lercanidipine should be avoided • Statins. Simvastatin: maximum dose 10mg/day • Nifedipine: use with caution • Digoxin: May increase the serum levels of digoxin • St. John's Wort: To be avoided decreases ciclosporin activity • Potassium sparing diuretics: increased risk of hyperkalaemia • Patients should be advised to avoid grapefruit or grapefruit juice one hour before or after taking ciclosporin. N.B. Occasional monitoring of drug levels of ciclosporin may be clinically appropriate when there is concomitant prescribing of drugs which affect ciclosporin blood levels
Cautions	• Grapefruit including grapefruit juice must be avoided for 1 hour before or after taking ciclosporin tablets as bioavailability is increased. • Due to potential risk of skin malignancy patients should be advised to avoid excessive exposure to the sun and to use high factor sunscreens. They should not receive concomitant ultraviolet B irradiation or PUVA photo chemotherapy. • NSAIDs due to risk of hypertension and renal impairment
Contraindications	• Hypersensitivity to ciclosporin • Uncontrolled hypertension. • Impaired renal function • Malignancy • Renal failure and liver failure. • Hyperkalemia • Suspected systemic infection or sepsis • Pregnancy (except where continuing treatment outweighs the risks – discuss with the specialist team) • Breastfeeding. • Live vaccines • Co-prescribing of Bosentan, Dabigatran, Aliskeran, Tacrolimus, products containing hypericum perforatium (St John's Wort), Colchicine

This guidance does not replace the SPC's, which should be read in conjunction with this guidance.

MONITORING AND ADVERSE EFFECTS

Treatment Status	FBC	LFT	U+E	K^+	Creatinine/ eGFR	ESR or CRP	Fasting lipids	BP
Initial monitoring in first 3 months	monthly	monthly	Every two weeks	Every three months	Every 2 weeks	Every 3 months (for RA only)	At baseline and after one month	At every appointment
After 3 months	Every three months	Every three months	monthly	Every three months	monthly	Every 3 months (for RA only)	N/A	monthly

***Please note:** If the patient is also being treated with **leflunomide**, increased monthly monitoring is required, as specified in the leflunomide shared care guidance. (Where other biologic/DMARDs are used in combination with ciclosporin, the standard monitoring requirements, as outlined above, continue to apply).

As per secondary care responsibilities, for clarity the frequency of monitoring should be specified in the initial shared care request.

- Blood pressure should be maintained ≤ 140/90. If BP ≥140/90 on 2 consecutive occasions 2 weeks apart, treat hypertension before considering stopping ciclosporin. Note interactions with several anti-hypertensives.
- Occasional monitoring of drug levels of ciclosporin may be clinically appropriate when there is concomitant prescribing of drugs which affect ciclosporin blood levels

In the event of the following adverse laboratory results or patient reported symptoms, withhold ciclosporin until discussed with specialist team and repeat test after two weeks:

- Platelets < 150 x 10^9/L or less than the lower limit of reference range as per lab
- AST/ALT >2 times the upper limit of reference range and no other explanation
- Creatinine raised >30% from baseline on two results 1 week apart
- Potassium raised above the reference ranges
- Fasting lipids raised significantly from baseline
- BP uncontrolled or non-responsive to treatment
- Abnormal bruising (check FBC)
- Patient systemically unwell with significant infection

Other adverse effects:

- Hypertension
- Decreased resistance to infection
- Benign gingival hyperplasia is relatively common. Patients should be advised on good oral hygiene
- Headache, tremor and paraesthesia are common. If persistent or severe they may reflect toxic levels of ciclosporin. Discuss with the specialist team
- Ciclosporin increases the risk of malignancies including skin cancer
- Hyperlipidaemia, hyperglycaemia, anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia, convulsions, renal dysfunction, leucopenia, nausea, vomiting, abdominal discomfort, pain, diarrhoea, peptic ulcer, hirsutism, myalgia, muscle cramps, pyrexia and fatigue are all common

This list is not exhaustive; please refer to SPCs and BNF.

References

1. http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmard_therapy.pdf
2. http://www.medicines.org.uk/emc/medicine/28677/SPC/Neoral+Solution/
3. http://www.medicines.org.uk/emc/medicine/1307/SPC/Neoral+Soft+Gelatin+Capsules/
4. BNF 66 September 2013-March2014
5. http://cks.nice.org.uk/dmards#!scenariorecommendation:3
6. Drug safety update, Vol 3, Issue 5 MHRA 2009. http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con065445.pdf

RELEVANT CONTACT LIST

Speciality	
Name and Title	Tel. No.