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 10mg, 25mg, 50mg, 100mg
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. • 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[3]: height, weight, blood pressure, FBC, LFT, albumin, creatinine/ calculated GFR, and glucose. It may be of value to obtain an electrocardiogram (ECG) in some patients, especially when commencing medications associated with hypertension. • Patients should be assessed for co-morbidities, including evaluation for respiratory disease and screening for occult viral infection. • Ensure that the patient understands not to expect improvement from the treatment straight away. • Provide the patient with prescriptions for Ciclosporin until on stable dose and they have undergone monthly monitoring for a minimum of 3 months. 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 once on stable dose and having undergone monthly monitoring for a minimum of 3 months. • 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. • Follow recommended immunisation programme.
Immunisation	• Annual flu vaccination is recommended. • Pneumococcal vaccination is recommended • Covid-19 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 unless specialist advice has been sought.

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 e.g. 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 • Live vaccines • Co-prescribing of Bosentan, Dabigatran, Aliskeran, Tacrolimus, products containing hypericum perforatium (St John's Wort), Colchicine
Pregnancy & Breastfeeding	• According to the BSR and BHPR guideline[4] on prescribing drugs in pregnancy and breastfeeding, ciclosporin is compatible throughout pregnancy at the lowest effective dose and mothers on ciclosporin should not be discouraged from breastfeeding. • Based on limited evidence, ciclosporin is compatible with paternal exposure.

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	K^+	Creatinine/ calculated GFR	Albumin	BP / Glucose
Initial monitoring until on stable dose for 6 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks
For next 3 months	Monthly	Monthly	Monthly	Monthly	Monthly	Monthly
Thereafter**	Monthly	Monthly	Monthly	Monthly	Monthly	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).

**Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis.

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

Dose increases should be monitored by FBC, creatinine / calculated GFR, albumin and LFTs every 2 weeks until on stable dose for 6 weeks and then revert to previous schedule

The team responsible for prescribing the medication should also hold responsibility for monitoring i.e. prescribing to be carried out in Primary care only once patient on stable dose and having undergone monthly monitoring for a minimum of three months

- Monitoring of therapeutic drug levels should be considered
- 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:

- WCC < 3.5 x 10^9/L or less than the lower limit of reference range as per lab
- Neutrophils < 1.6 x 10^9/L or less than the lower limit of reference range as per lab
- Platelets < 140 x 10^9/L or less than the lower limit of reference range as per lab
- AST/ALT > 100U/l
- MCV > 105Fl
- Creatinine increase >30% over 12 months and / or calculated GFR <60ml/min
- Unexplained eosinophilia >0.5 x 10^9/l
- Unexplained reduction in albumin <30g/l
- Potassium raised above the reference ranges
- BP uncontrolled or non-responsive to treatment
- Abnormal bruising (check FBC)
- Patient systemically unwell with significant infection

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results e.g. gradual decreases in white blood cells or albumin, or increasing liver enzymes.

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. Novartis Pharmaceuticals UK Ltd. Neoral Oral Solution. Last updated 3rd March 2021. Accessed via: http://www.medicines.org.uk/emc/medicine/28677/SPC/Neoral+Solution/ [accessed online 27th May 2022].

2. Novartis Pharmaceuticals UK Ltd. Neoral Soft Gelatin Capsules. Last updated 3rd March 2021. Accessed via: http://www.medicines.org.uk/emc/medicine/1307/SPC/Neoral+Soft+Gelatin+Capsules/ [accessed online 27th May 2022].
3. Ledingham et al. BSR/BHPR Non-Biologic DMARD Guidelines, June 2017. Accessed via: https://academic.oup.com/rheumatology/article/56/6/865/3053478
4. Flint et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding, January 2016. Accessed via: https://academic.oup.com/rheumatology/article/55/9/1693/1744535
5. UK Health Security Agency. Immunisation Against Infectious Disease 'The Green Book', 2021. Department of Health and Social Care. London, UK.

RELEVANT CONTACT LIST

Speciality	
Name and Title	Tel. No.