

Ciclosporin

Traffic light classification- Amber 1

Information sheet for Primary Care Prescribers

Part of the Shared Care Protocol: Management of Rheumatological Conditions with Disease-Modifying Anti Rheumatic Drugs in Adults

Indications^{1,2,3}

Rheumatoid arthritis – licensed

Any patient groups to be excluded from shared care

Patients receiving ciclosporin for an indication classified as RED on the Nottinghamshire Joint Formulary (www.nottinghamshireformulary.nhs.uk), e.g. for suppression of organ transplant rejection.

Therapeutic Summary⁴

Ciclosporin is used to induce remission or partial remission in patients with inflammatory conditions including arthritis, psoriasis, and prevent organ rejection in transplant patients. Clinical benefit may take up to 3 months. NSAIDs and simple analgesics may need to be continued. Patient reported adverse effects usually occur early in therapy, but please see explicit criteria for review below.

Products available^{1,2,3}

- Capimune® soft capsules containing 25mg, 50mg or 100mg ciclosporin
- Neoral® soft gelatin capsules containing 10mg, 25mg, 50mg, or 100mg ciclosporin
- Neoral® oral solution containing 100mg/ml ciclosporin
- Deximune® soft capsules containing 25mg, 50mg or 100mg ciclosporin
- Vanquoral soft gelatin capsules containing 10mg, 25mg, 50mg, or 100mg ciclosporin
- Sandimmun® capsules and oral solution are available direct from Novartis for patients who cannot be transferred to a different oral preparation

Other brands are available: see formulary for detail - <http://www.nottinghamshireformulary.nhs.uk>

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 switching⁷**. If it is necessary to switch a patient to a different brand of ciclosporin, the patient should be monitored closely for changes in serum creatinine and blood pressure.

Dosages and route of administration

Ciclosporin is given orally in two divided doses each day. Dose is usually determined by the patient's weight and response to treatment, but maintenance doses are approximately 100mg twice a day.

Duration of treatment

All DMARDs are long term treatments. Ciclosporin may take up to 3 months before any benefit is seen.

Monitoring Requirements and Responsibilities⁴

Pre-treatment assessment to be performed by the specialist and will include:

- FBC, LFT, U&E, creatinine (check twice, 2 weeks apart, to obtain a mean value for creatinine), fasting lipids, creatinine clearance, blood pressure and checking for prior PUVA exposure if psoriatic arthritis.

Ongoing monitoring comprises symptom review, U&E, LFT, FBC and blood pressure at the intervals specified below:

- Monitor blood pressure at each attendance and maintain below 140/90 (see explicit criteria for review and discontinuation of the medicine below).

- GP to assess and manage cardiovascular risk factors – patient at higher risk of cardiovascular events due to rheumatological disease activity.
- Therapeutic drug monitoring of ciclosporin levels is not required for rheumatoid arthritis patients unless signs of toxicity develop.
- Check fasting lipids periodically.⁴
- Routine influenza and pneumococcal vaccinations are highly recommended.

Time period in treatment	Frequency of monitoring	Tests to be done			
		FBC	LFTs	U&Es	BP
0-6 weeks	Fortnightly	✓	✓	✓	✓
>6 weeks and stable dose	Monthly	✓	✓	✓	✓
Any dose increase	2 weeks post dose increase then revert to above protocol	✓	✓	✓	✓

No additional monitoring requirements are required in primary care for patients receiving additional biological therapy including anti- TNF therapy.

Explicit criteria for review and discontinuation of the medicine⁴ – Other benchmark values may be set by secondary care in specific clinical circumstances.
This will be communicated by secondary care.

Adverse Event	Action
Creatinine rises >30% from baseline	Repeat creatinine in 1 week and if still >30% above baseline withhold and discuss with rheumatology specialist team.
Potassium rises to above reference range	Withhold until discussed with rheumatology specialist team.
Platelets <150x10 ⁹ /l	Withhold until discussed with rheumatology specialist team.
High BP ≥140/90 on two consecutive readings 2 weeks apart	Treat blood pressure before stopping ciclosporin (note interactions with several antihypertensives). If BP cannot be controlled, stop ciclosporin and obtain BP control before restarting ciclosporin. Discuss with rheumatology specialist team.
AST / ALT or ALP > twice upper limit of reference range	Withhold until discussed with rheumatology specialist team.
Abnormal bruising	Immediate FBC. Withhold until results available and discuss with rheumatology specialist team.
Signs and symptoms of benign intracranial hypertension.	Withhold until discussed with rheumatology specialist team.
Muscle weakness	Suggest check magnesium, calcium and potassium as ciclosporin can cause hypomagnesaemia – replace as necessary.

In addition to absolute values for haematological or biochemical indices a rapid fall or rise or consistent downward or upward trend in any value should prompt caution and extra vigilance.

For a full list of Side Effects refer to the BNF or Summary of Product Characteristics.

**IF YOU ARE IN ANY DOUBT ABOUT ANY POTENTIAL ADVERSE REACTION,
PLEASE CONTACT THE RHEUMATOLOGY SPECIALIST TEAM.**

Relevant Contraindications^{1,2,3,4}

- Uncontrolled hypertension.
- Malignancy of any kind, such as lymphomas.
- Concomitant use of tacrolimus.
- Concomitant use of simvastatin or rosuvastatin.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at www.dh.gov.uk): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. N.B. Routine influenza and pneumococcal vaccinations are highly recommended.
- Uncontrolled infections (BNF) Necessary to include as warning to pt to inform GP of infection.

Relevant Precautions^{1,2,3,4}

- Pregnancy and lactation – discuss with rheumatology specialist team.
- Elderly – increased risk of systolic hypertension or creatinine increases (monitor renal function with particular care).
- Hyperuricaemia
- Increased risk of malignancies – related to duration and degree of immunosuppression
- Can increase risk of hypomagnesaemia and hyperkalaemia.
- Patients who have no history of exposure to varicella zoster virus (VZV) i.e. chickenpox or herpes zoster (shingles), should avoid contact with individuals with chickenpox or herpes zoster. Varicella–zoster immunoglobulin (VZIG) is recommended for individuals who are at increased risk of severe varicella (including patients taking immunosuppressant medicines e.g. azathioprine, ciclosporin, methotrexate, leflunomide) and who have no antibodies to varicella–zoster virus and who have significant exposure to chickenpox or herpes zoster. See www.dh.gov.uk/en/PublicHealth/Immunisation/Greenbook for detailed guidance. If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.
- Infections – may be more severe, consider early and vigorous treatment
- Avoid excessive exposure to UV light, including sunlight (BNF)

Clinically relevant medicine interactions and their management^{1,2,3,5,6}

MULTIPLE MEDICINES CAN INCREASE OR DECREASE CICLOSPORIN PLASMA LEVELS OR CONTRIBUTE TO SYNERGISTIC NEPHROTOXICITY. IN ADDITION CICLOSPORIN CAN DECREASE THE METABOLISM AND ENHANCE TOXICITY OF OTHER MEDICINES.

FOR A FULL LIST OF INTERACTING MEDICINES see BNF and SPC

- NSAIDs - addition to ciclosporin therapy or an increase in dosage requires close monitoring of renal function.
- Grapefruit or grapefruit juice should not be ingested for 1 hour prior to a dose of ciclosporin due to increased risk of toxicity.
- Colchicine – increased risk of nephrotoxicity and myotoxicity, avoid.
- Simvastatin and Rosuvastatin⁸ – increased risk of myopathy, avoid concomitant use.
- Other statins⁸ – increased risk of myopathy:
 - Atorvastatin - maximum dose is 10mg daily
 - Pravastatin⁹ – starting dose 20mg daily, titrated to 40mg daily with caution
 - For details of interactions with other statins check the BNF
- Digoxin – may increase the serum levels of digoxin – monitor and adjust digoxin dose if necessary.
- Potassium sparing diuretics, ACE inhibitors, Angiotensin-II receptor antagonists, potassium containing medicines – risk of hyperkalaemia, caution - closely monitor creatinine and potassium.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at www.dh.gov.uk): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. Inactivated polio is available although a suboptimal response may be seen.
- Trimethoprim – increased risk of nephrotoxicity, monitor creatinine.

Information given to patient^{1,2,3,5}

- Although it is rare for ciclosporin to cause blood disorders, the patient must be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers) and liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine) to the GP.
- Patients should be advised to avoid contact between themselves and individuals with chickenpox or shingles if they have no prior history of exposure. Any exposure of patients with no varicella–zoster virus antibodies to chickenpox and shingles sufferers should be reported to the GP for assessment and possible treatment.
- Patients should be advised that grapefruit or grapefruit juice should not be taken for 1 hour before or after the dose of ciclosporin because these can increase the amount of ciclosporin available in the body and so increase the risk of side-effects.
- Patients are advised to avoid self-medication with over-the-counter aspirin or ibuprofen.
- The patient will also be given an approved drug information leaflet from Arthritis Research UK. Further copies available at www.arthritisresearchuk.org.

Patient's roles and responsibilities

The patient will:

- Take their medication as agreed, unless otherwise instructed by an appropriate healthcare professional.
- Attend for all regular blood tests and all follow-up appointments with GP and specialist. If they are unable to attend any appointments they should inform the relevant practitioner as soon as possible and arrange an alternative appointment.
- Inform all healthcare professionals of their current medication prior to receiving any new prescribed or over-the-counter medication.
- Report all suspected adverse reactions (as above) to medicines to their GP.
- The patient will report to their GP or specialist any vomiting or diarrhoea, fever, bruising, mouth ulcers or sore throat as these can be signs of toxicity or intolerance of ciclosporin.
- Store their medication securely away from children.
- Read the information supplied by their GP, specialist and pharmacist and contact the relevant practitioner if they do not understand any of the information given.

References

1. Neoral Soft Gelatin Capsules, Neoral Oral Solution – Novartis Pharmaceuticals UK Ltd. Summary of Product Characteristics [10/03/2020] on Electronic Medicines Compendium: (accessed on 22/06/2020 via www.medicines.org.uk/emc)
2. Deximune 25mg, 50mg, 100mg Capsules – Dexcel Pharma Ltd. Summary of Product Characteristics [01/06/2017] (accessed on 22/06/2020 via www.medicines.org.uk/emc)
3. Capimune 25mg, 50mg, 100mg soft capsules – Mylan. Summary of Product Characteristics [09/01/12] (accessed on 22/06/2020 via www.medicines.org.uk/emc)
4. Ledingham J, Gillick N, Irving K. et al. (2017) BSR and BHRP guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology doi:10.1093/rheumatology/kew149.
5. www.bnf.org Accessed 22/06/2020
6. Baxter K (ed), *Stockley's Drug Interactions*. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com (accessed on 22/06/2020)
7. MHRA Drug Safety Update vol 3, iss 5 Dec 2009 (Ciclosporin by brand)
8. MHRA Drug Safety Update vol 6, issue 1 Aug 2012 (Statin interactions)
9. Pravastatin 10mg, 20mg and 40mg tablets – Mylan. Summary of Product Characteristics [05/06/2018] on Electronic Medicines Compendium: (accessed on 22/06/2020) via www.medicines.org.uk/emc