Ciclosporin for rheumatoid arthritis and other rheumatological diseases (Adults)

It is vital for safe and appropriate patient care that there is a clear understanding of where clinical and prescribing responsibility rests between consultants and general practitioners (GPs).
This guideline reinforces the basic premise that:
When clinical and/or prescribing responsibility for a patient is transferred from hospital to GP, the GP should have full confidence to prescribe the necessary medicines. Therefore, it is essential that a transfer of care involving medicines that a GP would not normally be familiar with, should not take place without the "sharing of information with the individual GP and their mutual agreement to the transfer of care."
These are not rigid guidelines. On occasions, consultants and GPs may agree to work outside of this guidance. As always, the doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Indications:	**Dosage and administration:**
Ciclosporin is used in the management of rheumatoid arthritis and other rheumatological conditions	Initial starting dose is 2.5mg/kg/day orally in two divided doses for 6 weeks. May then increase by 25mg at 2-4 weekly intervals until clinically effective or the maximum daily dose of 4mg/kg is reached. N.B. Please see p4 for strengths of preparations available. If, after 3 months of treatment at the maximum permitted or tolerable dose the response is considered inadequate, treatment should be discontinued. Treatment should be reviewed after 6 months and continued only if benefits outweigh risk, at minimum effective dose

Additional Information

- There are **numerous drug interactions** – see next page, current BNF and/or SPC
- Grapefruit & Grapefruit juice should be avoided.
- Different brands of ciclosporin are not bioequivalent. Prescribing by brand is recommended. If the specialist does not specify a brand and the patient has not had ciclosporin previously please use the least expensive brand.

Monitoring requirements:

Before treatment:

- FBC including platelets, serum creatinine (on two occasions 2 weeks apart), U&Es, LFTs, fasting lipids
- Blood pressure should be ≤140/90mmHg on two occasions 2 weeks apart, if greater then start antihypertensive therapy (review interactions prior to selecting agent) prior to commencing ciclosporin

During treatment:

- FBC, serum creatinine, urea and potassium, and blood pressure weekly for the first four weeks, then fortnightly for 3 months and every 2 months thereafter if stable. Measure more frequently if dose increased or concomitant NSAIDs introduced or increased
- BP at each appointment - maintain at ≤140/90mmHg

- Annual fasting lipids (HDL, Cholesterol, HDL/Cholesterol ratio)
- ESR (discretionary) monthly for disease monitoring purposes

Responsibility for monitoring rests with the GP

Action to be taken if abnormal results/adverse effects:

- Platelets < 150 x 10^9/l, Monitor weekly. If drop below 100 x 10^9/l please contact helpline
- Elevated creatinine: Serum creatinine rise >30% over baseline (on 2 consecutive occasions a week apart) will require a dose reduction. Please contact the helpline
- Hypertension: If BP > 140/90 on 2 consecutive readings 2 weeks apart then start antihypertensive therapy (review interactions prior to selecting agent)
  If BP is uncontrolled despite medical treatment, reduce ciclosporin by at least 25mg/day and contact the helpline.
- 3 fold rise in ALT/AST may require a dose reduction – please contact helpline. Check any other reason e.g. alcohol, drug interactions.
- Abnormal bruising or bleeding: Repeat FBC and act on results as above or contact helpline.
- Potassium increase to above reference range - contact helpline
- 'Significant' increase in fasting lipids - contact helpline

Please note that in addition to absolute values for haematological indices, a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.

Contraindications:

- Concomitant use of tacrolimus, rosuvastatin, lercanidipine, simvastatin, St John's Wort, aliskerin, bosentan, dabigatran
- Abnormal renal function, uncontrolled hypertension, uncontrolled infections or any malignancy
- Live vaccines are contra-indicated in patients with impaired immune response

Drug interactions:

Extensive list, many of considerable clinical significance. There is a list of significant drug interactions below but please **consult current BNF and/or SPC** for comprehensive guidance.

Significant Drug interactions include:

- Ciclosporin plasma levels are *decreased* by barbiturates, carbamazepine, primidone, phenytoin, rifampicin, octreotide, orlistat, St John's Wort, sulfinpyrazone, terbinafine
- Ciclosporin plasma levels are *increased* by macrolides (including erythromycin and clarithromycin), amiodarone, diltiazem, verapamil, steroids, progestogens, danazol, ketoconazole, itraconazole, fluconazole, voriconazole, nicardipine, metoclopramide, carvedilol, chloroquine, hydroxychloroquine , methylprednisolone (high dose) and colchicine.
- The combination of non-steroidal anti-inflammatory drugs and ciclosporin should be used with caution and should be accompanied by particularly close monitoring of renal function as detailed above, particularly if diclofenac is added – reduce diclofenac dose by 50%.
- Ciclosporin increases plasma digoxin concentrations and levels of both drugs are increased when taken concomitantly with ezetimibe.
- Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis. Atorvastatin dose should not exceed 10mg daily
- Increased risk of hyperkalaemia, caution with potassium sparing diuretics, ACE inhibitors, angiotensin 2 antagonists and aldosterone antagonists.

Cautions:

- Mothers being treated with ciclosporin should not breastfeed their infants.
- Ciclosporin should only be used in pregnancy after a careful assessment of risk versus benefit
- Concommitant use with daptomycin should be avoided.

Adverse Effects:
GI disturbances, hypertension, gingival hypertrophy, hypercholesterolaemia, renal and hepatic toxicity, tremor, headache, paraesthesia, hyperkalaemia, hypomagnesaemia, hypertrichosis, bone marrow suppression
For full details see the current edition of the BNF and SPC for ciclosporin products.

Specialist responsibilities:

- Confirm the diagnosis of rheumatological disease
- Discuss with the patient the benefits and side effects of treatment with ciclosporin
- If the patient is a woman of child bearing potential – ensure that they are aware of the importance of effective contraception and the need to discuss with their consultant if they wish to become pregnant
- Ensure that the patient understands and accepts their responsibilities (see section below)
- Seek consent for treatment and document in the patient's notes.
- Ensure baseline monitoring of full blood count and biochemical profile.
- Discuss how the patient/carer can be aware of possible signs ciclosporin toxicity or intolerance
- Provide written instruction to the GP for initiation and escalation of ciclosporin.
- Provide the patient with a shared care booklet and enter the blood results into the booklet.
- Review the patient at the intervals specified below to monitor the patient's disease activity, the efficacy of the treatment and the ability to tolerate it, and consider whether continuation of treatment is appropriate.
- Discontinue if no response or patient has a significant adverse effect.
- Promptly communicate with the GP via a clinic letter any changes in treatment, results of monitoring undertaken, and assessment of adverse events. The clinic letter should clearly state if the dose has remained the same or if a dose adjustment had been made – specifically highlighting the new dose in comparison with the preceding one.
- Advise GPs when to stop treatment.
- Provide clear arrangements for back-up, advice and support.
- Report serious adverse events at https://yellowcard.mhra.gov.uk/

GP's responsibilities:

- Initial referral to Consultant Rheumatologist raising the possibility of rheumatological disease.
- Provide the patient with monthly repeat prescriptions of medication following written instructions for initiation and escalation by the specialist. The patient should allow at least 48 hours for the prescription from the GP to be generated.
- Continue monitoring as outlined on the first page and document the results in the shared care booklet.
- Ensure patient's shared care booklet and practice computer system are updated with any dose changes.
- Refer promptly to the specialist if there is a change in the patient's status or concerns regarding compliance. In most cases, do not stop treatment without discussion with the Rheumatology Helpline.
- If patient fails to attend more than 2 monitoring visits it is not safe to continue treatment – contact the Rheumatology Helpline for advice.
- Report serious adverse events to the specialist and at https://yellowcard.mhra.gov.uk/
- Administer Pneumococcal Vaccine/ Pneumovax® II and annual influenza vaccines.
- Consider passive immunisation with Varicella zoster immunoglobulin in non-immune patients exposed to chicken pox or shingles.

Patient responsibilities:

- Read the written patient information provided about the drug and have a clear understanding

of the risks / benefits of oral ciclosporin treatment.

- Attend for blood tests.
- Report any adverse effects to their GP and/or specialist whilst treated with ciclosporin.
- Limit alcohol to national safe weekly limits
- Take monitoring booklet every time the patient sees the GP, has a hospital appointment or visits the pharmacist.

Secondary care review: During initiation: 4 – 6 weekly until controlled
Once disease controlled: Annual review by consultant

Availability:
Deximune: Capsules: 30 x 25mg =£13.06, 30 x 50mg =£25.60, 30 x 100mg = £48.90.
or
Capimune: Capsules: 30 x 25mg =£13.05, 30 x 50mg =£25.50, 30 x 100mg = £48.50.
or
Neoral: Capsules: 60 x 10mg = £18.25, 30 x 25mg = £18.37, 30 x 50mg = £35.97, 30 x 100mg = £68.28
Oral solution: 100mg/ml x 50ml = £102.30

See additional information on first page regarding prescribing by brand.

Prices from MIMS online February 2016

Back up advice and support: Rheumatology Helpline	**Telephone:** 0151 604 7505

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