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Coventry & Warwickshire Area Prescribing Committee

Shared Care Agreement

Ciclosporin: *for the treatment of active rheumatoid arthritis, psoriasis and atopic dermatitis*

Prescribe by brand name

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement (SCA) outlines suggested ways in which the responsibilities for managing the prescribing of **Ciclosporin** for active rheumatoid arthritis / psoriasis / atopic dermatitis *(delete as applicable)* can be shared between the specialist and general practitioner (GP). GPs are **invited** to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so.

In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.
If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the specialist initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

Specialist Responsibilities

1. Discuss the benefits, side effects and expected outcomes of treatment with the patient.
2. Supply the drug information leaflet, counsel the patient and obtain informed consent.
3. Ensure that the patient understands the dosing, brand name and formulation to remain constant. Locally, Neoral preferred brand.
4. Obtain patient consent to shared care arrangement and agreement to hold personal and treatment details on rheumatology / dermatology computerised blood monitoring database.
5. Ask the GP whether he or she is willing to participate in shared care by emailing the shared care request letter, (continue to prescribe until GP has agreed to take over prescribing).
6. Undertake appropriate baseline blood tests. Height, weight, blood pressure, FBC, U&Es, LFTs, albumin, calculated GFR, CRP, VZV, and urinalysis.
7. Provide results of baseline tests and recommend frequency of monitoring to the GP and future, regular blood tests required.
8. The initial 3 month prescription (in instalments as appropriate) will be issued by the secondary care (consultant/ nurse prescriber) outlining dose and timing of any concomitant medications.
9. Review the patient's condition initially every 3 months for the initial 12 months then 6 - 12 months thereafter and communicate promptly with the GP when treatment is changed, providing a copy of most up to date blood tests.
10. Advise the GP on when to adjust the dose, stop treatment, or consult with specialist.
11. Ensure that clear backup arrangements exist for GPs to obtain advice and support

Report adverse events to the MHRA on a Yellow Card www.mhra.gov.uk/yellowcard, and to the GP and appropriate Medicines Optimisation team.

General Practitioner Responsibilities

1. Reply to the request for shared care as soon as practicable, preferably within 2 weeks, by emailing back the shared care letter. If declining the request please indicate the reason for declining.
   Prescribe ciclosporin at the dose, brand and formulation recommended.
3. Ensure blood forms issued by secondary care are used for routine blood test monitoring and if necessary patient to attend surgery for blood tests as specified on pre-printed blood form.
4. Patients living 'out of area' will have their blood results sent by their surgery to the rheumatology / dermatology blood monitoring database, staff who will then manually enter results onto the system.
5. Ensure blood pressure and glucose monitoring is arranged every 12 weeks or at dose increases for the duration of the treatment.
6. Ensure compatibility with other concomitant medication; adjust the dose as advised by the specialist.
7. Stop treatment on the advice of the specialist, or immediately if an urgent need to stop treatment arises.

Report adverse events to the MHRA on a Yellow Card (www.mhra.gov.uk/yellowcard), the specialist, and the appropriate Medicines Optimisation team.

Patient/carer's Role

1. Attend all appointments with GP and specialist.
2. Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
3. Agree to routine blood monitoring, blood pressure and glucose monitoring every 12 weeks or at dose increases for the duration of treatment.
   Ensure that you make routine appointments for this and agree with your GP on the best approach to ensuring that this is done.
   Share any concerns in relation to treatment with ciclosporin.
4. Inform specialist or GP of any other medication being taken, including over-the-counter products/ alternative therapies.
5. Report any adverse effects or warning symptoms to the specialist or GP.

The patient may also choose to report any adverse drug reaction direct to the MHRA on a Yellow Card , available at pharmacies, GP surgeries or from the Yellow Card hotline (freephone 0808 100 3352 during business hours).
The form can also be downloaded from www.mhra.gov.uk/yellowcard

Back-up Advice and Support: See patient letter and/or other supporting information for contact details of clinician(s) initiating and stabilising patient prior to request for shared care.

SUPPORTING INFORMATION:

Licensed indications: for soft gelatin capsules and oral solution include the treatment of severe, active rheumatoid arthritis in patients in whom classical, slow-acting anti-rheumatic agents are inappropriate or ineffective, psoriasis and atopic dermatitis.

Dosage and administration: Soft gelatin capsules containing 10, 25, 50, or 100 mg of ciclosporin.

*For Rheumatoid Arthritis***:** it is recommended that initiation of ciclosporin therapy should take place over a period of 12 weeks. For the first 6 weeks of treatment, the recommended dose is 2.5mg/kg per day, given orally in two divided doses. If the clinical effect is considered insufficient, the daily dose may be increased gradually as tolerability permits, but should not exceed 4mg/kg per day.
If, after 3 months of treatment at the maximum permitted or tolerable dose the response is considered inadequate, treatment should be discontinued.

For maintenance treatment the dose has to be titrated individually according to tolerability. Ciclosporin can be given in combination with low-dose corticosteroids. Pharmacodynamic interactions can occur between ciclosporin and NSAIDs and therefore this combination should be used with care. Long-term data on the use of ciclosporin in the treatment of rheumatoid arthritis are still limited. Therefore, it is recommended that patients are re-evaluated after 6 months of maintenance treatment and therapy only continued if the benefits of treatment outweigh the risks.

For psoriasis: the recommended initial dose, For inducing remission, the recommended initial dose is 2.5 mg/kg/day orally given in 2 divided doses. Initial doses of 5 mg/kg/day are justified in patients whose condition requires rapid improvement. If there is no improvement after 1 month, the daily dose may be gradually increased, but should not exceed 5 mg/kg. Treatment should be discontinued in patients in whom sufficient response of psoriatic lesions cannot be achieved within 6 weeks on 5 mg/kg/day, or in whom the effective dose is not compatible with the established safety guidelines. For maintenance treatment, doses have to be titrated individually to the lowest effective level, and should not exceed 5 mg/kg/day.

For atopic dermatitis: The recommended dose range is 2.5 to 5 mg/kg/day given in 2 divided oral doses. If a starting dose of 2.5 mg/kg/day does not achieve a satisfactory response within 2 weeks, the daily dose may be rapidly increased to a maximum of 5 mg/kg. In very severe cases, rapid and adequate control of the disease is more likely to occur with a starting dose of 5 mg/kg/day. Once satisfactory response is achieved, the dose should be reduced gradually and, if possible, should be discontinued. Subsequent relapse may be managed with a further course. An 8-week course of therapy may be sufficient to achieve clearing, but up to 1 year of therapy has been shown to be effective and well tolerated, provided the monitoring guidelines are followed.
The total daily dosage of ciclosporin Soft Gelatin Capsules or ciclosporin Oral Solution should always be given in two divided doses. Ciclosporin Soft Gelatin Capsules should be taken with a mouthful of water and should then be swallowed whole.

Monitoring: Pre-treatment assessment: Height, weight, blood pressure, FBC, LFTs, and albumin, U&Es, calculated GFR, CRP, BP and Urinalysis.

During treatment: Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks; then once on stable dose, monthly FBC, creatinine/calculated GFR, ALT and/ or AST and albumin for 3 months; thereafter, FBC, creatinine/calculated GFR, ALT and/or AST and albumin at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity.

- Dose increases should be monitored by FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks then revert to previous schedule.
- Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis.
- BP and glucose every 12 weeks or at dose increase.
- Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis.
- Combination DMARD therapy will be monthly monitoring.
- During a serious infection, temporarily discontinue until the patient has recovered from the infection.

Interruption of Treatment: white cell count <3.5 x 10^9/l; mean cell volume >105 Fl and if B12 or folate low start supplementation neutrophils <1.6 x 10^9/l; creatinine increase >30% over 12 months and/or calculated GFR <60 ml/min; unexplained eosinophilia >0.5 x10^9/l; ALT and/or AST >100 U/l; platelet count <140 x 10^9/l; unexplained reduction in albumin <30 g/l.

- 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).
- Nausea/dizziness/headache. If possible continue, may have to reduce dose or stop if symptoms severe. Abnormal bruising or sore throat Withhold until FBC result available.
- Unexplained acute widespread rash Withhold – seek urgent specialist (preferably dermatological) advice.
- Oral ulceration Withhold until discussed with specialist. If suspicion of blood dyscrasia then stop treatment immediately and perform blood count.

Contra-indications: Hypersensitivity to ciclosporin or to any of the other excipients of ciclosporin.

- Ciclosporin is contraindicated in psoriatic and atopic dermatitis patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy other than that of the skin
- Ciclosporin is contraindicated in rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy.
- Ciclosporin should not be used to treat rheumatoid arthritis in patients under the age of 18 years.
- Ciclosporin is contraindicated in nephrotic syndrome patients with uncontrolled hypertension, uncontrolled infections, or any kind of malignancy.
- Concomitant use of tacrolimus is specifically contraindicated. Concomitant use of rosuvastatin is specifically contraindicated.
- However there are no adequate and well controlled studies in pregnant women and therefore ciclosporin should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

Lactation: Ciclosporin passes into breast milk. Mothers receiving treatment with ciclosporin should not breast-feed.

Cautions: Pregnancy and lactation
Grapefruit including grapefruit juice must be avoided for 1 hour before or after taking ciclosporin tablets as bioavailability is increased.
Malignancy such as lymphomas etc

Use in the Elderly: Experience with ciclosporin in the elderly is limited. However, no particular problems have been reported following the use of ciclosporin at the recommended dose. Factors sometimes associated with ageing, in particular impaired renal function, make careful supervision essential and may necessitate dosage adjustment.

Patients with impaired renal function (except in nephrotic syndrome patients with a permissible degree of renal impairment), uncontrolled hypertension, uncontrolled infections, or any kind of malignancy should not receive ciclosporin.

Since ciclosporin can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals during the first 3 months of therapy and thereafter once a month.

After 6 months of therapy, serum creatinine needs to be measured every 4 to 8 weeks depending on the stability of the disease, its co-medication, and concomitant diseases.
More frequent checks are necessary when the ciclosporin dose is increased, or concomitant treatment with a non-steroidal anti-inflammatory drug is initiated or its dosage increased. Because the pharmacodynamic interaction between ciclosporin and NSAIDs may adversely affect renal function, caution should be exercised if NSAID therapy is to be continued.

If the serum creatinine remains increased by more than 30% above baseline at more than one measurement, the dosage of ciclosporin should be reduced. If the serum creatinine increases by more than 50%, a dosage reduction by 50% is mandatory. These recommendations apply even if the patient's values still lie within the laboratory normal range. If dose reduction is not successful in reducing levels within one month, ciclosporin treatment should be discontinued.

Discontinuation of the drug may also become necessary if hypertension developing during ciclosporin therapy cannot be controlled by appropriate antihypertensive therapy.

Side effects: Common Hypertrichosis, Tremor, Hypertension, Hyperkalaemia, Abnormal LFTs, Renal function, Nausea.
Less common - Gingival hypertrophy, Anorexia, Diarrhoea, Rash, Paraesthesia, Confusion, Mood changes

Ciclosporin does not have black triangle (▼) status. All serious suspected adverse reactions (even well recognised or causal link uncertain) should be reported to the MHRA.

Drug interactions (see also above under cautions):
Diclofenac - reduce the dose of diclofenac by 50%
Colchicine - to be avoided
Simvastatin - maximum dose 10 mg/day
Nifedipine - use with caution
Digoxin - may increase the serum levels of digoxin
St. John's Wort - decreases ciclosporin activity
Potassium sparing diuretics - increased risk of hyperkalaemia – monitor potassium levels
Grapefruit including grapefruit juice - increased risk of toxicity
See current BNF or SmPC for an up to date reference on drug interactions

Cost: At current prices one year's treatment of 200mg daily will cost £ 1638.72 (Prescription Pricing Division (PPD).
NHS Business Services Authority. Drug Tariff. Sept 2018. Accessed 6.9.18 via www.nhsbsa.nhs.uk)

References:

1. Summary of Product Characteristics. Neoral. Last updated 22/07/2015. Available via www.medicines.org.uk accessed 06/09/18
2. Ledingham J, Gullick N, Irving N et al. on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group; BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs, Rheumatology, Volume 56, Issue 6, 1 June 2017, Pages 865–868. Available athttps://academic.oup.com/rheumatology/article/56/6/865/3053478