NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT

Shared care guidelines for Use of Ciclosporin in the treatment of Rheumatic and Dermatological diseases

Monitoring level - AMBER 2 - Prescribe the drug and perform a more intense level of monitoring, e.g. quarterly

Generic and Proprietary/Brand Name

The brand of ciclosporin being taken should be specified in all communications between healthcare professionals. Ciclosporin is taken twice a day at a dose based on patient's weight. There are risks associated with any changes in bioavailability of ciclosporin. Recently licensed generic ciclosporin products have shown bioequivalence but there are concerns that with such a narrow therapeutic index and critical-dose level, even slight variations could become critical. This is particularly relevant in organ transplantation.

The MHRA therefore recommends as follows:

- Care should be taken to stabilise the patient on a single brand of ciclosporin, and to ensure that the same brand is always prescribed and dispensed to the patient.
- If switching a patient stabilised on one brand of ciclosporin is unavoidable, the patient should be closely monitored for side effects, drug blood concentrations, and transplant function

Indications for shared care

- Ciclosporin will be initiated in the Rheumatology or Dermatology clinic at NNUH for patients who require immunosuppression for active rheumatic or skin diseases.
- The Rheumatology / Dermatology Department is responsible for establishing baseline blood and urine tests and will prescribe until six weeks of stable treatment with ciclosporin has been achieved. Subsequently, the shared care guidelines will come into effect with monitoring accordingly shared between the patient's GP and the Rheumatology or Dermatology clinic with ciclosporin prescribed by the GP.
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Specialist Prescribing and Monitoring Responsibilities – summary. Full details in main body of document	GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities – summary. Full details in main body of document
• Rheumatology / Dermatology medical team are responsible for the initiation and six weeks' prescription of ciclosporin at a stable dose. • Patient education will be undertaken within the Rheumatology/Dermatology multidisciplinary team. Pregnancy testing / contraceptive cover to be checked. • Advice regarding care in the sun. • Check FBC, eGFR, ALT and albumin, BP and glucose, every 2 weeks, until a stable dose has been achieved for 6 weeks. • Watch creatinine if a NSAID is added (particularly diclofenac).	**Once the patient has been on a stable dose for 6 weeks:** • check FBC, eGFR, ALT and albumin, BP and glucose every month for 3 months. Where there is a *low risk of toxicity*, onward monitoring may then be reduced to 3-monthly as a minimum, after discussion with the relevant consultant, and usually not in children or those at high risk of toxicity, with renal impairment. • Check blood pressure as above and act on abnormal readings **If BP cannot be controlled, stop ciclosporin.**

Patient Information

- ARC information sheet; NNUH and BAD information sheets
- Patient to ensure disease is controlled and drug efficacy.

Specialist Contact Details

• Rheumatology Nurse Practitioner	01603 287801
• Dr. Karl Gaffney's secretary	01603 289670
• Professor MacGregor's secretary	01603 289906
• Dr. Tarnya Marshall's secretary	01603 287203
• Dr. Peter Merry's secretary	01603 287003
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GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, they are 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 if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment and Pharmacology

Ciclosporin was licensed in the 1980s to prevent organ rejection and in 1994 to treat severe rheumatoid arthritis and psoriasis. Also licensed to treat severe atopic dermatitis for up to eight weeks.

Ciclosporin is thought to bind to the cytosolic protein cyclophilin (immunophilin) of immunocompetent lymphocytes, especially T-lymphocytes. This complex of ciclosporin and cyclophilin inhibits calcineurin, which, under normal circumstances, is responsible for activating the transcription of interleukin 2. It also inhibits lymphokine production and interleukin release and, therefore, leads to a reduced function of effector T-cells.

Ciclosporin is an immunomodulator which acts upon T lymphoctes. Ciclosporin suppresses the immune system by preventing T lymphocytes from producing lymphokines. Lymphokines normally stimulate the growth of T and B lymphocytes, which are cells responsible for regulating and triggering immune responses. T cells are involved in producing inflammation as part of their immune function. Suppressing their action can help to reduce the inflammation in the joints of people who have rheumatoid arthritis or reduce inflammation in the skin of people who have cutaneous inflammatory conditions.

Ciclosporin can promote a Th1 response in atopic dermatitis, altering IL-4 transcription and monocyte IL-10 production. Ciclosporin also has a direct effect on keratinocytes.

40% of an oral dose of ciclosporin is absorbed from the gut. Metabolism is hepatic and excretion is mostly in the bile with only 6% via urinary tract.

Licensed use and agreed local off-label use

- Prevention of organ rejection
- Treatment of rheumatoid arthritis and psoriasis
- Short term treatment of severe atopic dermatitis

Non licensed dermatological indications include:

Behcet's disease, Chronic idiopathic urticaria, Connective tissue disease, immunobullous disease, Pyoderma gangrenosum, photodermatoses.

Criteria for Patient Selection

- Active rheumatic disease
- Severe psoriasis or atopic eczema, or non-licensed skin disease not controlled by topical or other systemic agents.

Pre-treatment assessments:

- Baseline FBC
- Liver Function tests (ALT) and albumin
- eGFR

- Glucose
- Weight and BP

Renal impairment:
Ciclosporin may be initiated at usual doses in renal impairment

Lung disease
Routine CXR are no longer undertaken but clinical assessment of co-existing pulmonary disease may result in pulmonary function tests to assess lung reserve, and also CT assessment being undertaken. Pre-existing lung disease is not a contraindication to DMARD use but prescription is undertaken with caution and following chest x-ray (excluding paediatrics)

Liver disease
In patients with deranged liver biochemistry, hepatotoxic DMARDs should be used with caution, with careful attention to trends in test results. In patients with impaired liver synthetic function (e.g. cirrhosis), DMARD therapy should be used with extreme caution. Patients with chronic viral hepatitis infection should be considered for anti-viral treatment prior to DMARD initiation.

Occult viral infections
Screening for occult viral infections such as HIV and hepatitis B and C should be offered and record Varicella status. GP to be advised of any abnormal results. In-house checklist to added to patient's notes.

BP
Consider an ECG in hypertensive patients. Ensure hypertension is treated prior to initiating treatment. Cardiovascular disease is not considered to be a contraindication to ciclosporin therapy.

In patients who have received PUVA for psoriasis, establish if the total dose given exceeds 1000J, and if so discuss with dermatologists.

Form and strength of preparation

Ciclosporin is given in divided doses from 2.5 to 4mg/kg/day in rheumatoid arthritis, and 2.5 to 5mg/kg/day in dermatology.

Ciclosporin (oral solution or soft gelatin capsule) given twice a day based on patient's weight, initially 2.5mg/kg/day.

Available in 10mg, 25mg, 50mg or 100mg gelatin capsules or 100mg/ml solution.
The solution can be mixed with fruit juice to improve the taste, but ***not grapefruit juice*** (this contains the flavinoid narigenin which inhibits CYP 3A4 activity and can increase plasma concentration of ciclosporin).

Side Effects and Management

- Tingling and numbness in the hands and feet: This usually subsides with time.
- Trembling hands and feet and muscle cramps: Tonic water may help to alleviate any cramp pain.
- Hypertrichosis: Increased growth of body hair can be removed by shaving, waxing or using a cream hair remover. A cosmetic bleach is helpful. Electrolysis and epilators risk infections.
- Swollen or bleeding gums: Good oral hygiene and regular dental check-ups are helpful.
- Metallic taste in the mouth, poor appetite and nausea: Take capsules after food.
- Hypertension: Observe pre treatment and prescribe anti-hypertensive medication if necessary prior to initiation of ciclosporin. Reduce salt intake. Treat with a calcium antagonist e.g.

amlodipine or possibly nifedipine (however ***avoid*** diltiazem, lercanidipine, nicardipine and verapamil, which can inhibit metabolism of ciclosporin).

- Gout can occur.
- Ciclosporin may cause renal impairment. Elevations in creatinine consistently >30% above patient's baseline (which is measured pre treatment), requires dose reduction of ciclosporin by 25-50%.
- Increases in potassium and cholesterol levels may occur.
- Irregular menstrual periods and slight breast enlargement may occur in females.
- Headaches, confusion and fits may *rarely* occur.
- Increased sensitivity to changes in temperature unusual but may occur.
- Increased risk of developing skin lesions may occur with all anti-rejection drugs particularly if PUVA used also to treat psoriasis. A sunscreen protection 15 or higher should be used. Patients should report any skin lesions or lumps to their doctor.
- Increased risk of lymphoproliferative and solid tumours.
- Increased risk of infections may occur. Patients should report any signs of infection (e.g. sore throat) to their doctor.

Drug Interactions

- For full information, refer to manufacturers' SPCs via Home - electronic medicines compendium (emc)
- N.B. Some drugs may potentiate or reduce the effects of ciclosporin or concomitant therapy.Diclofenac: reduce the dose of diclofenac by 50%
- Colchicine: to be avoided
- Simvastatin: maximum dose 10mg/day
- Nifedipine: use with caution; ciclopsorin increases plasma concentration
- Other calcium channel blockers: *Avoid* diltiazem, lercanidipine, nicardipine and verapamil which can inhibit metabolism of ciclosporin
- Digoxin: ciclosporin may increase the serum levels of digoxin
- St. John's Wort: decreases ciclosporin activity
- Potassium sparing diuretics: use with caution
- Compounds known to be nephrotoxic
- Antibiotics: erythromycin, clarithromycin, trimethoprim, ciprofloxacin, rifampicin and doxycycline
- Antifungals: fluconazole, itraconazole, ketoconazole and amphotericin
- Avoid taking grapefruit juice - contains the flavinoid narigenin which inhibits CYP 3A4 activity and can increase plasma concentration of ciclosporin

Cautions and Contraindications

Ciclosporin | Drugs | BNF | NICE

Vaccines and immunisation:

- **Influenza & Pneumoccocal:** Annual vaccination against influenza should be routinely offered, as should the one-off pneumococcal vaccination (polysaccharide PPV-23, *Pneumovax*)
- **Shingles:** Long term stable low dose corticosteroid therapy (defined as <20mg prednisolone per day for more than 14 days), either alone or in combination with low dose non-biological oral immune modulating drugs (e.g. methotrexate less than or taking 25mg/week), are not considered sufficiently immunosuppressive and these patients can receive the vaccine.

Patients on higher doses should be discussed with the consultant (Refn: Green Book Chapter 28a v3_0).

Initiation of therapy and ongoing dose regimen

- Rheumatology practitioner on advice of Consultant Rheumatologist.
- Consultant Dermatologist or member of Dermatology Team on the advice of Consultant Dermatologist

Rheumatoid Arthritis starting dose:

- 2.5mg/kg/day in two divided doses for six weeks
- Sensitive dose range:
- May be increased with caution at 4-week intervals by 25mg if clinically ineffective, to the maximum dose of 4mg/kg/day
- Often effective between 2.5 to 3.2mg/kg/day

Oral maintenance dose for Rheumatoid Arthritis:

- Often effective between 2.5 to 3.2mg/kg/ day. Sensitive dose range. Caution if increasing above this level.
- Adjust to patient's tolerance and benefit. Constantly evaluate response and toxicity before considering increasing to the maximum dose

Resist rapid escalation of dose otherwise fluctuations in creatinine will necessitate dose reductions and loss of efficacy

N.B. Constantly evaluate response and toxicity before increasing to the maximum dose.

Clinical response usually seen between 8 and 14 weeks

Dermatology starting dose:
Starting dose ciclosporin 2.5 to 5 mg/kg/day in two divided doses depending on disease severity.
If no response at the maximum tolerated dose at three months, then withdraw treatment.
Onset of clinical immunosuppression at one to two weeks.
Response does not level out until 12 to 16 weeks.

Administration Information

- If measuring ciclosporin trough levels, ask the patient to omit morning dose of ciclosporin.
- Levels not needed for dermatological doses but may be indicated to check for toxicity. There is no correlation between efficacy of treatment in psoriasis and serum levels of ciclosporin.

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

- Indefinite as long as efficacy and safety profiles are maintained.
- Licensed for 8 weeks' use in atopic dermatitis in patients aged over 16 years.

Baseline assessment and ongoing monitoring – by Specialist

- Check FBC, eGFR, ALT and albumin, BP and glucose, every 2 weeks, until a stable dose has been achieved for 6 weeks.
- Watch creatinine if a NSAID is added (particularly diclofenac).

GP / Community Team or other Primary Care monitoring responsibilities

Report any suspected adverse drug reactions to the hospital specialist.

Once the patient has been on a stable dose for 6 weeks:

- check FBC, eGFR, ALT and albumin, BP and glucose every month for 3 months. Where there is a *low risk of toxicity*, onward monitoring may then be reduced to 3-monthly as a minimum, after discussion with the relevant consultant, and usually not in children or those at high risk of toxicity, with renal impairment.

  Risk factors for toxicity include: a history of adverse drug events; medical co-morbidities including renal and liver impairment (e.g. NAFLD) and malignancy; patients at the extremes of weight (BMI <18 or >30 kg/m^2); old age (>80 years).

  Patients on concomitant DMARDs, especially leflunomide, should have monthly monitoring. Be aware that creatinine may increase if NSAID is added (particularly diclofenac).
- Check blood pressure as above and act on abnormal readings

If BP cannot be controlled, stop ciclosporin.

Consultant / Specialist prescribing responsibilities

- Rheumatology / Dermatology medical team are responsible for the initiation and six weeks' prescription of ciclosporin at a stable dose.
- Patient education will be undertaken within the Rheumatology/Dermatology multidisciplinary team. Pregnancy testing / contraceptive cover to be checked.
- Advice regarding care in the sun.
- Check FBC, eGFR, ALT and albumin, BP and glucose, every 2 weeks, until a stable dose has been achieved for 6 weeks.
- Patient to ensure disease is controlled and drug efficacy.
- Watch creatinine if a NSAID is added (particularly diclofenac).

GP prescribing responsibilities

From six weeks after the stable dose has been commenced, to prescribe and monitor ciclosporin therapy, and to communicate adverse events to the appropriate Rheumatology/Dermatology Consultant.

Indications for referral back to Specialist

Withhold ciclosporin and contact specialist if the patient's:

- WBC <3.5 x 10^9/L
- Neutrophils <1.6 x 10^9/L
- Platelets <140 x 10^9/L
- Unexplained eosinophilia >0.5x10^9/l
- ALT > twice upper limit of normal or
- Unexplained falling albumin <30g/l
- MCV >105fl (µm^3)
- Creatinine increase >30% over 12 months and/or eGFR <60ml/min/1.73m^2

Please Note:
A rapidly increasing or decreasing trend in any values should prompt caution and extra vigilance.

Some patients may have had abnormal baseline values; the specialist will advise.

- There is no indication to stop ciclosporin at the time of surgery
- Ciclosporin should be stopped in the event of a severe infection e.g. requiring hospitalisation.

- The decision to restart ciclosporin after a severe infection where the patient has had a break from therapy e.g. of more than one month, should be undertaken by the hospital specialist team.

Withdrawal of treatment

Psoriasis:

- Relapse rate for severe psoriasis is as for PUVA (i.e. 4 months).
- Rebound phenomena not usually seen
- Relapse rates are similar for sudden or tapered withdrawal

Eczema:

- May flare quickly if sudden withdrawal therefore taper dose

Further information and supporting documents

- BSR and BHPR guideline for the prescription and monitoring of non-biologic Disease-Modifying Anti-Rheumatic Drugs – February 2017 Rheumatology (Oxford) (2017) 56 (6): 865-868. https://doi.org/10.1093/rheumatology/kew479
- MHRA yellow Card Scheme http://yellowcard.mhra.gov.uk/
- NICE Clinical Guideline – Hypertension Overview | Hypertension in adults: diagnosis and management | Guidance | NICE

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Date of Approval	November 2023
Reviewed by	Sally Neave / Jen Carroll – MO Team (formatting review)
Last review date	July 2017
Date of next review	June 2024

Document history:

Version	Date	Author / Editor	Status	Comment
1.	July 2011	Dr Tarnya Marshall, Margaret Somerville – Rheumatology; Dr Anne-Marie Skellett – Dermatology, NNUH / Fiona	Superseded	Approved by the TAG

		Marshall TAG Lead Pharmacist		
2.	January 2014	Dr Tarnya Marshall, Corrinne Ellis – Rheumatology; Dr Anne-Marie Skellett – Dermatology, NNUH / Fiona Marshall TAG Lead Pharmacist, NHS Anglia CSU	Superseded	Additional monitoring of lipids a month after starting ciclosporin. Guidance regarding renal monitoring depending on BMI updated. Guidance regarding interacting medication updated. Units of biochemical / haematology monitoring parameters updated. BP monitoring threshold changed from ≤ to <140/90. Updated to reflect current national guidance. Author and local specialist contact details updated. Changes supported by the TAG and noted by the D&TCG January 2014.
3.	July 2016	TBC / Fiona Marshall TAG Lead Pharmacist, NEL CSU (Anglia)	Draft	Updated into format of current shared care agreement template. Sections requiring review / confirmation highlighted. Sent to authors at the NNUH – review delayed by anticipated publication of revised BSR/BHPR guidance on DMARDs.
4.	May to July 2017	Dr Tarnya Marshall, Consultant Rheumatologist, Heather Hasthorpe, Senior Rheumatology Practitioner, Dr Anne-Marie Skellett, Consultant Dermatologist, Norfolk and Norwich University Hospitals NHS Foundation Trust / Fiona Marshall TAG Lead Pharmacist, NEL CSU (Anglia)	Current	Reviewed and updated following publication of revised British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) guidance for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs Feb 2017. Circulated by the authors across all stakeholder

				specialisms and to the JPUH and the QEH for consultation. Changes made to monitoring requirements and responsibilities, side-effects, available products, advice to GPs regarding thresholds and responsibilities regarding referral back to specialists. Advice regarding shingles vaccination updated in line with the Green Book. Revised version supported by the TAG subject to being finalised– July 2017. Final version approved by the D&TCG August 2017
5.0	Aug 2021	Jen Carroll, TAG Lead Technician	FINAL	Discussed at August 2021 TAG meeting. Review dates extended for a year from meeting due to covid pressures
6.0	Nov 2023	Sally Neave / Jen Carroll – MO Team NWICB	Final	Transferred to new template and formatted ready for publication on new KNoW website