National shared care protocol adapted for local use:

# Ciclosporin (oral) for patients within adult services (non-transplant indications)

**The content of this shared care protocol was correct as of November 2023. As well these protocols, please ensure that summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites are reviewed for up-to-date information on any medicine.**

## Specialist responsibilities

- Assess the patient and provide diagnosis; ensure that this diagnosis is within scope of this shared care protocol (section 2) and communicated to primary care.
- Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and provide the appropriate counselling (section 11) to enable the patient to reach an informed decision. Obtain and document patient consent. Provide an appropriate patient information leaflet.
- Assess for contraindications and cautions (section 4) and interactions (section 7).
- Conduct required baseline investigations and initial monitoring (section 8).
- Initiate and optimise treatment as outlined in section 5. Once the patient is known to be tolerating the medicine, transfer to shared care would normally take place. Before transfer to shared care, the patient is expected to have had at least one specialist review and be stable (no increase in medication dose for at least 6 weeks alongside satisfactory investigation results). On transferring shared care, the specialist will provide at least 4 weeks medication to enable the practice to receive and process the shared care agreement and set up prescribing and ongoing monitoring. Any bloods required within the 4 weeks should be requested/organised and followed up by the specialist.
- If shared care is considered appropriate and once treatment is optimised, write to the patient's GP practice, and request shared care; detailing the diagnosis, the current and ongoing dose and brand, any relevant test results, date the next monitoring is required, and stop date for ciclosporin (if applicable). Include the specialist service contact information (section 13).
- The specialist should also provide the details of the treatment to be undertaken by the GP. Including the reasons for the choice of treatment, medicine combination, frequency of treatment, and the next review date by the specialist.
- Prescribe sufficient medication to enable transfer to primary care (usually 42 days). Further prescriptions will be issued where there are unforeseen delays to the transfer of care. Patients should not be put in a position where they are unsure where to obtain supplies of their medication. The specialist team will be responsible for monitoring and prescribing the medicine during this initial period.
- Conduct the required monitoring in section 8 and communicate the results in writing to primary care within 14 days, where possible. After each review, provide primary care with a

written summary within 14 days, advising whether treatment should be continued, confirming the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.
- Give advice to primary care on continuing treatment if a woman becomes or wishes to become pregnant.
- Provide advice to primary care on the management of adverse effects if required.
- Review patients annually. Review once every two years for patients under a Patient Initiated Follow-ups (PIFU) pathway.
- Provide the patient with details of their treatment, including any dosage changes made, follow-up appointments, monitoring requirements, and specialist team contact details. Highlight the importance of monitoring the patient and explain the potential withdrawal of treatment if monitoring appointments are not attended.
- Advise primary care if treatment should be discontinued.
- Contact details for primary care prescribers will be made available.
- Details for fast-track referral will be supplied.

## Primary care responsibilities

- If shared care is not accepted, inform the specialist of the decision in writing within 14 days with reasons as to why shared care cannot be entered into. If shared care is accepted, ensure knowledge and understanding of the therapeutic issues relating to the patient's clinical condition. Undergo any additional training necessary to carry out the prescribing and monitoring requirements.
- Agree that, in their opinion, the patient should receive shared care for the diagnosed condition unless good reasons exist for the management to remain within the secondary care.
- If accepted, prescribe ongoing treatment as detailed in the specialist's request and as per section 5, considering any potential drug interactions in section 7.
- Adjust the dose of ciclosporin prescribed as advised by the specialist and communicate any changes made to the patient.
- Conduct the required monitoring as outlined in section 9. Communicate any abnormal results to the specialist. Discuss with the referring specialist team if there are any amendments to the suggested monitoring schedule.
- Ensure the patient is given the appropriate follow-up and monitoring appointments. If a patient fails to attend, contact the patient in a timely manner to arrange alternative appointments. It is the GP's responsibility to decide whether to continue treatment in a patient who does not attend follow-up and monitoring appointments. If the patient regularly fails to attend the monitoring appointment, the GP may withhold the prescription and inform the consultant responsible for the patient's care.
- Assess for possible interactions with azathioprine when starting new medicines (section 7).
- Manage adverse effects as detailed in section 10 and discuss them with the specialist team when required. Refer the patient back to the specialist team if further investigation is required.
- Contact the specialist team for advice if the patient becomes or plans to become pregnant.
- Stop treatment as advised by the specialist.
- Offer patients vaccination in line with the current Joint Committee on Vaccination and Immunisation advice. (Immunisation against infectious disease).

## Patient and/or carer responsibilities

- Take ciclosporin as prescribed and avoid abrupt withdrawal unless advised by the primary care prescriber or specialist.
- Tell anyone who prescribes them a medicine that they are taking ciclosporin.
- Attend regularly for monitoring and review appointments with primary care and specialist and keep contact details up to date with both prescribers. If they are unable to attend any appointments, they should inform the relevant practitioner as soon as possible and arrange an alternative appointment. Be aware that medicines may be stopped if they do not attend.
- Take part in all national screening programmes, e.g., for breast, bowel, and cervical cancers.
- Report adverse effects to their primary care prescriber. Maintain good oral hygiene and seek immediate medical attention if they develop any symptoms as detailed in section 11.
- Report the use of any over the counter (OTC) medications to their prescriber and be aware they should discuss the use of ciclosporin with their pharmacist before purchasing any OTC medicines.
- Store the medication securely away from children.
- Read the information supplied by the GP, specialist, and pharmacist, and contact the relevant practitioner if they do not understand any of the information given.
- Patients of childbearing potential should take a pregnancy test if they think they could be pregnant and inform the specialist or GP immediately if they become pregnant or wish to become pregnant.

## Community pharmacist responsibilities

- Professionally check prescriptions to ensure they are safe for the patient and contact the GP if necessary to clarify their intentions.
- Fulfil the legal prescriptions unless they are considered unsafe.
- Counsel the patient on the proper use of their medication.
- Advise patients suspected of experiencing an adverse reaction with their medicines to contact their GP.

## 1. Background

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Ciclosporin is a potent immunosuppressant which is thought to act specifically and reversibly on lymphocytes. It is licensed for the prevention of transplant rejection, as well as some chronic inflammatory disorders. Ciclosporin is used to induce remission or partial remission in patients with inflammatory conditions including arthritis, psoriasis, and prevent organ rejection in transplant patients. It is not licensed for all the conditions it is used to treat, however its use for the indications below are well established and supported by clinical specialists.

This shared care protocol does not cover use post-transplant, or the treatment of people less than 18 years old.

## 2. Indications

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The licensed indications for ciclosporin include:

- Rheumatoid arthritis

This shared care protocol also includes treatment of chronic inflammatory conditions where off-label use of ciclosporin is appropriate, including, but not limited to, the following conditions:

- Licensed: Rheumatoid arthritis
- Unlicensed: Psoriatic arthritis, systemic lupus erythematosus, connective tissue disease, vasculitis, Behcet's disease, adult-onset Still's disease (AOSD)

The specialist must specify the indication for each patient when initiating shared care and clearly state when use is off label.

## 3. Locally agreed off-label use

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Psoriatic arthritis, systemic lupus erythematosus, connective tissue disease, vasculitis, Behcet's disease, AOSD

## 4. Contraindications and cautions

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This information does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it. Please see BNF & SPC for comprehensive information.

**Contraindications:**

- Hypersensitivity to ciclosporin or any excipients
- Malignancy
- Uncontrolled hypertension
- Uncontrolled infection

Concomitant use with *Hypericum perforatum* (St John's Wort), **tacrolimus**, or substrates for P-glycoprotein or organic anion transporter proteins (OATP) e.g., bosentan, dabigatran, aliskiren (section 7)**.**

**Cautions:**

- Hepatic impairment
- Elderly; monitor renal function particularly closely.
- Renal impairment – see section 10
- Hypertension
- Hyperlipidaemia; ciclosporin may induce a small reversible increase in blood lipids.
- Hyperkalaemia: the risk of hyperkalaemia is increased by ciclosporin treatment.
- Hypomagnesaemia: ciclosporin increases magnesium excretion, therefore supplementation may be required.
- Hyperuricaemia
- Vaccination may be less effective during treatment with ciclosporin. Live attenuated vaccines should be avoided (section 7). Routine influenza and pneumococcal vaccinations are highly recommended.
- 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. Contact the on-call microbiologist via the hospital switchboard for advice regarding those who have no antibodies to varicella–zoster virus and who have had significant exposure to chickenpox or herpes zoster. See The Green Book– chapter 34 for detailed guidance. If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.

- Active herpes simplex infections. Allow infection to clear before starting and withdraw if severe infections occur during treatment.
- Staphylococcus aureus skin infections. Not an absolute contraindication if infection is controlled but avoid erythromycin unless no other alternative (section 7).
- Treat patients with malignant or pre-malignant conditions of skin only after appropriate treatment (and if no other option).
- Neurological Behçet's syndrome – monitor neurological status.
- Lymphoproliferative disorders; discontinue treatment.
- Pregnancy and breastfeeding, see section 12.
- All oral dosage forms of ciclosporin contain a form of ethanol, see section 6.
- Due to the increased risk of skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

## 5. Initiation and ongoing dose regimen

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- Once the patient is known to be tolerating the medicine, transfer to shared care would normally take place. Before transfer to shared care, the patient is expected to have had at least one specialist review and be stable (no increase in medication dose for at least 6 weeks alongside satisfactory investigation results). On transferring shared care, the specialist will provide at least 4 weeks medication to enable the practice to receive and process the shared care agreement and set up prescribing and ongoing monitoring. Any bloods required within the 4 weeks should be requested/organised and followed up by the specialist.
- The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.
- Termination of treatment will be the responsibility of the specialist.

**Initial stabilisation:**

The dose is usually determined by the patient's weight and response to treatment.

Starting doses range from 2.5 mg/kg/day to 5 mg/kg/day in two divided doses depending on the indication. The selected dose will be tailored to the individual patient and decided by the specialist. **The initial stabilisation period must be prescribed by the initiating specialist.**

**Maintenance dose (following initial stabilisation):**

The maintenance dose will be tailored to the individual patient and should be the lowest effective and well tolerated dose. The usual maximum dose is 5 mg/kg/day in two divided doses.

**Maintenance doses are approximately 100mg twice a day**.

In certain conditions higher doses may be used for a limited period, this should be under the direct supervision of the specialist.

Please note for rheumatology conditions a patient may be initiated on more than one DMARD.

**The initial maintenance dose must be prescribed by the initiating specialist.**

All DMARDs are long-term treatments. The clinical benefit may take up to 3 months. The duration of treatment will be determined by the specialist based on clinical response and tolerability.

**Conditions requiring dose adjustment:**

- In patients with nephrotic syndrome and impaired renal function the initial dose should not exceed 2.5 mg/kg/day.
- Deteriorating renal function. See section 10.
- Elderly patients: dose selection should be cautious and start at the low end of the dose range.

## 6. Pharmaceutical aspects

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| Route of administration: | Oral |
| Formulation: | **Soft capsules**<br>Capimune®: 25 mg, 50 mg, 100 mg<br>Deximune®: 25 mg, 50 mg, 100 mg<br>Neoral®: 10 mg, 25 mg, 50 mg, 100 mg<br>Sandimmun®: 25 mg, 50 mg, 100 mg<br>**Oral solution**<br>Neoral®: 100 mg/mL<br>Capsorin®: 100mg/mL<br>Sandimmun®: 100mg/mL<br><br>Sandimmun® capsules and oral solution are available direct from Novartis for patients who cannot be transferred to a different oral preparation.<br><br>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. **Ciclosporin should be prescribed by brand and formulation, regardless of the indication, to avoid inadvertent switching**. 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, and it should be made under specialist supervision (section 8). Where possible, the brand preferred by the patient's local health system should be chosen. |
| Administration details: | Ciclosporin should be taken in two divided doses equally distributed throughout the day, and on a consistent schedule with regard to time of day and in relation to meals.<br>Neoral oral solution should be diluted prior to administration, preferably with orange or apple juice although other drinks can be used according to individual taste (licensed use). Grapefruit juice must not be used. The entire mixture should be stirred and taken immediately after preparation. |
| Other important information: | All oral dosage forms of ciclosporin contain a form of ethanol; a 500mg dose is the equivalent of up to approximately 15 ml beer or 6 ml wine. Neoral® |

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| | capsules and oral solution contain polyoxyl 40 hydrogenated castor oil, which may cause stomach upsets and diarrhoea.<br>Neoral® oral solution has a shelf life of 2 months once opened. |

## 7. Significant medicine interactions

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The following list is not exhaustive. Please see BNF or SPC for comprehensive information and recommended management.

**Ciclosporin is associated with a large number of interactions, some of which are significant enough to contraindicate concurrent use, require dose adjustment and/or additional monitoring (see section 4).**

- **Grapefruit and grapefruit juice:** predicted to increase ciclosporin exposure. It should not be ingested for 1 hour prior to a dose of ciclosporin due to increased risk of toxicity.
- ***Hypericum perforatum* (St John's Wort):** contraindicated due to risk of decreased ciclosporin levels.
- **Statins:** Doses of statins should be reduced, and temporarily withheld or discontinued if patients develop signs and symptoms of myopathy or have risk factors for severe renal injury secondary to rhabdomyolysis.
    - Simvastatin and Rosuvastatin – increased risk of myopathy, avoid concomitant use.
    - Other statins – increased risk of myopathy:
        - Atorvastatin - maximum dose is 10mg daily.
        - Pravastatin – starting dose 20mg daily, titrated to 40mg daily with caution.
        - For details of interactions with other statins check the BNF
- **Non-steroidal anti-inflammatory drugs (NSAIDs, including diclofenac, naproxen, sulindac):** addition to ciclosporin therapy or an increase in dosage requires close monitoring of renal function.
- **Antibiotics:**
    - **Nephrotoxic: ciprofloxacin, trimethoprim, co-trimoxazole, vancomycin, aminoglycosides** – long-term treatment (e.g., prophylaxis) will require monitoring of renal function
    - **Macrolide antibiotics: erythromycin** can increase ciclosporin exposure 4- to 7-fold and may result in nephrotoxicity. **Clarithromycin and azithromycin** also increase ciclosporin levels.
    - **Doxycycline, tigecycline:** may increase ciclosporin concentrations. Monitoring may be required.
    - **Rifampicin:** induces ciclosporin metabolism; ciclosporin doses may need to be increased 3- to 5-fold.
    - **Rifaximin:** levels markedly increased by ciclosporin. Caution advised.
- **Digoxin, edoxaban**: dose adjustment recommended; levels increased by ciclosporin.
- **Colchicine:** levels of ciclosporin and colchicine may be increased. Close clinical observation for toxicity is recommended.
- **Azole antimycotics (e.g., ketoconazole, fluconazole, itraconazole and voriconazole), verapamil, telaprevir:** increase exposure to ciclosporin by at least 2-fold.
- **Inhibitors of CYP3A4, P-glycoprotein, or OATP**: may increase plasma levels of ciclosporin. Frequent assessment of renal function and careful monitoring for ciclosporin-related side effects may be required; seek specialist advice, e.g., **nicardipine, metoclopramide, oral contraceptives, methylprednisolone (high dose), allopurinol, cholic acid and derivatives, protease inhibitors, imatinib, nefazodone.**

- **Inducers of CYP3A4, P-glycoprotein, or OATP**: may reduce plasma levels of ciclosporin, e.g., **barbiturates, carbamazepine, oxcarbazepine, phenytoin and fosphenytoin, primidone; nafcillin, intravenous sulfadimidine, probucol, orlistat, ticlopidine, sulfinpyrazone, terbinafine, apalutamide, enzalutamide, lumacaftor, pitolisant.**
- **Nephrotoxic drugs,** e.g., **colistimethate, amphotericin B, fibric acid derivatives (e.g., bezafibrate, fenofibrate); melphalan, histamine H2-receptor antagonists (e.g., cimetidine, ranitidine); methotrexate:** may have synergistic effects; close monitoring of renal function is recommended.
- **Substrates for P-glycoprotein or organic anion transporter proteins (OATP)** for which elevated plasma concentrations are associated with serious or life-threatening events e.g., **bosentan, dabigatran, aliskiren**. Concomitant use is contraindicated.
- **Potassium-sparing medicines, including potassium-sparing diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), and potassium-containing medicines**: may lead to significant increases in serum potassium.
- **Ticagrelor:** exposure increased by ciclosporin. Use with caution or avoid.
- **Lercanidipine:** exposure increased by ciclosporin, avoid, or use with caution and separate doses by at least 3 hours.
- **Nifedipine:** increased risk of gingival hyperplasia.
- **Amiodarone and dronedarone:** increases ciclosporin levels. This interaction can occur for a long time after withdrawal of amiodarone, due to its very long half-life (about 50 days). Amiodarone increases serum creatinine.
- **Danazol, diltiazem** (at doses of 90 mg/day)**:** may increase ciclosporin blood concentrations by up to 50%.
- **Etoposide, repaglinide, ambrisentan:** plasma levels may be increased by ciclosporin; close clinical observation for toxicity is recommended.
- **Caspofungin:** exposure increased by ciclosporin. Liver monitoring recommended.
- **Octreotide, pasireotide, lanreotide:** decreases oral absorption of ciclosporin; increase in the ciclosporin dose or a switch to intravenous administration could be necessary.
- **Tacrolimus:** risk of pharmacokinetic interaction and nephrotoxicity. Avoid.
- **Everolimus and sirolimus**: ciclosporin increases levels of both drugs and may increase serum creatinine.
- **Baricitinib, filgotinib, tofacitinib**: Increased risk of immunosuppression.
- **Ritonavir**: close monitoring advised, ciclosporin dose adjustment may be needed.
- **Vaccination:** During treatment with ciclosporin, vaccination may be less effective, and the use of live attenuated vaccines should be avoided. Clinician discretion is advised. Please refer to the Green Book Chapter 6 for current advice, and advice for patients taking higher doses.
- **Aprepitant, netupitant:** predicted to increase ciclosporin levels. Use caution.
- **Anti-cancer medicines:** levels of either medicine may be altered, or risk of immunosuppression increased.

## 8. Baseline investigations, initial monitoring, and ongoing monitoring to be undertaken by specialist

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Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in the immediate future will prescribing and monitoring be transferred to primary care.

**Baseline investigations:**

- Height and weight

- Blood pressure (BP)
- HbA1c
- Full blood count (FBC)
- Urea and electrolytes (U&Es) & creatinine clearance (CrCl), Check creatinine twice, 2 weeks apart, to obtain a mean value.
- Serum magnesium
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), albumin, and bilirubin
- Serum lipids and uric acid
- Check for prior PUVA exposure if psoriatic arthritis.
- Screening for HIV and hepatitis B and C should be undertaken at clinician discretion.
- Screening for lung disease, including tuberculosis, should be undertaken at clinician discretion on a case-by-case basis.
- Consider baseline pregnancy testing, if clinically appropriate
- Provide or request appropriate vaccination prior to treatment initiation, according to local arrangements (e.g., pneumococcal, shingles, influenza, COVID-19)

**Initial monitoring and at dose change:**

To be repeated every 2 weeks until the dose has been stable for 6 weeks and then monthly thereafter.

- BP: Monitor at each attendance and maintain below 140/90 (see explicit criteria for review and discontinuation of the medicine).
- HbA1c
- FBC
- U&Es, including creatinine and CrCl.
- AST and/or ALT, albumin, and bilirubin
- Rheumatology patients C-reactive protein (CRP) – may or may not be monitored by specialist. The decision to monitor is dependent on the patient's risk.

After one month of treatment:

- Serum lipids

Following a dose change repeat every 2 weeks until the dose has been stable for 6 weeks, then revert to previous schedule.

More frequent monitoring is appropriate in patients at higher risk of toxicity. Monitoring of ciclosporin drug levels is not required for rheumatoid arthritis patients unless signs of toxicity develop.

Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching.

If it is necessary to switch a patient to a different brand, this should be done cautiously under specialist supervision. The patient should be monitored closely for changes in the following:

- Serum creatinine
- BP

**Ongoing monitoring:**

The specialist will retain the responsibility for monitoring the patient's ongoing response to treatment and advise if a dose change or treatment cessation is appropriate. This should usually be undertaken **annually.**

When a patient is reviewed, the specialist will advise primary care whether treatment should be continued and for how long, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.

## 9. Ongoing monitoring requirements to be undertaken by primary care

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See section 10 for further guidance on management of adverse effects/responding to monitoring results.

| Monitoring | Frequency |
|---|---|
| • BP<br>• FBC<br>• U&Es including creatinine and CrCl.<br>• ALT and/or AST, albumin, and bilirubin<br>• HbA1c | Monthly.<br>HbA1c - annually<br>Patients who have been stable for 12 months can be considered for reduced frequency monitoring on a case-by-case basis.<br>**The exact frequency of monitoring to be communicated by the specialist team in all cases**. |
| • Serum lipids<br>• Uric acid<br>• Serum magnesium | Annually |
| • Patients aged from 50 years who are severely immunosuppressed and have not received the shingles vaccine before will be eligible for the shingles vaccine (varicella zoster). This will be provided as two doses of the non-live vaccine. If patient is taking additional DMARDs, check advice for all drugs. Refer to Green Book Chapter 6 (Contraindications and special considerations) and Green Book Chapter 28a (Shingles) for further details.<br>• **Annual** influenza (The Green Book, Chapter 19) vaccinations are recommended.<br>• COVID-19 vaccination is safe and recommended. | • Shingles vaccination: Chapter 28a (Shingles).<br>• Influenza vaccination: annual. It is advisable to add the patient to the influenza vaccine list.<br>• Other vaccinations as per national schedule, e.g., pneumococcal vaccine, COVID-19. |

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| • Repeat pneumococcal vaccine may be indicated. See Green Book Chapter 25 for advice. | |

**(If relevant) If monitoring results are forwarded to the specialist team, please include clear clinical information on the reason for sending, to inform action to be taken by secondary care.**

## 10. Adverse effects and other management

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**Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit** www.mhra.gov.uk/yellowcard

For a full list of side effects and information on incidence of ADRs, refer to the BNF or see relevant summaries of product characteristics.

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

| Result | Action for primary care |
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| **As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance.**<br>Other benchmark values may be set by secondary care in specific clinical circumstances. This will be communicated by the specialist. | |
| **Full blood count**:<br>• White blood cells less than $3.5x10^9$/L<br>• Lymphocytes less than $0.5x10^9$/L<br>• Neutrophils less than$1.6x10^9$/L<br>• Platelets less than$140x10^9$/L<br>• Eosinophilia greater than$0.5x10^9$/L | Withhold and discuss with specialist team. |
| Mean cell volume >105 fL | Consider interruption in treatment.<br>Check serum folate, B12, alcohol history and TSH and treat any underlying abnormality. If results of these additional investigations are normal discuss with specialist team urgently. |
| Infection requiring antibiotics | During serious infections temporarily withhold ciclosporin until the patient has recovered. Consider additional investigations (e.g., FBC), if clinically appropriate. |
| **Liver function tests**:<br>• ALT or AST >100 units/L, or any sudden increases (e.g., double of baseline),<br>• Unexplained fall in serum albumin <30g/L (in the absence of active disease) | Withhold and discuss with specialist team.<br>Assess for other causes of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication. |

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| • Jaundice | |
| **Renal function**:<br>Creatinine increases of greater than 30% from baseline in the last 12 months or CrCl reduces to less than 60mL/min | Withhold and discuss with specialist team. |
| Hyperkalaemia | Review other medicines affecting potassium levels, e.g., ACE inhibitors, diuretics. Withhold and discuss with specialist team. |
| Elevated uric acid | If intending to treat as gout, discuss with specialist team due to the potential for interaction of urate-lowering medicines with ciclosporin. |
| Blood pressure<br>High BP ≥140/90 on two consecutive readings 2 weeks apart | Manage hypertension according to local pathways before stopping ciclosporin. Care should be taken to avoid drugs which may interact (section 7). If BP cannot be controlled, stop ciclosporin and obtain BP control before restarting ciclosporin. Discuss with rheumatology specialist team. |
| Hyperlipidaemia | Discuss with specialist team; reduction of ciclosporin dose may be considered. |
| Gum hypertrophy | Discuss with specialist team. |
| Signs or symptoms of bone marrow suppression, e.g., unexplained bleeding or bruising with or without sore throat, purpura, mouth ulcers. | Check FBC immediately, withhold treatment while awaiting results, and discuss with the specialist team. See haematological monitoring above. |
| 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. |

## 11. Advice to patients and carers

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The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.

**The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:**

- Symptoms of chickenpox or contact with a person with chickenpox or shingles.
- Sore throat, high temperature, skin rash, swollen glands, or any other signs or symptoms of infection.
- Signs or symptoms of liver problems, such as yellow skin or eyes (jaundice), itching all over, nausea or vomiting.
- Unexplained bleeding or bruising, black stools, or blood in the vomit or stools.
- Seizures, confusion, disorientation, visual disturbance
- Mouth ulcers, gum swelling or growth (gingival hyperplasia)
- Suspected or confirmed pregnancy.

**The patient should be advised:**

- To use effective contraception, and to take a pregnancy test if they think they could be pregnant. Patients should inform the specialist or GP immediately if they become pregnant or if they or their partners are planning a pregnancy.
- Tell anyone who prescribes them a medicine that they are taking ciclosporin. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe. Patients are advised to avoid self-medication with over-the-counter aspirin or ibuprofen.
- That vaccination in line with current national advice (e.g., for COVID-19, influenza) is safe and recommended.
- To maintain good oral hygiene, to reduce the risk of gum swelling.
- Patients have a small increased risk of skin cancers so should be advised to wear high factor sunscreen and to wear a hat and protective clothing when in strong sunshine. Sun beds should be avoided. Patients should be advised to carry out regular self-examination of the skin and report if there are any new lesions and/or changes to skin.
- That grapefruit or grapefruit juice should not be taken within 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.
- To avoid contact with people with chicken pox or shingles and report any such contact urgently to their primary care prescriber. If the patient is exposed, contact the specialist for advice. For detailed advice on risk assessment and post exposure prophylaxis following exposure to chicken pox and shingles, see:
    - the Green Book (Chapter 34)
    - UKHSA Guidance: Guidelines on post exposure prophylaxis (PEP) for varicella/shingles.
- All oral dosage forms of ciclosporin contain a form of ethanol, a 500mg dose is the equivalent of up to approximately 15 ml beer or 6 ml wine.

Patient information:

- VersusArthritis Ciclosporin

## 12. Pregnancy, paternal exposure, and breast feeding

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It is the responsibility of the specialist to provide advice on the need for contraception to all patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist.

**All patients should be informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The specialist team should be contacted if a patient becomes pregnant or is planning to become pregnant or breastfeed.**

**Pregnancy:**

Ciclosporin is compatible throughout pregnancy at the lowest effective dose. Regular clinical review and monitoring of maternal whole blood ciclosporin concentration is recommended both during and after pregnancy due to the risk of sub-therapeutic or toxic blood concentrations as a consequence of the pharmacokinetic changes which may be associated with pregnancy. All oral dosage forms of ciclosporin contain a form of ethanol, see section 6.

Information for healthcare professionals: Ciclosporin in pregnancy (UKTIS)

Information for patients and carers: Ciclosporin in pregnancy (Bumps)

**Breastfeeding:**

Patients taking ciclosporin should not be discouraged from breastfeeding. There is limited published evidence of safety, but small amounts are found in breast milk. Infants should be monitored for signs of infection or immunosuppression, and infant plasma levels should be monitored if there is any concern about toxicity. All oral dosage forms of ciclosporin contain a form of ethanol, see section 6.

Information for healthcare professionals: https://www.sps.nhs.uk/medicines/ciclosporin/

**Paternal exposure**:

Based on limited evidence, ciclosporin is compatible with paternal exposure.

**Fertility**

There is limited data on the effect of ciclosporin on human fertility.

## 13. Specialist contact information

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Name: **Named Rheumatology Consultant as per clinic letter**

Role and specialty: **Consultant Rheumatologist**

Daytime telephone number: **NUH**: 0115 919 4477 Secretaries Extension: 78947

**SFH**: 01623 676002 then dial option 2.

Email address: **NUH**: Nuhnt.ntcrheumatologysecretaries@nhs.net

**SFH**: sfh-tr.rheumqueries@nhs.net

## 14. Additional information

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Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed. Ensure that the specialist is informed in writing of any changes to the patient's GP or their contact details.

## 15. References

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- eBNF. Ciclosporin. Accessed via https://bnf.nice.org.uk/.
- Ciclosporin 100 mg soft capsules (Capimune®).

- Ciclosporin 100 mg soft capsules (Deximune®). Accessed via https://www.medicines.org.uk/emc/product/2613/smpc.
- Ciclosporin soft gelatin capsules (Neoral®). Accessed via https://www.medicines.org.uk/emc/product/1034/smpc.
- Ciclosporin oral solution (Neoral®). Accessed via https://www.medicines.org.uk/emc/product/5300/smpc.
- British Society of Rheumatology and British Health Professionals in Rheumatology. 2017. Guidelines for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Accessed via https://academic.oup.com/rheumatology/article/56/6/865/3053478.
- British Society of Rheumatology and British Health Professionals in Rheumatology. 2016. Guideline on prescribing drugs in pregnancy and breastfeeding – Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Accessed via https://academic.oup.com/rheumatology/article/55/9/1693/1744535.
- SPS Ciclosporin monitoring guidance. Date of revision of the text 13.07.21. Accessed via: https://www.sps.nhs.uk/monitorings/ciclosporin-monitoring/.


## 16. Other relevant national guidance

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- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

## 17. Local arrangements for referral

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Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.

- The request for shared care should be accompanied by individual patient information, outlining all relevant aspects of the patient's care and which includes direction to the shared care protocols the APC website.
- The specialist will request shared care with the GP in writing.
- If the GP doesn't agree to shared care, they should inform the specialist of their decision in writing within 14 days, outlining the reason for the decline. The agreement can be assumed if the GP does not provide a written decline.
- In cases where shared care arrangements are not in place or where problems have arisen within the agreement, and patient care may be affected, the responsibility for the patient's management, including prescribing, reverts to the specialist.
- Should the patient's condition change, the GP should contact the relevant specialist using the details provided with the shared care request letter