

# NEW ZEALAND DATA SHEET

## 1 PRODUCT NAME

NEORAL® 25 mg Soft Gelatine Capsules

NEORAL® 50 mg Soft Gelatine Capsules

NEORAL® 100 mg Soft Gelatine Capsules

NEORAL® 100 mg/ml Oral Solution

*(ciclosporin)*

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Neoral® soft gelatine capsules containing 25 mg, 50 mg, or 100 mg ciclosporin.

Neoral® oral solution containing 100 mg ciclosporin per mL. Each bottle of 50 mL contains 5000 mg of ciclosporin.

For a full list of excipients see Section 6.1.

## 3 PHARMACEUTICAL FORM

### Neoral soft gelatine capsules for oral administration

25 mg: blue-grey oval shaped gelatin capsule, soft, imprinted with "NVR 25mg" in red

50 mg: yellow-white oblong shaped gelatin capsule, soft, imprinted with "NVR 50mg" in red

100 mg: blue-grey oblong shaped gelatin capsule, soft, imprinted with "NVR 100mg" in red

### Neoral oral solution for oral administration

A clear, faintly yellow to browning yellow solution for oral administration. The formulation is a microemulsion concentrate.

Neoral is a pharmaceutical form of the active ingredient ciclosporin based on the microemulsion principle, which reduces the variability of pharmacokinetic parameters and provides dose linearity of ciclosporin exposure with a more consistent absorption profile and less influence from concomitant food intake. The formulation is a microemulsion pre concentrate, which in pharmacokinetic and clinical studies has demonstrated that the correlation between trough concentration and exposure to ciclosporin is much stronger when ciclosporin is given as Neoral than when it is given as Sandimmun. The formation of the microemulsion itself takes place in the presence of water, either in the form of a beverage or in the form of the gastric fluid.

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## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### Transplantation indications

##### *Solid organ transplantation*

Prevention of graft rejection following kidney, liver, heart, combined heart-lung, lung or pancreas allogeneic transplantations.

Treatment of transplant rejection in patients previously receiving other immunosuppressive agents.

##### *Bone marrow transplantation*

Prevention of graft rejection following bone marrow transplantation.

Prevention or treatment of graft-versus-host disease (GVHD).

#### Non-transplantation indications

##### *Endogenous uveitis*

Treatment of active sight-threatening intermediate or posterior uveitis of non-infectious aetiology in patients where conventional therapy fails, or causes unacceptable side effects.

Treatment of Behçet uveitis with repeated inflammatory attacks involving the retina.

##### *Nephrotic syndrome*

Steroid-dependent and steroid-resistant nephrotic syndrome in adults and children, due to glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis, or membranous glomerulonephritis.

Neoral can be used to induce and maintain remissions. It can also be used to maintain steroid-induced remission, allowing withdrawal of steroids.

##### *Rheumatoid arthritis*

Treatment of severe, active rheumatoid arthritis.

##### *Psoriasis*

Treatment of severe psoriasis in patients in whom conventional therapy is ineffective or inappropriate.

##### *Atopic dermatitis*

Neoral is indicated in patients with severe atopic dermatitis when systemic therapy is required.

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## 4.2 Dose and method of administration

### Dosage

The daily doses of Neoral should always be given in 2 divided doses.

Because of considerable inter- and intra-individual variations in absorption and elimination and the possibility of pharmacokinetic drug interactions (see Section 4.5 Interaction with other medicines and other forms of interaction), doses should be titrated individually according to clinical response and tolerability.

In transplant patients, routine monitoring of ciclosporin blood levels is required to avoid adverse effects due to high levels and to prevent organ rejection due to low levels (see Section 4.4 Special warnings and precautions for use).

In patients treated for non-transplant indications, monitoring of ciclosporin blood levels is of limited value except in the case of unexpected treatment failure or relapse, where it may be appropriate to establish the possibility of very low levels caused by non-compliance, impaired gastrointestinal absorption, or pharmacokinetic interactions (see Section 4.4 Special warnings and precautions for use).

### General target population

### Transplantation

#### *Solid organ transplantation*

Treatment with Neoral should be initiated within 12 hours before surgery at a dose of 10 to 15 mg/kg given in 2 divided doses. This dose should be maintained as the daily dose for 1 to 2 weeks post-operatively before being gradually reduced in accordance with blood levels until a maintenance dose of about 2 to 6 mg/kg given in 2 divided doses is reached.

When Neoral is given with other immunosuppressants (e.g. with corticosteroids or as part of a triple or quadruple drug therapy), lower doses (e.g. 3 to 6 mg/kg given in 2 divided doses for the initial treatment) may be used.

#### *Bone marrow transplantation*

The initial dose should be given on the day before transplantation. In most cases, Sandimmun i.v. infusion is preferred for this purpose; the recommended i.v. dose is 3 to 5 mg/kg per day. Infusion is continued at this dose level during the immediate post-transplant period of up to 2 weeks, before a change is made to oral maintenance therapy with Neoral at daily doses of about 12.5 mg/kg given in 2 divided doses. Maintenance treatment should be continued for at least 3 months (and preferably for 6 months) before the dose is gradually decreased to zero by 1 year after transplantation. If Neoral is used to initiate therapy, the recommended daily dose is 12.5 to 15 mg/kg given in 2 divided doses, starting on the day before transplantation.

Higher doses of Neoral, or the use of i.v. therapy, may be necessary in the presence of gastrointestinal disturbances which might decrease drug absorption.

In some patients, GVHD occurs after discontinuation of Neoral treatment, but usually responds favourably to re-introduction of therapy. In such cases, an initial oral loading dose of 10 to 12.5 mg/kg should be given, followed by daily oral administration of the maintenance dose previously found to be satisfactory. Low doses of Neoral should be used to treat mild, chronic GVHD.

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## Non-transplantation

When using Neoral in any of the established non-transplant indications, the following general rules should be adhered to:

- Before initiation of treatment a reliable baseline level of serum creatinine should be established by at least two measurements, and renal function must be assessed regularly throughout therapy to allow dosage adjustment (see Section 4.4 Special warnings and precautions for use).
- The only accepted route of administration is by mouth (the concentrate for intravenous infusion must not be used), and the daily dose should be given in two divided doses.
- Except in patients with sight-threatening endogenous uveitis and in children with nephrotic syndrome, the total daily dose must never exceed 5 mg/kg.
- For maintenance treatment the lowest effective and well tolerated dosage should be determined individually.
- In patients in whom within a given time (for specific information see below) no adequate response is achieved or the effective dose is not compatible with the established safety guidelines, treatment with Neoral should be discontinued.

## Endogenous uveitis

For *inducing remission*, initially 5 mg/kg per day orally given in 2 divided doses are recommended until remission of active uveal inflammation and improvement in visual acuity are achieved. In refractory cases, the dose can be increased to 7 mg/kg per day for a limited period.

To achieve initial remission, or to counteract inflammatory ocular attacks, systemic corticosteroid treatment with daily doses of 0.2 to 0.6 mg/kg prednisone or an equivalent may be added if Neoral alone does not control the situation sufficiently.

For *maintenance treatment*, the dose should be slowly reduced to the lowest effective level, which, during the remission phases, should not exceed 5 mg/kg per day.

## Nephrotic syndrome

For *inducing remission*, the recommended daily dose, given in 2 divided oral doses, is 5 mg/kg for adults and 6 mg/kg for children if, except for proteinuria, renal function is normal. In patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg per day.

The combination of Neoral with low doses of oral corticosteroids is recommended if the effect of Neoral alone is not satisfactory, especially in steroid-resistant patients.

If no improvement has been observed after 3 months' treatment, Neoral therapy should be discontinued.

The doses need to be adjusted individually according to efficacy (proteinuria) and safety (primarily serum creatinine), but should not exceed 5 mg/kg per day in adults and 6 mg/kg per day in children.

For *maintenance treatment*, the dose should be slowly reduced to the lowest effective level.

## Rheumatoid arthritis

For the *first 6 weeks of treatment* the recommended dose is 3 mg/kg per day orally given in 2 divided doses. If the effect is insufficient, the daily dose may then be increased gradually as tolerability permits, but should not exceed 5 mg/kg. To achieve full effectiveness, up to 12 weeks of Neoral therapy may be required.

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For *maintenance treatment* the dose has to be titrated individually to the lowest effective level according to tolerability.

Neoral can be given in combination with low-dose corticosteroids and/or non-steroidal anti-inflammatory drugs (see Section 4.4 Special warnings and precautions for use). Neoral can also be combined with low-dose weekly methotrexate in patients who have insufficient response to methotrexate alone, by using initially 2.5 mg/kg Neoral in 2 divided doses per day, with the option to increase the dose as tolerability permits.

## Psoriasis

Due to the variability of this condition, treatment must be individualized. For *inducing remission*, the recommended initial dose is 2.5 mg/kg per day orally given in 2 divided doses. 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 per day, or in whom the effective dose is not compatible with the established safety guidelines (see Section 4.4 Special warnings and precautions for use).

Initial doses of 5 mg/kg per day are justified in patients whose condition requires rapid improvement. Once satisfactory response is achieved, Neoral may be discontinued and subsequent relapse managed with re-introduction of Neoral at the previous effective dose. In some patients, continuous maintenance therapy may be necessary.

For *maintenance treatment*, doses have to be titrated individually to the lowest effective level, and should not exceed 5 mg/kg per day.

## Atopic dermatitis

Due to the variability of this condition, treatment must be individualized. The recommended dose range is 2.5 to 5 mg/kg per day given in 2 divided oral doses. If a starting dose of 2.5 mg/kg per day does not achieve a satisfactory response within two weeks of therapy, 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 per day. Once satisfactory response is achieved, the dose should be reduced gradually and, if possible, Neoral should be discontinued. Subsequent relapse may be managed with a further course of Neoral.

Although a course of 8 weeks' therapy may be sufficient to achieve clearing, up to 1 year's therapy has been shown to be effective and well tolerated, provided the monitoring guidelines are followed.

## Conversion from oral Sandimmun to Neoral

The available data indicate that after a 1:1 conversion from Sandimmun to Neoral, the trough concentrations of ciclosporin in whole blood are comparable. In many patients, however, higher peak concentrations ( $C_{max}$ ) and an increased exposure to the drug (AUC) may occur. In a small percentage of patients these changes are more marked and may be of clinical significance. Their magnitude depends largely on the individual variance in the absorption of ciclosporin from the originally used Sandimmun, which is known to be highly variable in its bioavailability. Patients with variable trough levels or very high doses of Sandimmun may be poor or inconsistent absorbers of ciclosporin (e.g. patients with cystic fibrosis, liver transplant patients with cholestasis or poor bile secretion, children or some kidney transplant recipients) who may, on conversion to Neoral, become good absorbers. Therefore, in this population, the increase in bioavailability of ciclosporin following a 1:1 conversion from Sandimmun to Neoral might be greater than usually observed. The dose of Neoral should therefore be down titrated individually according to their target trough level range.

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It needs to be emphasized that the absorption of ciclosporin from Neoral is less variable and the correlation between ciclosporin trough concentrations and exposure (in terms of AUC) is much stronger than with Sandimmun. This makes ciclosporin blood trough concentrations a more robust and reliable parameter for therapeutic drug monitoring.

Since the conversion from Sandimmun to Neoral may result in an increased drug exposure, the following rules must be observed:

In *transplant patients* Neoral should be started with the same daily dose as was previously used with Sandimmun. Ciclosporin trough concentrations in whole blood should be monitored initially within 4 to 7 days after the conversion to Neoral. In addition, clinical safety parameters such as serum creatinine and blood pressure are to be monitored during the first 2 months after the conversion. If the ciclosporin trough blood levels are beyond the therapeutic range, and/or worsening of the clinical safety parameters occur, the dosage must be adjusted accordingly.

In *patients treated for non-transplant indications*, Neoral should be started with the same daily dose as was used with Sandimmun. Two, 4 and 8 weeks after the conversion, serum creatinine levels and blood pressure should be monitored. If serum creatinine levels or blood pressure significantly exceed the pre-conversion levels or if serum creatinine levels increase to more than 30% above creatinine levels prior to Sandimmun therapy at more than one measurement, the dose should be reduced (see also 'Additional precautions' in Section 4.4 Special warnings and precautions for use). In case of unexpected toxicity or inefficacy of ciclosporin, blood trough levels should also be monitored.

## Conversion between oral ciclosporin formulations

Switching from one oral ciclosporin formulation to another should be made with caution and under physician supervision. The introduction of the new formulation must be made with monitoring of blood levels of ciclosporin to ensure that pre-conversion levels are attained.

## Administration

The dose ranges given for oral administration and i.v. administration are intended to serve as guidelines only. The recommended dose of Sandimmun concentrate for solution for infusion is approximately one third of the appropriate oral dose. Routine monitoring of ciclosporin blood levels is required; this can be carried out by means of a RIA method based on monoclonal antibodies. The results obtained will serve as a guide for determining the actual dosage required to achieve the desired target concentrations in individual patients.

## Oral administration

The daily doses of Neoral should always be given in 2 divided doses.

Neoral capsules should be swallowed whole.

Neoral oral solution should be diluted with, preferably, orange or apple juice; however, other drinks such as soft drinks can be used according to individual taste. Immediately before taking the oral solution, it should be stirred well. Owing to its possible interference with the cytochrome P450-dependent enzyme system, grapefruit juice should be avoided for dilution (see Section 4.5 Interaction with other medicines and other forms of interaction). The syringe should not come in contact with the diluent. If the syringe is to be cleaned, do not rinse it but wipe the outside with a dry tissue (see Section 3 Pharmaceutical form).

## Use in the elderly

Experience with Sandimmun in the elderly is limited, but no particular problems have been reported following the use of the drug at the recommended dose.

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In rheumatoid arthritis clinical trials with ciclosporin, 17.5% of patients were aged 65 or older. These patients were more likely to develop systolic hypertension on therapy, and more likely to show serum creatinine rises  $\geq 50\%$  above the baseline after 3 to 4 months of therapy.

Clinical studies of Neoral in transplant and psoriasis patients did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experiences have not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## Use in children

Experience with Neoral in children is limited. Clinical studies have included children from 1 year of age using standard ciclosporin dosage with no particular problems. In several studies, paediatric patients required and tolerated higher doses of ciclosporin per kg body weight than those used in adults.

Neoral use in children for non-transplant indications other than nephrotic syndrome cannot be recommended (see Section 4.4 Special warnings and precautions for use).

## Use in Renal impairment

### All indications

Ciclosporin undergoes minimal renal elimination and its pharmacokinetics is not affected by renal impairment (see Section 5 Pharmacological properties). However, due to its nephrotoxic potential (see Section 4.8 Undesirable effects), a careful monitoring of the renal function is recommended (see Section 4.4 Special warnings and precautions for use).

### Non-transplant indications

Patients with impaired renal function, except nephrotic syndrome patients, should not receive ciclosporin (see Section 4.4 Special warnings and precautions for use). In nephrotic syndrome patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg per day.

## Use in Hepatic impairment

Ciclosporin is extensively metabolized by the liver. The terminal half-life varied between 6.3 hours in healthy volunteers to 20.4 hours in severe liver disease patients (see PHARMACEUTICAL PROPERTIES). Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see Section 4.4 Special warnings and precautions for use and Section 5 Pharmacological Properties).

## **4.3 Contraindications**

Hypersensitivity to ciclosporin or to any of the excipients of Neoral.

## **4.4 Special warnings and precautions for use**

### All indications

### Medical supervision

Neoral should be prescribed only by physicians who are experienced in immunosuppressive therapy, and can provide adequate follow-up, including regular full physical examination, measurement of

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blood pressure, and control of laboratory safety parameters. Transplantation patients receiving the drug should be managed in facilities with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should receive complete information for the follow-up of the patient.

## Lymphomas and other malignancies

Like other immunosuppressants, ciclosporin increases the risk of developing lymphomas and other malignancies, particularly those of the skin. The increased risk appears to be related to the degree and duration of immunosuppression rather than to the use of specific agents. Hence a treatment regimen containing multiple immunosuppressants (including ciclosporin) should be used with caution as this could lead to lymphoproliferative disorders and solid organ tumours, some with reported fatalities (see Section 4.8 Undesirable effects).

In view of the potential risk of skin malignancy, patients on Neoral should be warned to avoid excess ultraviolet light exposure.

## Infections

Like other immunosuppressants, ciclosporin predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections, often with opportunistic pathogens. Activation of latent Polyomavirus infections that may lead to Polyomavirus associated nephropathy (PVAN), especially to BK virus nephropathy (BKVN), or to JC virus associated progressive multifocal leukoencephalopathy (PML) have been observed in patients receiving ciclosporin. These conditions are often related to a high total immunosuppressive burden and should be considered in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Serious and/or fatal outcomes have been reported. Effective pre-emptive and therapeutic strategies should be employed particularly in patients on multiple long-term immunosuppressive therapy.

## Acute and chronic nephrotoxicity

A frequent and potentially serious complication, an increase in serum creatinine and urea, may occur during the first few weeks of Neoral therapy. These functional changes are dose-dependent and reversible, usually responding to dose reduction. During long-term treatment, some patients may develop structural changes in the kidney (e.g. arteriolar hyalinosis, tubular atrophy and interstitial fibrosis) which, in renal transplant patients, must be differentiated from changes due to chronic rejection (see Section 4.8 Undesirable effects). Close monitoring of parameters that assess renal function is required. Abnormal values may necessitate dose reduction (see Section 4.2 Dose and method of administration and Section 5 Pharmacological properties).

## Hepatotoxicity and liver injury

Neoral may also cause dose-dependent, reversible increases in serum bilirubin and in liver enzymes (see Section 4.8 Undesirable effects). There have been solicited and spontaneous postmarketing reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients treated with ciclosporin. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and comedications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see Section 4.8 Undesirable effects). Close monitoring of parameters that assess renal and hepatic function is required. Abnormal values may necessitate dose reduction (see Section 4.2 Dose and method of administration and Section 5 Pharmacological properties)..

## Geriatrics

In elderly patients, renal function should be monitored with particular care.



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## Monitoring ciclosporin levels in transplant patients

When Neoral is used in transplant patients, routine monitoring of ciclosporin blood levels is an important safety measure (see Section 4.2 Dose and method of administration). For monitoring ciclosporin levels in whole blood, a specific monoclonal antibody (measurement of parent drug) is preferred; a HPLC method, which also measures the parent drug, can be used as well. If plasma or serum is used, a standard separation protocol (time and temperature) should be followed. For the initial monitoring of liver transplant patients, either the specific monoclonal antibody should be used, or parallel measurements using both the specific monoclonal antibody and the nonspecific monoclonal antibody should be performed, to ensure a dosage that provides adequate immunosuppression.

It must be remembered that the ciclosporin concentration in blood, plasma, or serum is only one of many factors contributing to the clinical status of the patient. Results should therefore serve only as a guide to dosage in relationship to other clinical and laboratory parameters (see Section 4.2 Dose and method of administration).

## Hypertension

Regular monitoring of blood pressure is required during Neoral therapy; if hypertension develops, appropriate antihypertensive treatment must be instituted (see Section 4.8 Undesirable effects). Preference should be given to an antihypertensive agent that does not interfere with the pharmacokinetics of ciclosporin, e.g. isradipine (see Section 4.5 Interaction with other medicines and other forms of interaction).

## Blood lipids increased

Since Neoral has been reported to induce a reversible slight increase in blood lipids, it is advisable to perform lipid determinations before treatment and after the first month of therapy. In the event of increased lipids being found, restriction of dietary fat and, if appropriate, a dose reduction, should be considered (see Section 4.8 Undesirable effects).

## Hyperkalaemia

Ciclosporin enhances the risk of hyperkalaemia, especially in patients with renal dysfunction (see Section 4.8 Undesirable effects). Caution is also required when ciclosporin is co-administered with potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) and potassium containing drugs as well as in patients on a potassium rich diet (see Section 4.5 Interaction with other medicines and other forms of interaction). Control of potassium levels in these situations is advisable.

## Hypomagnesaemia

Ciclosporin enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplant period (see Section 4.8 Undesirable effects). Control of serum magnesium levels is therefore recommended in the peri-transplant period, particularly in the presence of neurological symptom/signs. If considered necessary, magnesium supplementation should be given.

## Hyperuricemia

Caution is required in treating patients with hyperuricaemia (see Section 4.8 Undesirable effects).

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## Live-attenuated vaccines

During treatment with ciclosporin, vaccination may be less effective; the use of live-attenuated vaccines should be avoided (see Section 4.5 Interaction with other medicines and other forms of interaction).

## Interactions

Caution should be observed while co-administering lercanidipine with ciclosporin (see Section 4.5 Interaction with other medicines and other forms of interaction).

Ciclosporin may increase blood levels of concomitant medications that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) such as aliskiren, dabigatran or bosentan. Co-administration of ciclosporin with aliskiren is not recommended. Co-administration of ciclosporin together with dabigatran or bosentan should be avoided. These recommendations are based upon the potential clinical impact of these interactions (see Section 4.5 Interaction with other medicines and other forms of interaction).

## Special Excipient: ethanol

The ethanol (alcohol) content (see Section 6.1 List of excipients) should be taken into account when given to pregnant or breast feeding women, in patients presenting with liver disease or epilepsy, in alcoholic patients, or if Neoral is being given to a child.

## Additional precautions in non-transplant indications

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.

## Additional precautions in endogenous uveitis

Since Neoral can impair renal function, it is necessary to assess renal function frequently, and if serum creatinine remains increased to more than 30% above baseline at more than one measurement, to reduce the dosage of Neoral by 25 to 50%. If the increase from baseline exceeds 50%, further reduction should be considered. These recommendations apply even if the patient's values still lie within the laboratory's normal range.

Neoral should be administered with caution in patients with neurological Behcet's syndrome. The neurological status of patients with neurological Behcet's syndrome should be carefully monitored

There is only limited experience with the use of Neoral in children with endogenous uveitis.

## Additional precautions in nephrotic syndrome

Since Neoral can impair renal function, it is necessary to assess renal function frequently, and if the serum creatinine remains increased to more than 30% above baseline at more than one measurement, to reduce the dosage of Neoral by 25 to 50%. If the increase from baseline exceeds 50%, further reduction should be considered. Patients with abnormal baseline renal function should initially be treated with 2.5 mg/kg per day and must be monitored very carefully.

In some patients, it may be difficult to detect Neoral-induced renal dysfunction because of changes in renal function related to the nephrotic syndrome itself. This explains why, in rare cases, Neoral-associated structural kidney alterations have been observed without increases in serum creatinine.

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Therefore, renal biopsy should be considered for patients with steroid-dependent minimal-change nephropathy, in whom Neoral therapy has been maintained for more than 1 year.

In patients with nephrotic syndrome treated with immunosuppressants (including ciclosporin), the occurrence of malignancies (including Hodgkin's lymphoma) has occasionally been reported.

## Additional precautions in rheumatoid arthritis

Since Neoral 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 for 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 comedication, and concomitant diseases. More frequent checks are necessary when the Neoral dose is increased, or concomitant treatment with a non-steroidal anti-inflammatory drug is initiated or its dosage increased (see Section 4.5 Interaction with other medicines and other forms of interaction).

If the serum creatinine remains increased to more than 30% above baseline at more than one measurement, the dosage of Neoral 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's normal range. If dose reduction is not successful in reducing levels within one month, Neoral treatment should be discontinued.

Discontinuation of the drug may also become necessary if hypertension developing during Neoral therapy cannot be controlled by appropriate antihypertensive therapy (see Section 4.5 Interaction with other medicines and other forms of interaction).

As with other long-term immunosuppressive treatments (including ciclosporin), an increased risk of lymphoproliferative disorders must be borne in mind. Special caution should be observed if Neoral is used in combination with methotrexate (see Section 4.5 Interaction with other medicines and other forms of interaction).

## Additional precautions in psoriasis

Since Neoral 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 for the first 3 months of therapy. Thereafter, if creatinine remains stable, measurements should be made at monthly intervals. If the serum creatinine increases and remains increased to more than 30% above baseline at more than one measurement, the dosage of Neoral must be reduced by 25 to 50%. If the increase from baseline exceeds 50%, further reduction should be considered. These recommendations apply even if the patient's values still lie within the laboratory's normal range. If dose reduction is not successful in reducing creatinine levels within one month, Neoral treatment should be discontinued.

Discontinuation of Neoral therapy is also recommended if hypertension developing during Neoral treatment cannot be controlled with appropriate therapy (see Section 4.5 Interaction with other medicines and other forms of interaction).

Elderly patients should be treated only in the presence of disabling psoriasis, and renal function should be monitored with particular care.

There is only limited experience with the use of Neoral in children with psoriasis.

In psoriatic patients on ciclosporin, as in those on conventional immunosuppressive therapy, development of malignancies (in particular of the skin) has been reported. Skin lesions not typical for psoriasis, but suspected to be malignant or pre-malignant should be biopsied before Neoral treatment

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is started. Patients with malignant or pre-malignant alterations of the skin should be treated with Neoral only after appropriate treatment of such lesions, and if no other option for successful therapy exists.

In a few psoriatic patients treated with ciclosporin, lymphoproliferative disorders have occurred. These were responsive to prompt drug discontinuation.

Patients on Neoral should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

## Additional precautions in atopic dermatitis

Since Neoral 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 for the first 3 months of therapy. Thereafter, if creatinine remains stable, measurements should be made at monthly intervals. If the serum creatinine increases and remains increased to more than 30% above baseline at more than one measurement, the dosage of Neoral must be reduced by 25 to 50%. If the increase from baseline exceeds 50%, further reduction should be considered. These recommendations apply even if the patient's creatinine values still lie within the laboratory's normal range. If dose reduction is not successful in reducing creatinine levels within 1 month, Neoral treatment should be discontinued.

Discontinuation of Neoral therapy is also recommended if hypertension developing during Neoral treatment cannot be controlled with appropriate therapy (see Section 4.8 Undesirable effects).

The experience with Neoral in children with atopic dermatitis is limited.

Elderly patients should be treated only in the presence of disabling atopic dermatitis and renal function should be monitored with particular care.

Benign lymphadenopathy is commonly associated with flares in atopic dermatitis, and invariably disappears spontaneously or with general improvement in the disease. Lymphadenopathy observed on treatment with ciclosporin should be regularly monitored. Lymphadenopathy which persists despite improvement in disease activity should be examined by biopsy as a precautionary measure to ensure the absence of lymphoma.

Active herpes simplex infections should be allowed to clear before treatment with Neoral is initiated, but are not necessarily a reason for drug withdrawal if they occur during treatment unless infection is severe.

Skin infections with *Staphylococcus aureus* are not an absolute contraindication for Neoral therapy, but should be controlled with appropriate antibacterial agents. Oral erythromycin, known to have the potential to increase the blood concentration of ciclosporin (see Section 4.5 Interaction with other medicines and other forms of interaction) should be avoided, or, if there is no alternative, it is recommended to closely monitor blood levels of ciclosporin, renal function, and for side effects of ciclosporin.

Patients on Neoral should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

## **4.5 Interactions with other medicines and other forms of interaction**

Of the many drugs reported to interact with ciclosporin, those for which the interactions are adequately substantiated and considered to have clinical implications are listed below.

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## Interactions resulting in concomitant use not being recommended

During treatment with ciclosporin, vaccination may be less effective, the use of live-attenuated vaccines should be avoided (see Section 4.4 Special warnings and precautions for use).

## Interactions to be considered

Caution is required for concomitant use of potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) or potassium containing drugs since they may lead to significant increases in serum potassium (see Section 4.4 Special warnings and precautions for use).

Following concomitant administration of ciclosporin and lercanidipine, the AUC of lercanidipine was increased threefold and the AUC of ciclosporin was increased 21 %. Therefore caution is recommended when co-administering ciclosporin together with lercanidipine (see Section 4.4 Special warnings and precautions for use).

Care should be taken when using ciclosporin together with methotrexate in rheumatoid arthritis patients due to the risk of nephrotoxic synergy (see Section 4.4 Special warnings and precautions for use).

## Interactions increasing or decreasing ciclosporin levels to be considered

Various agents are known to either increase or decrease plasma or whole blood ciclosporin levels usually by inhibition or induction of enzymes involved in the metabolism of ciclosporin, in particular CYP3A4.

If the concomitant use of drugs known to interact with ciclosporin cannot be avoided, the following basic recommendation should be observed in transplant patients. Frequent measurement of ciclosporin levels and, if necessary, ciclosporin dosage adjustment is required, particularly during the introduction or withdrawal of the co-administered drug.

If the concomitant use of drugs known to interact with ciclosporin cannot be avoided, the following basic recommendations should be observed:

- In transplant patients: frequent measurement of ciclosporin levels and, if necessary, ciclosporin dosage adjustment are required, particularly during the introduction or withdrawal of the co-administered drug.
- In non-transplant patients: the value of ciclosporin blood level monitoring is questionable, as in these patients the relationship between blood level and clinical effects is less well established. If drugs known to increase ciclosporin levels are given concomitantly, frequent assessment of renal function and careful monitoring for ciclosporin-related side effects may be more appropriate than blood level measurement.

## Interactions decreasing ciclosporin levels

Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, sulfadimidine i.v.; rifampicin, octreotide, probucol, orlistat, *hypericum perforatum* (St. John's wort), ticlopidine, sulfapyrazone, terbinafine, and bosentan.

## Interactions increasing ciclosporin levels

Macrolide antibiotics (e.g. erythromycin [see Section 4.4 Special warnings and precautions for use in atopic dermatitis], azithromycin and clarithromycin); ketoconazole, fluconazole, itraconazole, voriconazole; diltiazem, nifedipine, verapamil; metoclopramide; oral contraceptives; danazol;

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methylprednisolone (high dose); allopurinol; amiodarone; cholic acid and derivatives; protease inhibitors; imatinib; colchicine; and nefazodone.

## Other relevant interactions

### Drug-food/drink interactions

The concomitant intake of grapefruit juice has been reported to increase the bioavailability of ciclosporin (see Section 4.2 Dose and method of administration).

### Interactions resulting in a potential increased nephrotoxicity

During the concomitant use of a drug that may exhibit nephrotoxic synergy, close monitoring of renal function (in particular serum creatinine) should be performed. If a significant impairment of renal function occurs, the dosage of the co-administered drug should be reduced or alternative treatment considered.

Care should be taken when using ciclosporin together with other drugs that exhibit nephrotoxic synergy such as: aminoglycosides (incl. gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); non-steroidal anti-inflammatory drugs (incl. diclofenac, naproxen, sulindac); melphalan, histamine H<sub>2</sub>-receptor-antagonists (e.g. cimetidine, ranitidine); methotrexate (see Section 4.4 Special warnings and precautions for use).

Concomitant use with tacrolimus should be avoided due to increased potential for nephrotoxicity.

The concomitant use of diclofenac and ciclosporin has been found to result in a significant increase in the bioavailability of diclofenac, with the possible consequence of reversible renal function impairment. The increase in the bioavailability of diclofenac is most probably caused by a reduction of its high first-pass effect. If non-steroidal anti-inflammatory drugs with a low first-pass effect (e.g. acetylsalicylic acid) are given together with ciclosporin, no increase in their bioavailability is to be expected. Non-steroidal anti-inflammatory drugs known to undergo strong first-pass metabolism (e.g. diclofenac) should be given at doses lower than those that would be used in patients not receiving ciclosporin.

In graft recipients there have been isolated reports of considerable but reversible impairment of kidney function (with corresponding increase in serum creatinine) following concomitant administration of fibric acid derivatives (e.g. bezafibrate, fenofibrate). Kidney function must therefore be closely monitored in these patients. In the event of significant impairment of kidney function the co-medication should be withdrawn.

### Interactions resulting in an increased rate of gingival hyperplasia

The concurrent administration of nifedipine with ciclosporin may result in an increased rate of gingival hyperplasia compared with that observed when ciclosporin is given alone. The concomitant use of nifedipine should be avoided in patients in whom gingival hyperplasia develops as a side effect of ciclosporin ( see Section 4.8 Undesirable effects).

### Interactions resulting in an increase of other drug levels

Ciclosporin is also an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein and may increase plasma levels of co-medications that are substrates of this enzyme and/or transporter.

Ciclosporin may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins), etoposide, aliskiren, bosentan or dabigatran.

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Severe digitalis toxicity has been seen within days of starting ciclosporin in several patients taking digoxin. There are also reports on the potential of ciclosporin to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. If digoxin or colchicine is used concurrently with ciclosporin, close clinical observation is required in order to enable early detection of toxic manifestations of digoxin or colchicine, followed by reduction of dosage or its withdrawal.

Literature and postmarketing cases of myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of ciclosporin with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely, fluvastatin. When concurrently administered with ciclosporin, the dosage of these statins should be reduced according to label recommendations. 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.

If digoxin, colchicine or HMG-CoA reductase inhibitors (statins) are used concurrently with ciclosporin, close clinical observation is required in order to enable early detection of toxic manifestations of the drugs, followed by reduction of its dosage or its withdrawal.

Elevations in serum creatinine were observed in the studies using everolimus or sirolimus in combination with full-dose ciclosporin for microemulsion. This effect is often reversible with ciclosporin dose reduction. Everolimus and sirolimus had only a minor influence on ciclosporin pharmacokinetics. Co-administration of ciclosporin significantly increases blood levels of everolimus and sirolimus.

Ciclosporin may increase the plasma concentrations of repaglinide and thereby increase the risk of hypoglycaemia.

Co administration of bosentan and ciclosporin in healthy volunteers resulted in an approximately 2-fold increase in bosentan exposure and a 35% decrease in ciclosporin exposure (see above subsection drug interactions decreasing ciclosporin levels and Section 4.4 Special warnings and precautions for use).

Following concomitant administration of ciclosporin and aliskiren, the C<sub>max</sub> of aliskiren was increased by approximately 2.5 fold and the AUC by approximately 5 fold. However, the pharmacokinetic profile of ciclosporin was not significantly altered (see Section 4.4 Special warnings and precautions for use).

Concomitant administration of dabigatran and ciclosporin leads to increased plasma level of dabigatran due to the P-gp inhibitory activity of ciclosporin (see Warnings and precautions). Dabigatran has a narrow therapeutic index and an increase in plasma level may be associated with an increased risk of bleeding.

Multiple dose administration of ambrisentan and ciclosporin in healthy volunteers resulted in an approximately 2-fold increase in ambrisentan exposure while the ciclosporin exposure was marginally increased (approximately 10%).

A significant increased exposure in anthracycline antibiotics (e.g doxorubicine, mitoxantrone, daunorubicine) was observed in oncology patients with the intravenous co-administration of anthracycline antibiotics and very high doses of ciclosporin.

## 4.6 Fertility, pregnancy and lactation

### Women of child-bearing potential

There are no special recommendations for women of child-bearing potential.

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## Fertility

There is limited data on the effect of Sandimmun on human fertility. No impairment in fertility was demonstrated in studies in male and female rats (see Section 5.3 Preclinical safety data).

## Pregnancy

Animal studies have shown reproductive toxicity in rats and rabbits (see Section 5.3 Preclinical safety data).

There is moderate amount of data on the use of Sandimmun in pregnant patients. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks).

A limited number of observations in children exposed to ciclosporin in utero is available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal.

However there are no adequate data in pregnant women and, therefore, Neoral should not be used during pregnancy unless the expected benefit to the mother outweighs the potential risk to the foetus. The ethanol content of the Sandimmun formulations should also be taken into account in pregnant women (see Section 4.4 Special warnings and precautions for use).

## Lactation

Ciclosporin passes into breast milk. The ethanol content of the Neoral should also be taken into account in breastfeeding mothers (see Section 4.4 Special warnings and precautions for use). Mothers receiving treatment with Neoral should not breast-feed. Because of the potential of Neoral to cause serious adverse drug reactions in breast-fed newborns/infants, a decision should be made whether to abstain from breast-feeding or to abstain from using the medicinal drug, taking into account the importance of the medicinal product to the mother.

## **4.7 Effects on ability to drive and use machines**

No data exist on the effects of Neoral on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Summary of the safety profile

The principal adverse reactions observed in clinical trials and associated with the administration of ciclosporin include renal dysfunction, tremor, hirsutism, hypertension, diarrhea, anorexia, nausea and vomiting.

Many side effects associated with ciclosporin therapy are dose-dependent and responsive to dose reduction. In the various indications the overall spectrum of side effects is essentially the same; there are, however, differences in incidence and severity. As a consequence of the higher initial doses and longer maintenance therapy required after transplantation, side effects are more frequent and usually more severe in transplant patients than in patients treated for other indications.

### Infections and Infestations

Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic) (see Section 4.4 Special warnings and precautions for use). Both generalised and localised infections can occur. Pre-existing infections may also be aggravated and reactivation of Polyomavirus infections may lead to



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Polyomavirus associated nephropathy (PVAN) or to JC virus associated progressive multifocal leukoencephalopathy (PML). Serious and/or fatal outcomes have been reported.

## Neoplasms benign, malignant and unspecified (including cysts and polyps)

Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin- containing regimens, are at increased risk of developing lymphomas or lymphoproliferative disorders and other malignancies, particularly of the skin. The frequency of malignancies increases with the intensity and duration of therapy (see Section 4.4 Special warnings and precautions for use). Some malignancies may be fatal.

## Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first, using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ) very rare ( $< 1/10,000$ ), including isolated reports.

### **Table 1 Adverse drug reactions from clinical trials**

Blood and lymphatic system disorders

Common	Leucopenia
--------	------------

#### **Metabolism and nutrition disorders**

Very common	Anorexia, hyperglycaemia
-------------	--------------------------

Nervous system disorders

Very common	Tremor, headache
-------------	------------------

Common	Convulsions, paraesthesia
--------	---------------------------

#### **Vascular disorders**

Very common	Hypertension (see Section 4.4 Special warnings and precautions for use).
-------------	--

Common	Flushing
--------	----------

#### **Gastrointestinal disorders**

Very common	Nausea, vomiting, abdominal discomfort, diarrhoea, gingival hyperplasia
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Common	Peptic ulcer
--------	--------------

#### **Hepatobiliary disorders**

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Common            Hepatotoxicity (see Section 4.4 Special warnings and precautions for use).

## **Skin and subcutaneous tissue disorders**

Very common      Hirsutism

Common            Acne, rash

## **Renal and urinary disorders**

Very common      Renal dysfunction (see Section 4.4 Special warnings and precautions for use).

## **Reproductive system and breast disorders**

Rare                Menstrual disturbances

## **General disorders and administration site conditions**

Common            Pyrexia, oedema

## Adverse drug reactions from post-marketing experience (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Neoral via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each organ class, ADRs are presented below in Table 2 in order of decreasing seriousness.

**Table 2      Adverse drug reactions from spontaneous reports and literature (frequency not known)**

<b>Blood and lymphatic system disorders</b>	Thrombotic microangiopathy, haemolytic uremic syndrome, thrombotic thrombocytopenic purpura; anaemia; thrombocytopenia
<b>Metabolism and nutrition disorders</b>	Hyperlipidemia; hyperuricemia; hyperkalemia; hypomagnesemia
<b>Nervous system disorders</b>	Encephalopathy including Posterior Reversible Encephalopathy Syndrome (PRES), signs and symptoms such as convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia; optic disc oedema including papilledema, with possible visual impairment secondary to benign intracranial hypertension; peripheral neuropathy; migraine

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<b>Gastrointestinal disorders</b>	Pancreatitis acute
<b>Hepatobiliary disorders</b>	Hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure with some fatal outcome (see Section 4.4 Special warnings and precautions for use)
<b>Skin and subcutaneous tissue disorders</b>	Hypertrichosis
<b>Musculoskeletal and connective tissue disorders</b>	Myopathy; muscle spasm; myalgia; muscular weakness, pain of lower extremities
<b>Reproductive system and breast disorders</b>	Gynecomastia
<b>General disorders and administration site conditions</b>	Fatigue; weight increase

## Description of selected adverse drug reactions

### Hepatotoxicity and liver injury

There have been solicited and spontaneous postmarketing reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients with ciclosporin. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and comedications with hepatotoxicity potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see Section 4.4 Special warnings and precautions for use).

### Acute and chronic nephrotoxicity

Patients receiving calcineurin inhibitors (CNIs) therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of acute or chronic nephrotoxicity. There have been reports from clinical trials and from the post marketing setting associated with the use of Sandimmun. Cases of acute nephrotoxicity reported disorders of ion homeostasis, such as hyperkalemia, hypomagnesemia, hyperuricemia. Cases reporting chronic morphological changes included arteriolar hyalinosis, tubular atrophy and interstitial fibrosis (see Section 4.4 Special warnings and precautions for use).

### Pain of lower extremities

Isolated cases of pain of lower extremities have been reported in association with ciclosporin. Pain of lower extremities has also been noted as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS) as described in the literature.

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## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via <https://nzphvc.otago.ac.nz/reporting/>

## **4.9 Overdose**

The oral LD<sub>50</sub> of ciclosporin is 2,329 mg/kg in mice; 1,480 mg/kg in rats and > 1,000 mg/kg in rabbits. The i.v. LD<sub>50</sub> is 148 mg/kg in mice, 104 mg/kg in rats, and 46 mg/kg in rabbits.

## Symptoms

Experience with acute overdosage of ciclosporin is limited. Oral doses of ciclosporin of up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia and, in a few patients, moderately severe, reversible impairment of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with ciclosporin in premature neonates.

## Treatment

In all cases of overdosage, general supportive measures should be followed and symptomatic treatment applied. Forced emesis and gastric lavage may be of value within the first few hours after oral intake. Ciclosporin is not dialysable to any great extent, nor is it well cleared by charcoal haemoperfusion.

## Reporting of suspected adverse reactions

For advice on the management of overdose please contact the National Poisons Centre 0800 POISON (0800 764766).

# 5 PHARMACOLOGICAL PROPERTIES

## **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Immunosuppressive agents, calcineurin inhibitors (ATC code L04A D01).

## Mechanism of action

Ciclosporin (also known as ciclosporin A) is a cyclic polypeptide consisting of 11 amino acids. It is a potent immunosuppressive agent, which in animals prolongs survival of allogeneic transplants of skin, heart, kidney, pancreas, bone marrow, small intestine or lung. Studies suggest that ciclosporin inhibits the development of cell-mediated reactions, including allograft immunity, delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, graft-versus-host disease (GVHD), and also T-cell dependent antibody production. At the cellular level it inhibits production and release of lymphokines including interleukin 2 (T-cell growth factor, TCGF). Ciclosporin appears to block the resting lymphocytes in the G0 or G1 phase of the cell cycle, and inhibits the antigen-triggered release of lymphokines by activated T-cells.

All available evidence suggests that ciclosporin acts specifically and reversibly on lymphocytes. Unlike cytostatic agents, it does not depress haemopoiesis and has no effect on the function of phagocytic cells. Patients treated with Neoral are less prone to infection than those receiving other immunosuppressive therapy.

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Successful solid organ and bone marrow transplantations have been performed in man using Neoral to prevent and treat rejection and GVHD. Ciclosporin has been used successfully both in Hepatitis C Virus (HCV) positive and HCV negative liver transplants recipients. Beneficial effects of Neoral therapy have also been shown in a variety of conditions that are known, or may be considered to be of autoimmune origin.

## 5.2 Pharmacokinetics properties

When Neoral is given, it provides improved dose linearity in ciclosporin exposure ( $AUC_B$ ), a more consistent absorption profile, and less influence from concomitant food intake and from diurnal rhythm than does Sandimmun. These properties combined yield a lower within-patient variability in pharmacokinetics of ciclosporin, and a stronger correlation between trough concentration and total exposure ( $AUC_B$ ). As a consequence of these additional advantages, the time schedule of Neoral administration need no longer take that of meals into account. In addition, Neoral produces a more uniform exposure to ciclosporin throughout the day, and from day to day on a maintenance regimen.

Neoral soft gelatine capsules and Neoral oral solution are bioequivalent. The data available indicate that following a 1:1 conversion from Sandimmun to Neoral, trough concentrations in whole blood are comparable, thereby remaining in the desired therapeutic trough level range. Compared to Sandimmun (with which peak blood concentrations are achieved within 1 to 6 hours), Neoral is more quickly absorbed (resulting in a 1 hour earlier mean  $t_{max}$  and a 59 % higher mean  $C_{max}$ ), and exhibits, on average, a 29 % higher bioavailability.

Ciclosporin is distributed largely outside the blood volume. In the blood, 33 to 47 % is present in plasma, 4 to 9 % in lymphocytes, 5 to 12 % in granulocytes, and 41 to 58 % in erythrocytes. In plasma, approximately 90 % is bound to proteins, mostly lipoproteins.

Ciclosporin is extensively biotransformed to approximately 15 metabolites. There is no single major metabolic pathway. Elimination is primarily biliary, with only 6 % of the oral dose excreted in the urine; only 0.1 % is excreted in the urine as unchanged drug.

There is a high variability in the data reported on the terminal half-life of ciclosporin depending on the assay applied and on the target population. The terminal half-life ranged from 6.3 hours in healthy volunteers to 20.4 hours in patients with severe liver disease (see Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use).

### Special Populations

#### Renal impairment

In a study performed in patients with terminal renal failure, following an intravenous infusion of 3.5 mg/kg over 4 hours mean peak blood levels of 1,800 ng/mL (range 1,536 to 2,331 ng/mL) resulted. The mean volume of distribution ( $V_{dss}$ ) was 3.49 L/kg and systemic clearance (CL) was 0.369 L/hr/kg. This systemic CL (0.369 L/hr/kg) was approximately two thirds of the mean systemic CL (0.56 L/hr/kg) in patients with normally functioning kidneys. Renal impairment had no significant effect on the elimination of ciclosporin.

#### Hepatic impairment

In a study performed in severe liver disease patients with biopsy-proven cirrhosis, the terminal half-life was 20.4 hours (range between 10.8 to 48.0 hours compared to 7.4 to 11.0 hours in healthy subjects).

## 5.3 Preclinical safety data

Ciclosporin gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally). At toxic doses (rats at

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30 mg/kg and rabbits at 100 mg/kg per day orally), ciclosporin was embryo- and fetotoxic as indicated by increased prenatal and postnatal mortality, and reduced fetal weight together with related skeletal retardations.

In two published research studies, rabbits exposed to ciclosporin in utero (10 mg/kg/day subcutaneously) demonstrated reduced numbers of nephrons, renal hypertrophy, systemic hypertension, and progressive renal insufficiency up to 35 weeks of age.

Pregnant rats which received 12 mg/kg/day of ciclosporin intravenously (twice the recommended human intravenous dose) had foetuses with an increased incidence of ventricular septal defect.

These findings have not been demonstrated in other species and their relevance for humans is unknown.

Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg per day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study conducted at 0.5, 2, and 8 mg/kg per day, pancreatic islet cell adenomas significantly exceeded the control rate at the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.

No impairment in fertility was demonstrated in studies in male and female rats.

Ciclosporin has not been found mutagenic/genotoxic in the Ames test, the v79–hgprt test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone marrow, the mouse dominant lethal assay, and the DNA repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by ciclosporin using human lymphocytes in vitro gave indication of a positive effect (i.e. induction of SCE) at high concentrations in this system.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies during ciclosporin treatment is higher than in the normal, healthy population, but similar to that in patients receiving other immunosuppressive therapies. It has been reported that reduction or discontinuance of immunosuppression may cause the lesions to regress.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Soft gelatine capsules

Capsule content: dl–alpha–tocopherol, ethanol anhydrous, propylene glycol, corn oil–mono–di–triglycerides, macroglycerol hydroxystearate (Ph.Eur)/ polyoxyl 40 hydrogenated castor oil (NF).

Capsule shell: Iron oxide black (E 172) (25- and 100-mg capsules), titanium dioxide (E 171), glycerol 85%, propylene glycol, gelatine.

Imprint: carminic acid (E 120).

#### Oral solution

DI–alpha–tocopherol, ethanol anhydrous, propylene glycol, corn oil–mono–di–triglycerides, macroglycerol hydroxystearate (Ph.Eur)/polyoxyl 40 hydrogenated castor oil (USP).

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## 6.2 Incompatibilities

None

## 6.3 Shelf life

Soft gelatine capsules: 3 years.

Oral solution: 3 years.

## 6.4 Special precautions for storage

Neoral capsules may be stored at room temperature not exceeding 25°C. Occasional increases in temperatures up to 30°C for a total of maximum 3 months do not affect the quality of the product.

Neoral capsules should be left in the blister pack until required for use. When a blister is opened, a characteristic smell is noticeable. This is normal and does not mean that there is anything wrong with the capsule.

Neoral oral solution should be used within 2 months of opening the bottle and be stored between 15 and 30°C, but not below 20°C for more than one month, as it contains oily components of natural origin which tend to solidify at low temperatures. A jelly-like formation may occur below 20°C, which is however reversible at temperatures up to 30°C. Minor flakes or a slight sediment may still be observed. These phenomena do not affect the efficacy and safety of the product, and the dosing by means of the pipette remains accurate. After opening, Neoral oral solution should be used within 2 months.

## 6.5 Nature and contents of container

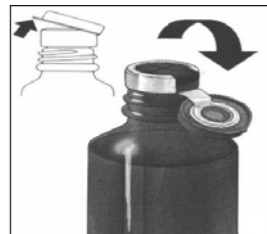
Neoral soft gelatine capsules: Blister packs of double-sided aluminium containing 50 capsules. Each pack contains 10 blister strips containing 5 capsules per strip

Neoral oral solution: 50 mL amber glass bottles with an aluminium cap and rubber stopper. A dispenser set is also provided.

## 6.6 Instructions for use/handling of Neoral oral solution

### Initial use of Neoral oral solution

1. Raise flap in centre of the metal sealing ring.



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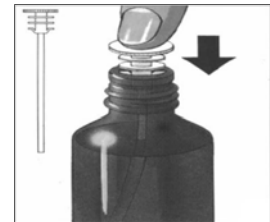
2. Tear off the sealing ring completely.



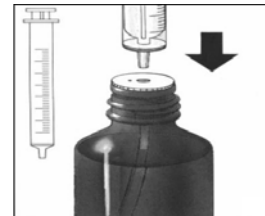
3. Remove the black stopper and throw it away.



4. Push the tube unit with the white stopper firmly into the neck of the bottle.



5. Insert the nozzle of the syringe into the white stopper.



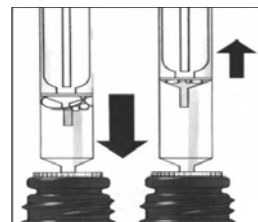
6. Draw up prescribed volume of solution (position the lower part of the plunger ring in front of the graduation corresponding to the prescribed volume).



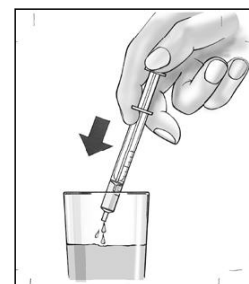


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7. Expel any large bubbles by depressing and withdrawing plunger a few times before removing syringe containing prescribed dose from bottle. The presence of a few tiny bubbles is of no importance and will not affect the dose in any way.



8. Push the medicine out of the syringe into a small glass with some liquid, but no grapefruit juice. Avoid any contact between the syringe and the liquid in the glass. The medicine can be mixed just before it is taken. Stir and drink the entire mixture right away. Once mixed, it should be taken immediately after preparation!



9. After use, wipe syringe on outside only with a dry tissue and replace in its cover. White stopper and tube should remain in bottle. Close bottle with cap provided.



## Subsequent use

Commence at point 5.

Neoral should be kept out of the reach and sight of children.

## 7 MEDICINE SCHEDULE

Prescription Medicine

## 8 SPONSOR

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## 9 DATE OF FIRST APPROVAL

9 March 1995

## 10 DATE OF REIVSION OF THE TEXT

27 May 2019

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Updated to Summary of Product Characteristics (SPC) format with minor editorial changes as required.

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Internal document code: neo110619iNZ based on CDS dated 5 August 2014