

DATA SHEET

NEORAL[®] cyclosporin

25, 50 or 100 mg Soft Gelatine Capsules 100 mg/ml Oral Solution

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Qualitative and quantitative composition

Neoral[®] soft gelatine capsules containing 25, 50 or 100 mg cyclosporin.

Neoral oral solution containing 100 mg cyclosporin per mL.

For a full list of excipients see List of excipients.

Pharmaceutical form

Neoral soft gelatine capsules and oral solution for oral administration.

Neoral is a pharmaceutical form of the active ingredient cyclosporin based on the microemulsion principle, which reduces the variability of pharmacokinetic parameters and provides dose linearity of cyclosporin exposure with a more consistent absorption profile and less influence from concomitant food intake. The formulation is a microemulsion concentrate, which in pharmacokinetic and clinical studies has demonstrated that the correlation between trough concentration and exposure to cyclosporin is much stronger when cyclosporin 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.

Clinical particulars

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

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

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 remissions and to maintain them. 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.

Dosage and method of administration

Dosage

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

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, i.v. infusion is preferred for this purpose; the recommended 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 Sandimmun treatment, but usually responds favourably to re-introduction of therapy. Low doses of Neoral should be used to treat mild, chronic GVHD.

Non-transplantation

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 is 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.

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

Neoral can be given in combination with low-dose corticosteroids and/or non-steroidal anti-inflammatory drugs. 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.

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 Sandimmun to Neoral

The available data indicate that after a 1:1 conversion from Sandimmun to Neoral, the trough concentrations of cyclosporin 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 cyclosporin 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 cyclosporin (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 cyclosporin 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.

It needs to be emphasized that the absorption of cyclosporin from Neoral is less variable and the correlation between cyclosporin trough concentrations and exposure (in terms of AUC) is much stronger than with Sandimmun. This makes cyclosporin 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. Cyclosporin 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 cyclosporin 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 case of unexpected toxicity or inefficacy of cyclosporin, blood trough levels should also be monitored.

Conversion between oral cyclosporin formulations

Switching from one oral cyclosporin 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 cyclosporin 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 cyclosporin 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.

Capsules should be swallowed whole.

The 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 P450-dependent enzyme system, grapefruit juice should be avoided for dilution. 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 Instructions for use/handling).

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.

In rheumatoid arthritis clinical trials with cyclosporin, 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 still limited. However, children from 1 year of age have received Sandimmun in standard dosage with no particular problems. In several studies, pediatric patients required and tolerated higher doses of Sandimmun per kg body weight than those used in adults.

Contraindications

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

Special warnings and precautions for use

Neoral and Sandimmun concentrate for solution for infusion 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 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.

Like other immunosuppressants, cyclosporin 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 cyclosporin) should be used with caution as this could lead to lymphoproliferative disorders and solid organ tumours, some with reported fatalities.

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

Like other immunosuppressants, cyclosporin 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 cyclosporin. 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.

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. interstitial fibrosis) which, in renal transplant patients, must be differentiated from changes due to chronic rejection. Neoral may also cause dose-dependent, reversible increases in serum bilirubin and, occasionally, in liver enzymes (see ADVERSE 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 cyclosporin. 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 ADVERSE EFFECTS). Close monitoring of parameters that assess renal and hepatic function is required. Abnormal values may necessitate dose reduction.

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

For monitoring cyclosporin 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 are 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 cyclosporin 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.

Regular monitoring of blood pressure is required during Neoral therapy; if hypertension develops, appropriate antihypertensive treatment must be instituted.

Since, on rare occasions, Sandimmun 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.

Cyclosporin enhances the risk of hyperkalaemia, especially in patients with renal dysfunction. Caution is also required when cyclosporin 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 Interaction with other medicinal products and other forms of interaction). Control of potassium levels in these situations is advisable.

Cyclosporin enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplant period. 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.

Caution is required in treating patients with hyperuricaemia.

During treatment with cyclosporin, vaccination may be less effective; the use of live-attenuated vaccines should be avoided.

Caution should be observed while co-administering lercanidipine with cyclosporin (see Interaction with other medicinal products and other forms of interaction).

Cyclosporin may increase blood levels of concomitant medications that are substrates of Pgp such as aliskiren (see Interaction with other medicinal products and other forms of interaction).

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 cyclosporin.

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%. These recommendations apply even if the patient's values still lie within the laboratory's normal range.

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%. 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. 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 cyclosporin), 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 during the first 3 months of therapy and thereafter once a month. After 6 months of therapy, serum creatinine needs to be measured every 4 to 8 weeks depending on the stability of the disease, its 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.

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.

As with other long-term immunosuppressive treatments (including cyclosporin), an increased risk of lymphoproliferative disorders must be borne in mind. Special caution should be observed if Neoral is used in combination with methotrexate.

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%. 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 Neoral therapy is also recommended if hypertension developing during Neoral treatment cannot be controlled with appropriate therapy.

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 cyclosporin, 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 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 Sandimmun, 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%. 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 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.

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 cyclosporin 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 cyclosporin (see section 4.5 Interactions with other medicinal products and other forms of interaction) should be avoided, or, if there is no alternative, it is recommended to closely monitor blood levels of cyclosporin, renal function, and for side effects of cyclosporin.

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

Interaction with other medicinal products and other forms of interaction

Food interactions

The concomitant intake of grapefruit juice has been reported to increase the bioavailability of cyclosporin.

Drug interactions

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

Various agents are known to either increase or decrease plasma or whole blood cyclosporin levels usually by inhibition or induction of enzymes involved in the metabolism of cyclosporin, in particular CYP3A4. Cyclosporin is also an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein and may increase plasma levels of comedications that are substrates of this enzyme and/or transporter.

Drugs that decrease cyclosporin levels

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

Drugs that increase cyclosporin levels

Macrolide antibiotics (e.g. erythromycin, azithromycin and clarithromycin); ketoconazole, fluconazole, itraconazole, voriconazole; diltiazem, nifedipine, verapamil; metoclopramide; oral contraceptives; danazol; methylprednisolone (high dose); allopurinol; amiodarone; cholic acid and derivatives; protease inhibitors; imatinib; colchicine; nefazodone.

Other relevant drug interactions

Care should be taken when using cyclosporin 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 H₂-receptor-antagonists (e.g. cimetidine, ranitidine); methotrexate (see Special warnings and precautions for use).

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

The concurrent administration of nifedipine with cyclosporin may result in an increased rate of gingival hyperplasia compared with that observed when cyclosporin is given alone.

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

Cyclosporin is a highly potent Pgp inhibitor and may increase blood levels of concomitant medications that are substrates of Pgp such as aliskiren. Following concomitant administration of cyclosporin and aliskiren, the C_{max} of aliskiren was increased by approximately 2.5 fold and the AUC by approximately 5 fold. However, the pharmacokinetic profile of cyclosporin was not significantly altered. Caution is recommended when co-administering cyclosporin together with aliskiren (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

The concomitant use of diclofenac and cyclosporin 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 cyclosporin, no increase in their bioavailability is to be expected.

Cyclosporin may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins) and etoposide.

Severe digitalis toxicity has been seen within days of starting cyclosporin in several patients taking digoxin. There are also reports on the potential of cyclosporin to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. If digoxin or colchicine are used concurrently with cyclosporin, 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 cyclosporin with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely, fluvastatin. When concurrently administered with cyclosporin, 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.

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

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 Special warnings and precautions for use).

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

Recommendations

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

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.

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.

Drugs known to reduce or increase the bioavailability of cyclosporin: in *transplant* patients frequent measurement of cyclosporin levels and, if necessary, cyclosporin dosage adjustment are required, particularly during the introduction or withdrawal of the co-administered drug. In *non-transplant* patients the value of cyclosporin 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 cyclosporin levels are given concomitantly, frequent assessment of renal function and careful monitoring for cyclosporin-related side effects may be more appropriate than blood level measurement.

The concomitant use of nifedipine should be avoided in patients in whom gingival hyperplasia develops as a side effect of cyclosporin.

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 cyclosporin.

If digoxin, colchicine or HMG-CoA reductase inhibitors (statins) are used concurrently with cyclosporin, 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.

Pregnancy and lactation

Pregnancy

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

Experience with Sandimmun in pregnant women is limited. Pregnant women receiving immunosuppressive therapies after transplantation, including cyclosporin and cyclosporin-containing regimens, are at risk of premature delivery (<37 weeks).

A limited number of observations in children exposed to cyclosporin 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 and well-controlled studies in pregnant women and, therefore, Neoral should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

Lactation

Cyclosporin passes into breast milk. Mothers receiving treatment with Neoral should not breast-feed.

Effects on ability to drive and use machines

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

Adverse effects

Many side effects associated with cyclosporin 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 cyclosporin and cyclosporin-containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic) (see '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 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 cyclosporin and cyclosporin-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 'Special warnings and precautions for use'). Some malignancies may be fatal.

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent 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

Blood and lymphatic system disorders

Uncommon Anaemia, thrombocytopenia.

Rare Microangiopathic haemolytic anaemia, haemolytic uraemic syndrome.

Metabolism and nutrition disorders

Very Hyperlipidaemia.

common	
Common	Anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia.
Rare	Hyperglycaemia.
Nervous system disorders	
Very common	Tremor, headache, including migraine.
Common	Paraesthesia.
Uncommon	Signs of encephalopathy such as convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia.
Rare	Motor polyneuropathy.
Very rare	Optic disc oedema including papilloedema, with possible visual impairment secondary to benign intracranial hypertension.
Vascular disorders	
Very common	Hypertension.
Gastrointestinal disorders	
Common	Nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia
Rare	Pancreatitis.
Hepatobiliary disorders	
Common	Hepatic function abnormal (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
Skin and subcutaneous tissue disorders	
Common	Hypertrichosis.
Uncommon	Allergic rashes.
Musculoskeletal and connective tissue disorders	
Common	Muscle cramps, myalgia.
Rare	Muscle weakness, myopathy.
Renal and urinary disorders	
Very common	Renal dysfunction (see Special warnings and precautions for use).
Reproductive system and breast disorders	
Rare	Menstrual disturbances, gynecomastia.
General disorders and administration site conditions	
Common	Fatigue.
Uncommon	Oedema, weight increase.

Other adverse drug reactions from post-marketing experience

There have been solicited and spontaneous postmarketing reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients with cyclosporin. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and comedication with hepatotoxicity potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Overdose

The oral LD50 of cyclosporin is 2,329 mg/kg in mice, 1,480 mg/kg in rats and > 1,000 mg/kg in rabbits. The i.v. LD50 is 148 mg/kg in mice, 104 mg/kg in rats, and 46 mg/kg in rabbits.

Symptoms

Experience with acute overdosage of cyclosporin is limited. Oral doses of cyclosporin 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 cyclosporin 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. Cyclosporin is not dialysable to any great extent, nor is it well cleared by charcoal haemoperfusion.

Pharmacological properties

Pharmacodynamic properties

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

Cyclosporin (also known as cyclosporin 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 cyclosporin 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). Cyclosporin 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 cyclosporin 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 Sandimmun are less prone to infection than those receiving other immunosuppressive therapy.

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

Pharmacokinetics properties

When Neoral is given, it provides improved dose linearity in cyclosporin exposure (AUCB), 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 cyclosporin, and a stronger correlation between trough concentration and total exposure (AUCB). 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 cyclosporin 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.

Cyclosporin 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.

Cyclosporin 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 cyclosporin 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.

Preclinical safety data

Cyclosporin 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 30 mg/kg and rabbits at 100 mg/kg per day orally), cyclosporin 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 cyclosporin 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 cyclosporin 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.

Cyclosporin has not been found mutagenic/genotoxic in the Ames test, the v79–hgpvt 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 cyclosporin 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 cyclosporin 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.

Pharmaceutical particulars

List of excipients

Soft gelatine capsules

Capsule content: dl–alpha–tocopherol, ethanol anhydrous, propylene glycol, corn oil–mono–di–triglycerides, macrogolglycerol 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

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

Incompatibilities

None

Shelf life

Soft gelatine capsules: 3 years.

Oral solution: 3 years.

Special precautions for storage

Neoral capsules may be stored at room temperature not exceeding 25°C. Occasional increases in temperatures up to 30°C 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, preferably not below 20°C for prolonged periods, 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.

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.

Instructions for use/handling of Neoral oral solution

Initial use of Neoral oral solution

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



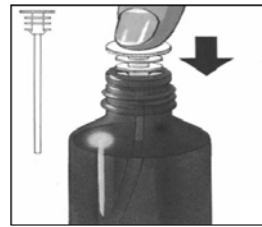
2. Tear off the sealing ring completely.



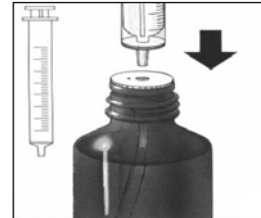
3. Remove the black stopper and throw it away.



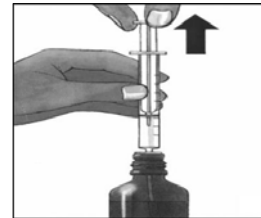
4. Push the tube unit with the white stopper firmly into the neck of the bottle.



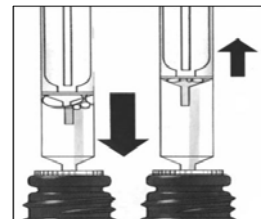
5. Insert the nozzle of the syringe into the white stopper.



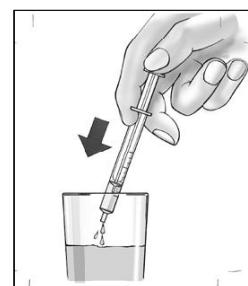
6. Draw up prescribed volume of solution (position the lower part of the plunger ring in front of the graduation corresponding to the prescribed volume).



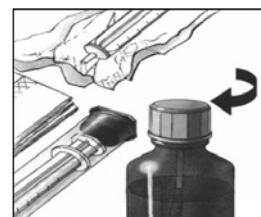
7. Expel any large bubbles by depressing and withdrawing plunger a few times before removing syringe containing prescribed dose from bottle. The presence of a few tiny bubbles is of no importance and will not affect the dose in any way.



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 you take it. Stir and drink the entire mixture right away. Please take the medicine 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.

Medicine classification

Prescription Medicine

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2 September 2010