NOVARTIS

Sandimmun Neoral®

Composition

Active substance: Ciclosporin.

Excipients:

Soft-gelatin capsules

Capsule content: alpha–tocopherol, ethanol anhydrous, propylene glycol, corn oil–mono–di–triglycerides, macrogolglycerol hydroxystearate (Ph.Eur)/ polyoxyl 40 hydrogenated castor oil (NF). Sandimmun Neoral soft gelatin capsules contain 11.8% v/v ethanol (9.4% w/v).

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

Imprint: carminic acid (E 120).

Oral solution

alpha–tocopherol, ethanol anhydrous, propylene glycol, corn oil-mono–di–triglycerides, macrogolglycerol hydroxystearate (Ph.Eur)/polyoxyl 40 hydrogenated castor oil (USP).Sandimmun Neoral oral solution contains 12% v/v ethanol (9.5% w/v).

Information might differ in some countries.

Pharmaceutical form and quantity of active substance per unit

Capsules containing 10, 25, 50 or 100 mg.

Oral solution containing 100 mg/ml.

Sandimmun is also available as a concentrate for i.v. infusion. See corresponding prescribing information.

Indications/Potential uses

Transplantation

Organ transplantation

Prevention of rejection of kidney, liver, heart, combined heart-lung, lung and pancreas allografts.

Treatment of transplant rejection in patients previously treated with other immunosuppressive agents.

Bone marrow transplantation

Prevention of graft rejection following bone marrow transplantation.

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

Non-transplantation indications

Endogenous uveitis

Active sight-threatening intermediate or posterior uveitis of non-infectious aetiology in which alternative therapy has proved ineffective or inappropriate.
Uveitis in Behçet's disease, with recurrent inflammatory attacks involving the retina, in patients with normal renal function who are 7 to 70 years of age.
Psoriasis
Treatment of severe cases of psoriasis in which alternative therapies are ineffective or inappropriate.
Atopic dermatitis
Treatment of severe cases of atopic dermatitis in which alternative therapies are ineffective or inappropriate.
Rheumatoid arthritis
Treatment of severe cases of rheumatoid arthritis in which standard basic therapies are ineffective or inappropriate.
Nephrotic syndrome
Idiopathic steroid-dependent or steroid-resistant nephrotic syndrome (biopsy shows minimal-change disease [MCD] or focal segmental glomerulosclerosis [FSGS] in most cases) in adults or children which has failed to respond to conventional cytostatic therapy, but only if renal function indices are at least 50% below normal values.
Induction or maintenance of remission
Maintenance of steroid-induced remission, in order to enable corticosteroids to be withdrawn.

Dosage/Administration

Sandimmun Neoral, which is administered orally, is recommended for the majority of clinical conditions requiring ciclosporin therapy. Exceptions are listed in the prescribing information for Sandimmun concentrate for i.v. infusion. *Concentrate for solution for infusion* The following dosage information relates to **oral administration**.
The total daily dose of Sandimmun Neoral should always be taken in two divided doses (mornings and evenings). If the prescribed dose cannot be precisely attained using capsules, particularly in patients with low body weight, the use of the oral solution is recommended.
A) Transplantation
The dosage recommendations given below are intended as guidelines only. Routine monitoring of blood ciclosporin levels is essential and may be done by RIA using monoclonal antibodies. The results obtained serve as a guide to determining the dose required to achieve the target concentration.
1. Organ transplantation
The starting dose is 10 to 15 mg/kg, given in two divided doses within 12 hours before transplantation. This dosage should be maintained for 1 to 2 weeks post-surgery. The dose may then be gradually reduced to a maintenance dose of 2 to 6 mg/kg/day (depending on blood ciclosporin levels), to be taken in two divided doses.

In renal transplant patients it has been found that doses below 3 to 4 mg/kg/day, which result in trough blood levels below 50 to 100 ng/ml, are associated with an increased risk of rejection.
In cases where Sandimmun Neoral is given in conjunction with other immunosuppressive agents (e.g. corticosteroids or as part of a 3- or 4-drug regimen), lower doses (e.g. 3 to 6 mg/kg/day orally as a starting dose) may be given.

Renal transplantation in combination with everolimus

If ciclosporin is given concomitantly with everolimus for a prolonged period, an attempt should be made to reduce exposure to ciclosporin. Reduction of ciclosporin exposure should begin one month post-transplantation. The following target ranges for ciclosporin exposure are recommended: [Ciclosporin blood levels measured 2 hours after administration (C_2)]: weeks 0 to 4: 1,000 to 1,400 ng/ml; weeks 5 to 8: 700 to 900 ng/ml; weeks 9 to 12: 550 to 650 ng/ml; weeks 13 to 52: 350 to 450 ng/ml.
Prior to dose reduction of ciclosporin, it must be ensured that steady-state everolimus trough levels (C_0) are ≥ 3 ng/ml.
If reduction in ciclosporin exposure leads to signs of graft rejection, continuation of everolimus treatment must be reconsidered. In order to minimise the risk of failed efficacy, it is important to ensure that neither everolimus nor ciclosporin blood levels fall below the therapeutic range after transplantation.
Data on everolimus dosages are limited in long-term therapy (i.e. more than 12 months) in patients with ciclosporin trough levels (C_0) below 50 ng/ml or C_2 levels below 350 ng/ml.

Cardiac transplantation in combination with everolimus

In heart transplant patients with renal dysfunction, the dose of ciclosporin should be reduced as much as possible during the maintenance phase (i.e. after 3 months) in order to improve renal function. If impairment of renal function progresses or the calculated creatinine clearance falls to <60 ml/min, the dosage should be adjusted. In heart transplant patients, the ciclosporin dose may be based on ciclosporin trough blood levels (also see prescribing information for everolimus).
In heart transplantation, data are limited on the combination with everolimus in patients with trough levels (C_0) of ciclosporin below 175 ng/ml in the first 3 months, below 135 ng/ml at 6 months and below 100 ng/ml after 6 months.
Prior to dose reduction of ciclosporin, it must be ensured that steady-state everolimus trough levels (C_0) are ≥ 3 ng/ml.

2. Bone marrow transplantation

The starting dose should be given on the day before transplantation. It is recommended that patients started on oral therapy be given 12.5 to 15 mg/kg/day initially. The maintenance dose of approx. 12.5 mg/kg/day, administered in two divided doses, should be given for at least 3 to 6 months (preferably 6 months). The dose may then be gradually tapered off completely within a period of 1 year after transplantation.

Higher oral doses or administration by i.v. infusion may be required in patients with gastrointestinal disorders impairing absorption (see separate prescribing information for Sandimmun concentrate for i.v. infusion).
GVHD may occur in some patients following withdrawal of ciclosporin treatment, but it usually responds to reinstitution of therapy. In such cases, a starting dose of 10 to 12.5 mg/kg should be given, followed by the daily oral maintenance dose found to be satisfactory prior to withdrawal. Low doses of ciclosporin should be given to treat chronic mild GVHD.

B) Non-transplantation indications

Preliminary note: Monitoring of renal function and blood pressure

As Sandimmun Neoral may impair renal function, a reliable baseline serum creatinine level – derived from at least two determinations – must be established prior to the start of therapy. Both determinations must indicate normal renal function. For this purpose, creatinine clearance can be calculated from the measured serum creatinine levels by means of a suitable equation (e.g. Dettli's).
Serum creatinine should be monitored at weekly intervals during the first month of treatment and at monthly intervals thereafter or more frequently if the Sandimmun Neoral dosage is increased. If creatinine exceeds the baseline value by 20 to 30%, transient non-renal increases must be ruled out by means of repeat determinations.
If hypertension occurring during Sandimmun Neoral therapy cannot be normalised by means of appropriate antihypertensive therapy, the Sandimmun Neoral dose should be reduced or, if necessary, withdrawn (see 6. "Blood pressure monitoring" under "Warnings and precautions").

1. Endogenous uveitis

5 mg/kg/day in two divided doses is recommended as the starting dose until uveitis subsides and visual acuity improves. In resistant cases, the dose may be temporarily increased to 7 mg/kg/day.
To achieve particularly rapid remission and thus combat acute inflammatory episodes, in the eye and/or if Sandimmun Neoral alone proves insufficiently effective, a systemic corticosteroid – either prednisone (0.2 to 0.6 mg/kg/day) or an equivalent substance – may be added.
Sandimmun Neoral should be withdrawn if no improvement is evident after three months of treatment.
For maintenance therapy, the dosage should gradually be reduced to the lowest effective dose, which should not exceed 5 mg/kg/day during periods of remission.
The daily dose must be reduced by 25 to 50% if serum creatinine exceeds the baseline value by more than 30% in more than one measurement, even if it is still within the normal range (see "Monitoring of renal function"). If the dose reduction has no effect within one month, Sandimmun Neoral must be withdrawn.

2. Dermatological indications

Special instructions

Prior to treatment, the patient must be informed fully about the benefits and possible risks of Sandimmun Neoral therapy and about the frequent problem of recurrence following withdrawal.
Patients with renal impairment, uncontrolled hypertension or infection or a malignancy of any type - apart from skin malignancies (see "Psoriasis: skin tumours" and "Contraindications") - should not be given Sandimmun Neoral. Caution is indicated in patients with hyperkalaemia or hyperuricaemia (see 7. "Biochemical changes" under "Warnings and precautions").

a) Psoriasis

To induce remission, the recommended starting dose is 2.5 mg/kg/day in two divided doses, increasing gradually – if there is no improvement after one month – by 0.5 to 1 mg/kg per month up to a maximum of 5 mg/kg/day.
A starting dose of 5 mg/kg/day, given in two divided doses, is justified in patients whose condition requires particularly rapid improvement.
For maintenance treatment, the dose should be individually adjusted to the lowest effective level and should not exceed 5 mg/kg/day.
Treatment should be withdrawn in patients in whom no sufficient improvement in psoriatic lesions is achieved within one month of treatment at 5 mg/kg/day.
Sandimmun Neoral should be gradually withdrawn if remission is maintained for a period of 6 months. However, the risk of recurrence following withdrawal is very high.

Skin tumours

Development of malignancies (particularly of the skin) has been reported in psoriasis patients treated with Sandimmun Neoral as well as in those receiving conventional immunosuppressive therapy. Skin lesions that are not typical of psoriasis and that might possibly be malignant or premalignant should be biopsied before Sandimmun Neoral is given. Patients found to have malignant or premalignant skin changes should only be given Sandimmun Neoral after curative treatment of these lesions and if no other potentially effective therapy is available (see "Contraindications").

b) Atopic dermatitis

The recommended dose range in adults and adolescents above 16 years of age is 2.5 to 5 mg/kg/day, given in two divided doses.
If the response is not satisfactory after two weeks at a starting dose of 2.5 mg/kg/day, 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 may be achieved with a starting dose of 5 mg/kg/day.
Treatment should be withdrawn in patients in whom no sufficient improvement in atopic dermatitis is achieved within one month of treatment at 5 mg/kg/day.
Current experience with Sandimmun Neoral in the long-term treatment of atopic dermatitis is limited and it is therefore recommended that individual treatment cycles be restricted to a maximum of 8 weeks.

Skin infections

Active herpes simplex infections should be allowed to clear before starting Sandimmun Neoral therapy. However, they are not necessarily a reason for withdrawal of the medicine if they occur during treatment, unless infection is severe.

Skin infections with Staphylococcus aureus are not an absolute contraindication for Sandimmun Neoral therapy, but should be treated with appropriate antibiotics. Oral erythromycin should be avoided as it may increase blood ciclosporin levels (see "Interactions"). If there is no alternative, blood ciclosporin levels, renal function and signs of adverse effects should be closely monitored.

3. Rheumatoid arthritis

Special instructions

Prior to treatment, the patient must be informed fully about the benefits and possible risks of Sandimmun Neoral therapy and about the frequent problem of recurrence following withdrawal.

Patients with renal impairment, uncontrolled hypertension or infection or a malignancy of any type should not be given Sandimmun Neoral. Caution is indicated in patients with hyperkalaemia or hyperuricaemia (see 7. "Biochemical changes" under "Warnings and precautions").

For the first six weeks of treatment, the recommended dose is 3 mg/kg/day, given in two divided doses. If the effect is considered insufficient, the daily dose may be increased gradually to a maximum of 5 mg/kg, subject to the conditions listed below.

For long-term treatment, the dose must be titrated individually on the basis of tolerability.

Sandimmun Neoral should be withdrawn if no improvement is evident after three months of treatment.

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

The daily Sandimmun Neoral dose must be reduced if serum creatinine exceeds the mean pre-treatment baseline by more than 30%, even if it is still within the normal range (see “Monitoring of renal function”). If the baseline value is exceeded by more than 50%, the dose must be halved. If the dose reduction has no effect within one month, Sandimmun Neoral must be withdrawn.

More frequent serum creatinine determinations are also necessary when an NSAID is introduced or when the dose of such an agent is increased.

As with other long-term immunosuppressive agents, the increased risk of lymphoproliferative disorders must be borne in mind (see 9. "Early detection of lymphoproliferative disorders and solid malignant tumours" under "Warnings and precautions").

4. Nephrotic syndrome

The recommended dose for induction of remission (to be taken in two divided doses) is 5 mg/kg/day in adults and 6 mg/kg/day in children. In such patients, ciclosporin can be used if creatinine levels are <200 µmol/l in adults and <140 µmol/l in children. The starting dose should not exceed 2.5 mg/kg/day (see "Contraindications").

The dosage should be individually adjusted based on efficacy (proteinuria) and safety (primarily serum creatinine), but should not exceed 5 mg/kg/day in adults and 6 mg/kg/day in children.
For maintenance therapy, the dosage should gradually be reduced to the lowest effective dose.
The dose should be reduced by 25 to 50% if serum creatinine exceeds the baseline value by more than 30%.
Sandimmun Neoral should be discontinued if no effect is apparent after three months of therapy.
Combination of Sandimmun Neoral with low-dosed oral corticosteroids is recommended in patients responding inadequately to Sandimmun Neoral alone, particularly those with steroid-resistant nephrotic syndrome.
Patients whose renal function is abnormal at baseline (maximum serum creatinine levels of 200 µmol/l in adults and 140 µmol/l in children) must be given a starting dose not exceeding 2.5 mg/kg/day and must be very closely monitored.
In some patients, it may be difficult to detect renal dysfunction caused by Sandimmun Neoral since nephrotic syndrome itself involves changes in renal function. This is why, in rare cases, Sandimmun Neoral-induced structural changes in the kidneys have been observed without any apparent increase in serum creatinine. Kidney biopsy should therefore be considered in patients with steroid-dependent minimal-change nephropathy receiving Sandimmun Neoral for longer than one year.
Paediatric use
There is limited data available on ciclosporin use in children. No data are available on the use of Sandimmun Neoral in the treatment of infants. No particular problems were reported in children over one year of age given the standard dosage of Sandimmun. Several paediatric studies have shown that children both need and tolerate higher doses per kg body weight of ciclosporin than adults. Patients with severe hepatic dysfunction require close monitoring of serum creatinine and, where possible, of ciclosporin levels, with dosage adjustment if necessary.
Use in elderly patients
In clinical studies on the use of oral ciclosporin in rheumatoid arthritis, 17.5% of the patients were 65 years of age or older. After 3 to 4 months of treatment, these patients were more likely to develop systolic hypertension and to show increases in serum creatinine exceeding the baseline value by 50% or more.
Clinical studies with Sandimmun Neoral in graft recipients and psoriasis patients did not include a sufficient number of patients 65 years of age or older to allow any conclusions as to whether their response differs from that of younger patients. In general, dose selection should be cautious in elderly patients, with consideration being given to the increased frequency of reduced hepatic, renal or cardiac function, concomitant disease or other drug therapy. Treatment should normally be started with a dose at the lower end of the dosage range.

Contraindications

All indications

Hypersensitivity to ciclosporin or to any of the excipients.

Non-transplantation indications

The following contraindications also apply:

- Renal impairment, except in patients with nephrotic syndrome and moderately increased baseline serum creatinine values of max. 200 µmol/l in adults and 140 µmol/l in children. In nephrotic syndrome, cautious therapy (not more than 2.5 mg/kg/day) is permitted, provided that disease-related increased creatinine values improve with ciclosporin treatment.
- Inadequately controlled hypertension.
- Inadequately controlled infection.

History of known or diagnosed malignancy of any kind, except premalignant or malignant skin lesions following curative treatment.

Warnings and precautions

1. General

Only physicians with experience of immunosuppressive therapy who are able to perform the necessary follow-up examinations (regular full physical examinations, blood pressure checks, laboratory tests) should prescribe Sandimmun Neoral. Transplant patients receiving Sandimmun Neoral should be treated at centres with the requisite laboratory and medical equipment. The physician responsible for maintenance therapy must be given all information necessary for the patient's proper care.

Absorption of calcineurin inhibitors may be impaired in patients with cystic fibrosis.

Due to the potential risk of malignant skin changes, patients receiving Sandimmun Neoral should be warned against excessive exposure to the sun without appropriate protection.

Paediatric use: Owing to insufficient data, the use of Sandimmun Neoral in patients under 16 years of age cannot be recommended in non-transplantation indications other than nephrotic syndrome.

2. Switching to other ciclosporin formulations

Once treatment with Sandimmun Neoral has started, appropriate monitoring of blood ciclosporin levels, serum creatinine levels and blood pressure is necessary before a switch to another oral formulation of ciclosporin can be attempted, as differences in bioavailability may occur.

3. Combination with other immunosuppressive agents

Like other immunosuppressive agents, ciclosporin increases the risk of developing lymphomas and other malignancies, particularly of the skin.

This increased risk seems to be related more to the degree and duration of immunosuppression than to the use of specific medicines.

In addition, a treatment regimen containing several immunosuppressive agents (including ciclosporin) must be used with caution, since it may lead to lymphoproliferative disorders and solid tumours of other organs that may be fatal.

As is the case in patients using other immunosuppressive agents, those using ciclosporin are susceptible to a number 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 BK virus nephropathy (BKVN) or JC-virus-associated progressive multifocal leucoencephalopathy (PML) – have been observed in patients receiving ciclosporin. These conditions are often secondary to high immunosuppression and should be considered in the differential diagnosis of immunosuppressed patients with deteriorating renal function or neurological symptoms. Serious and/or fatal outcomes have been reported. BKVN can cause graft loss. Effective preventive and therapeutic strategies should be employed, particularly in patients on multiple long-term immunosuppressive therapy. A reduction in total immunosuppression should be considered in patients with PVAN or PML, but reduced immunosuppression may also jeopardise the graft.

4. Renal and hepatic function

A frequent and potentially serious complication during the first few weeks of Sandimmun Neoral treatment is a rise in serum levels of creatinine and urea. These functional changes are dose-dependent and reversible and usually return to normal when the dose is reduced. In some patients, long-term use may lead to structural changes in the kidneys (e.g. interstitial fibrosis), which must be distinguished from signs of chronic rejection in kidney transplant patients.

Sandimmun Neoral may also cause a dose-dependent and reversible increase in serum bilirubin and liver enzyme levels (see "Adverse effects").

Regular monitoring of the appropriate hepatic and renal parameters is required. Dose reduction may be necessary should results be abnormal.

Renal function should be monitored particularly closely in elderly patients.

5. Determination of blood ciclosporin levels

Ciclosporin blood levels should preferably be monitored by measuring the proportion of parent drug using a specific monoclonal antibody or a HPLC-based analysis method. If plasma or serum is used, a standard separation protocol should be followed, with defined values for time and temperature.

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 non-specific monoclonal antibody should be performed, to ensure a dosage that provides adequate immunosuppression.

It must also 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. The results should therefore only be viewed as a guideline for treatment in the context of a whole range of other clinical and biochemical parameters (see "Organ transplantation" under "Dosage/administration").

6. Blood pressure monitoring

Blood pressure should be checked regularly during Sandimmun Neoral therapy. In the event of hypertension, appropriate treatment should be given to lower blood pressure. Preference should be given to an antihypertensive agent that has no pharmacokinetic interactions with ciclosporin (see "Interactions").

7. Biochemical changes

There have been reports of treatment with Sandimmun Neoral being associated with a slight, reversible increase in blood lipids; blood lipid levels should therefore be measured prior to and one month after, the start of treatment. In the event of an increase in lipid levels, a reduction in dietary fat intake and possibly a dose reduction should be considered.

Ciclosporin increases the risk of hyperkalaemia, particularly in patients with renal dysfunction. Caution is required when administering ciclosporin concomitantly with potassium-sparing drugs (e.g. potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists) or medicines containing potassium or in patients with a potassium-rich diet (see "Interactions"). In such situations, it is advisable to monitor potassium levels.

Ciclosporin enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplantation period. Moreover, monitoring of serum magnesium levels is recommended during the peri-transplantation period, particularly in the presence of neurological symptoms. If considered necessary, magnesium supplementation should be given.

Caution is required in treating patients with hyperuricaemia.

8. Concomitant medication (see "Interactions")

Vaccination may be less effective during treatment with ciclosporin and the use of live vaccines should be avoided.

Caution is required when giving ciclosporin concomitantly with lercanidipine (see "Interactions").

Ciclosporin may increase the plasma concentrations and the dose-dependent risk of side effects of co-administered medicines which are substrates of the multidrug efflux transporter, p-glycoprotein or of the organic anion transporter proteins (OAPTs), such as aliskiren, dabigatran or bosentan. Co-administration of ciclosporin and aliskiren or dabigatran or bosentan should be avoided (see "Interactions").

Psoriasis patients should not be given concomitant treatment with beta blockers or diuretics.

9. Early detection of lymphoproliferative disorders and solid malignant tumours

As with other immunosuppressive therapies (including ciclosporin), the increased risk of lymphoproliferative disorders and solid tumours (particularly of the skin) should be borne in mind. Patients receiving long-term Sandimmun Neoral therapy should be monitored closely in order to ensure early detection. Treatment must be withdrawn if premalignancy or malignancy is determined.

10. Exposure to UV light

Due to the potential risk of malignant skin changes, patients receiving Sandimmun Neoral, in particular those being treated for psoriasis or atopic dermatitis, should be warned against excessive exposure to the sun without adequate protection and should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy (see "Interactions").

11. Ethanol

The ethanol content of the oral solution should be taken into account when using Sandimmun Neoral in patients at risk, particularly pregnant or breast-feeding women, patients with liver disease or epilepsy, alcoholic patients or children.

12. Endogenous uveitis

A possible connection between ciclosporin and neurological manifestations of Behçet's syndrome has been reported. Sandimmun Neoral should therefore be administered with caution in such patients and patients' neurological status should be carefully monitored.

Interactions

Food interactions

Concomitant intake of grapefruit juice increases the bioavailability of ciclosporin.

Drug interactions

Interactions with many different drugs have been reported with ciclosporin. Listed below are those which are well documented and considered to be clinically relevant.

A comprehensive document entitled "Sandimmun Neoral Drug Interactions", which lists all known drug interactions, including those based on isolated observations or contradictory reports, is available on request.

Medicines that inhibit or induce the hepatic enzymes involved in the metabolism and excretion of ciclosporin, particularly CYP3A4, affect the plasma or whole blood levels of ciclosporin accordingly. Ciclosporin is also an inhibitor of CYP3A4 and a potent inhibitor of the multidrug efflux transporter, P-glycoprotein (P-gp). It may increase plasma levels of co-medications that are substrates of CYP3A4 or P-gp.

Medicines that reduce ciclosporin levels

Barbiturates, carbamazepine, oxcarbazepine, phenytoin, nafcillin, sulfadimidine i.v., rifampicin, octreotide, probucol, orlistat, trimethoprim i.v., *Hypericum* (St. John’s wort) preparations, ticlopidine, sulfinpyrazone, terbinafine, bosentan.

Medicines that increase ciclosporin levels

Chloroquine, macrolide antibiotics (e.g. erythromycin, azithromycin and clarithromycin); ketoconazole and, with contradictory and less pronounced effect, fluconazole and itraconazole, voriconazole, diltiazem, nicardipine, verapamil, metoclopramide, oral contraceptives, danazol, methylprednisolone (high doses), allopurinol, amiodarone, cholic acid and derivatives, protease inhibitors, imatinib, colchicine, nefazodone.

Other relevant drug interactions

Caution is required when using ciclosporin with other medicines that cause nephrotoxicity: aminoglycosides (including gentamicin and tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole), NSAIDs (including diclofenac, indometacin, naproxen and sulindac), melphalan, histamine H2-receptor antagonists (e.g. cimetidine, ranitidine), methotrexate, tacrolimus.

Co-administration of nifedipine with ciclosporin may lead to an increased incidence of gingival hyperplasia, as compared with administration of ciclosporin alone.

Following concomitant administration of ciclosporin and lercanidipine, the AUC of lercanidipine increased three-fold and the AUC of ciclosporin increased by 21%. Preference should be given to an antihypertensive agent that has no pharmacokinetic interactions with ciclosporin.

The concomitant use of diclofenac and ciclosporin results in a significant increase in the bioavailability of diclofenac, with the possible consequence of reversible renal impairment. The increase is most probably caused by a reduction in the high first-pass effect of diclofenac. Co-administration of ciclosporin with NSAIDs having a low first-pass effect (e.g. acetylsalicylic acid) is not normally associated with an increase in their bioavailability.

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

Severe digitalis intoxication has been observed within days of starting ciclosporin therapy in a number of patients on digoxin. There have also been reports on the potential of ciclosporin to potentiate toxic effects of colchicine such as myopathy and neuropathy, particularly in patients with renal dysfunction. If digoxin or colchicine are used concomitantly with ciclosporin, close clinical observation is required in order to enable early detection of toxic manifestations of digoxin or colchicine and to reduce the dose or withdraw the medicine, if appropriate.

A significant increase in exposure to anthracycline antibiotics (e.g doxorubicine, mitoxanthrone, daunorubicine) was observed in oncology patients with the intravenous co-administration of anthracycline antibiotics with ciclosporin.

Cases of myotoxicity, including muscle pain and weakness, myositis and rhabdomyolysis, have been described in the literature and in post-marketing studies in patients taking ciclosporin concomitantly with lovastatin, simvastatin, atorvastatin, pravastatin and, in rare cases, fluvastatin. When used concomitantly with ciclosporin, the dose of these statins should be reduced in accordance with the instructions given in the relevant prescribing information. Statin therapy must be temporarily withdrawn or discontinued in patients with symptoms of myopathy or in patients with risk factors predisposing to severe renal impairment, including renal failure secondary to rhabdomyolysis.

Elevations in serum creatinine were observed in combination with everolimus or sirolimus. This effect is often reversible with ciclosporin dose reduction. Everolimus and sirolimus had only a minor

effect on the pharmacokinetics of ciclosporin. In contrast, blood levels of everolimus and sirolimus were significantly increased.
Caution is called for when co-administering ciclosporin with potassium-sparing drugs (e.g. potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists) or medicines containing potassium, as this may result in a significant increase in serum potassium.
Ciclosporin may raise plasma levels of repaglinide, thereby increasing the risk of hypoglycaemia.
Pharmacokinetic interaction studies in healthy volunteers showed that bosentan can decrease ciclosporin levels by around 35%, while bosentan exposure increases by around 2-fold.
Co-administration of ciclosporin and aliskiren increases the C_{max} concentration of aliskiren 2.5-fold and AUC 5-fold. By contrast, the pharmacokinetic profile of ciclosporin was not significantly altered.
Co-administration of dabigatran etexilate and ciclosporin results in an increase in the plasma concentration of dibigatran due to the P-gp inhibitory effect (see "Warnings and precautions"). Dabigatran has a narrow therapeutic index and an increase in plasma concentrations is accompanied by an increased risk of bleeding.
Co-administration of ambrisentan and ciclosporin resulted in a 2-fold increase in ambrisentan exposure and a 10% increase in ciclosporin exposure.
Recommendations
If co-administration of medicines reported to interact with Sandimmun Neoral cannot be avoided, the following basic recommendations should be followed:
Renal function (in particular serum creatinine levels) should be closely monitored in patients concomitantly using a medicine that may cause synergistic nephrotoxicity. In the event of significant renal impairment, the dosage of the other medicine should be reduced or alternative treatment considered.
In transplant recipients, there have been isolated cases of considerable, but reversible, renal dysfunction (with corresponding increases in serum creatinine) following concomitant administration of fibrates (e.g. bezafibrate, fenofibrate). Renal function must therefore be closely monitored in such patients. In the event of significant renal dysfunction, the co-medication should be withdrawn.
Medicines known to decrease or increase the bioavailability of ciclosporin
Frequent determinations of blood ciclosporin levels should be performed in transplant recipients, particularly at the start and end of treatment with the other medicine and the Sandimmun Neoral dosage should be adjusted, if necessary.
In non-transplantation indications the value of blood ciclosporin determinations is uncertain, as the relationship between blood levels and clinical effects has been less clearly established. In the case of co-administration of medicines known to increase blood ciclosporin levels, frequent monitoring of renal function and close monitoring of adverse effects of Sandimmun Neoral may be more appropriate than blood level determinations.

Nifedipine: Concomitant treatment with nifedipine should be avoided in patients who have previously developed gingival hyperplasia during Sandimmun Neoral therapy.
NSAIDs: NSAIDs subject to a high first-pass effect (e.g. diclofenac) should be given at lower doses than those used in patients not receiving Sandimmun Neoral.
Digoxin, colchicine, HMG-CoA reductase inhibitors: If any of these medicines is given concomitantly with Sandimmun Neoral, close clinical monitoring is necessary to allow early detection of toxic effects and subsequent dose reduction or withdrawal of the medicine.
Drug interactions are more likely to occur in elderly patients.

Pregnancy/Breast-feeding

Animal studies have shown reproductive toxicity in rats and rabbits (see "Preclinical data").
There are limited data on the use of Sandimmun Neoral in pregnant women. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at increased 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 7 years (data collected in 12 children). Renal function and blood pressure in these children were normal.
Based on the data available, Sandimmun should not be used during pregnancy unless the expected benefit outweighs the potential risk.
The ethanol content of Sandimmun Neoral oral solution should also be taken into account in pregnant women (see "Warnings and precautions").
Ciclosporin passes into the breast milk.
As Sandimmun Neoral can lead to severe adverse effects in breastfed infants, women being treated with Sandimmun Neoral should not breastfeed.

Effects on the ability to drive and to use machines

No data are available on the effect of Sandimmun Neoral on the ability to drive or to use machines.

Adverse effects

Many adverse effects associated with ciclosporin treatment are dose-dependent. In the various indications, the overall spectrum of adverse effects is essentially the same; however, as a consequence of the higher initial doses and longer maintenance therapy required, adverse effects are more frequent and more severe in transplantation than in the other indications.
Anaphylactoid reactions have been observed following i.v. administration (see "Warnings and precautions").
Infections

Patients receiving immunosuppressive therapies, including ciclosporin and regimens containing ciclosporin, are at increased risk of viral, bacterial, fungal and parasitic infection (see "Warnings and precautions"). Generalised and localised infections may occur and pre-existing infections may be aggravated. Reactivation of polyomavirus infections may lead to polyomavirus-associated nephropathy (PVAN) or JC-virus-associated progressive multifocal leucoencephalopathy (PML). Serious and/or fatal outcomes have been reported.

Benign, malignant and unspecified neoplasms (including cysts and polyps)
Patients receiving immunosuppressive therapies, including ciclosporin and regimens containing ciclosporin, 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 "Warnings and precautions"). Some malignancies may be fatal.
Adverse effects are listed according to their frequencies (starting with the most frequent), which are defined as: "*Very common" (≥1/10); "common" (≥1/100 to <1/10); "uncommon" (≥1/1,000 to <1/100); "rare" (≥1/10,000 to <1/1,000); "very rare" (<1/10,000), including isolated reports.*
Blood and lymphatic system disorders
Common: Leukopenia.
Uncommon: Anaemia, thrombocytopenia.
Rare: Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome).
Metabolism and nutrition disorders
Very common: Hyperlipidaemia.
Common: Anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia.
Rare: Hyperglycaemia.
Nervous system disorders
Very common: Tremor (10 to 20%), headache – including migraine (up to about 15%).
Common: Paraesthesia.
Uncommon: Signs of encephalopathy, incl. posterior reversible encephalopathy syndrome (PRES), such as convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia.
Rare: Motor polyneuropathy.
Very rare: Papillooedema, with possible visual impairment, due to benign intracranial hypertension.
Vascular disorders
Very common: Hypertension (15 to 40%).
Gastrointestinal disorders
Very common: Nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia.
Common: Peptic ulcer.

Rare: Pancreatitis.

Hepatobiliary disorders

Common: Liver injury (see "Warnings and precautions").

Skin and subcutaneous tissue disorders

Very common: Hypertrichosis.

Common: Acne, rash.

Uncommon: Allergic skin reactions.

Musculoskeletal disorders

Common: Muscle cramps, myalgia.

Rare: Muscle weakness, myopathy, pain in the extremeties.

Renal and urinary disorders

Very common: Renal dysfunction (see 4. "Renal and hepatic function" under "Warnings and precautions"; incidence 10 to 50%, according to indication).

Reproductive system and breast disorders

Rare: Menstrual disturbances, gynaecomastia.

General disorders and administration site reactions

Common: Fatigue, pyrexia, oedema.

Uncommon: Weight increase.

Other adverse effects, based on post-marketing experience

There have been solicited and spontaneous post-marketing reports of hepatotoxicity and liver injury – including cholestasis, jaundice, hepatitis and hepatic failure – in patients treated with ciclosporin. Most reports included patients with significant comorbidities, underlying conditions and other confounding factors, including infectious complications and co-medications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see "Warnings and precautions").

Overdose

Symptoms

Data are limited on acute ciclosporin overdose. Oral doses 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 overdose in premature neonates.

Treatment

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

Properties/Actions

ATC code: L04AD01

Mechanism of action/Pharmacodynamics

Ciclosporin (also known as ciclosporin A) is a cyclic polypeptide consisting of 11 amino acids. It is a highly effective immunosuppressive agent that has been shown in animal studies to prolong skin, heart, kidney, pancreas, bone marrow, small intestine and lung allograft survival. Studies show that ciclosporin inhibits both 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 T-cell-dependent antibody production – and the production and release of lymphokines, including interleukin-2 (T-cell growth factor, TCGF). There is evidence that ciclosporin blocks the resting lymphocytes in the G_0 or early G_1 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 or affect phagocyte function. Transplant patients treated with ciclosporin are thus less prone to infection than those receiving other immunosuppressive therapy.

Successful solid organ and bone marrow transplantations have been performed in patients using Sandimmun Neoral to prevent and treat rejection and GVHD.

Ciclosporin has been used successfully both in hepatitis C-positive and hepatitis C-negative transplant recipients.

Beneficial effects have also been seen in a number of conditions known or assumed to be of autoimmune origin.

Sandimmun Neoral is a microemulsion preconcentrate; the actual microemulsion, which is formed as soon as the solution comes into contact with water (in the form of a drink or gastric fluid), reduces variability in pharmacokinetic parameters and achieves dose linearity in ciclosporin exposure.

Pharmacokinetics

Sandimmun Neoral displays linearity between dose and ciclosporin exposure (AUC) over the whole clinical dose range, a low level of dependence on the bile and a consistent absorption profile and is only negligibly affected by concomitant food intake or diurnal rhythm. As a result of these properties, intraindividual pharmacokinetic variability is low (between 10 and 22% in renal transplant patients), correlation between trough blood levels and total ciclosporin exposure (AUC) is high and ingestion can take place independently of food intake.

Results from various studies have shown that monitoring of the AUC for ciclosporin during the first 4 hours following administration of the dose (AUC_{0-4}) allows more accurate prediction of Sandimmun

Neoral exposure than does the monitoring of this parameter at the time of administration of the dose (C_0 monitoring).
The results of other studies show that in transplant patients, one-time monitoring 2 hours after dose administration (C_2 monitoring) correlates well with AUC_{0-4}.
Sandimmun Neoral soft gelatin capsules and Sandimmun Neoral oral solution are bioequivalent.
Absorption
Ciclosporin is rapidly absorbed (t_{max} = 1 to 2 hours) following administration of Sandimmun Neoral to organ transplant patients. Absolute bioavailability is 30 to 60%. In stable renal transplant recipients, mean C_{max} and AUC at steady state (dosage standardised to 100 mg/day) are 793 ng/ml and 2,741 hours×ng/ml, respectively.
Distribution
Ciclosporin is distributed largely in the extravascular space, with a mean apparent distribution volume of 3.5 litres/kg. In the blood, distribution depends on the active substance concentration: 33 to 47% is found in plasma, 4 to 9% in lymphocytes, 5 to 12% in granulocytes and 41 to 58% in erythrocytes. At high concentrations, leukocyte and erythrocyte uptake is saturated. In plasma, approx. 90% of ciclosporin is bound to proteins, mostly lipoproteins.
Metabolism
Ciclosporin is extensively metabolised, the main site of metabolism being the cytochrome P450 (CYP450 3A4)-dependent monooxygenase system. Over 15 metabolites are known thus far. Metabolites primarily result from monohydroxylation, dihydroxylation and N-demethylation at various molecular sites. Medicines that affect the cytochrome P450 (CYP450 3A4)-dependent enzyme system have been found to increase or reduce ciclosporin levels (see "Interactions"). All metabolites identified so far contain the intact peptide structure of the unchanged drug. Some possess a slight immunosuppressive action (up to 10% of that of ciclosporin).
Elimination
Figures for the terminal elimination half-life of ciclosporin vary considerably depending on the method of determination used and the subjects involved. They range from 6.3 hours in healthy volunteers to 7 to 16 hours in renal transplant patients and 20.4 hours in patients with severe liver disease. Elimination is primarily biliary. Only 6% of an oral dose is excreted in the urine and less than 1% as unchanged drug.
Pharmacokinetics in special populations
Elderly patients
No data are available on the absorption of Sandimmun Neoral in elderly patients. However, distribution of ciclosporin is no different than in middle-aged patients.
Children
On average, elimination of ciclosporin is somewhat more rapid in children than in adults. Higher doses (relative to body weight) may therefore be necessary to obtain the same blood levels.

Renal impairment

Renal impairment has no clinically-relevant effect on pharmacokinetics, as ciclosporin is eliminated primarily via the bile.

Hepatic impairment

Hepatic impairment slows down elimination of ciclosporin. Close monitoring of serum creatinine and blood ciclosporin levels, with corresponding dose adjustment, is therefore necessary in patients with severe hepatic dysfunction.

Nephrotic syndrome

Oral administration to patients with nephrotic syndrome does not result in pharmacokinetic data deviating from the reference values. Dose adjustment is thus not necessary.

Preclinical data

Ciclosporin showed no mutagenic or teratogenic effects in the standard test systems with oral administration (oral daily doses of up to 17 mg/kg in rats and up to 30 mg/kg in rabbits). However, it was embryotoxic and fetotoxic at maternally toxic doses (100 mg/kg/day in rabbits and 30 mg/kg/day in rats), as indicated by increased prenatal and postnatal mortality and reduced birth weight together with delayed growth.

In two published studies, exposure to ciclosporin *in utero* (10 mg/kg/day) was associated with reduced numbers of nephrons, renal hypertrophy, systemic hypertension and progressive renal insufficiency in rabbits up to 35 weeks of age.

Pregnant rats given i.v. ciclosporin doses of 12 mg/kg/day (twice the recommended human i.v. dose) had fetuses with an increased incidence of ventricular septal defects.

These findings have not been demonstrated in other species and their relevance to humans is unclear.

Carcinogenicity studies were carried out in male and female rats and mice. In a 78-week study in mice given doses of 1, 4 and 16 mg/kg per day, there was evidence of a statistically-significant trend towards the formation of lymphocytic lymphomas in females and the incidence of hepatocellular carcinomas in males given doses in the middle dose range significantly exceeded the control value.

In a 24-month study in rats given doses of 0.5, 2 and 8 mg/kg per day, the incidence of pancreatic islet cell adenomas significantly exceeded that of controls given low doses. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose-related.

Doses of up to 5 mg/kg/day did not impair fertility in either male or female rats.

An increased incidence of malignancy is a recognised complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin’s lymphoma and carcinomas of the skin (see "Warnings and precautions" for information regarding the risk of developing lymphomas and other malignancies). 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 discontinuation of immunosuppression may cause the lesions to regress.

Other information

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Once the bottle has been opened, the contents should be used within 2 months.

Special precautions for storage

Sandimmun Neoral capsules should not be stored above 25°C. Increased temperatures of up to 30°C for a total of maximum 3 months do not affect the quality of the product.

Sandimmun Neoral oral solution should be stored between 15 to 30°C (but not in a refrigerator), but not below 20°C for more than one month.

As the solution contains oily components of natural origin that may solidify at low temperatures, it may become gel-like at temperatures below 20°C. However, this is reversible at temperatures of 30°C. Warm the solution until the gel-like consistency is no longer apparent. Minor flakes or slight sediment may remain; however, these do not affect the efficacy and safety of the product. Dosing using the syringe also remains reliable.

After opening, Sandimmun Neoral should be used within 2 months. Keep out of the reach of children.

Instructions for use and handling

Capsules

The capsules should not be removed from the blister until immediately before 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 capsules.

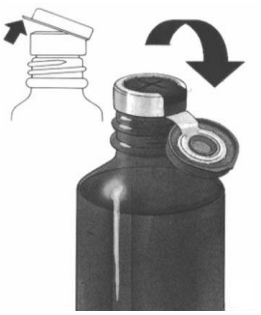
The capsules should be swallowed whole.

Oral solution

Sandimmun Neoral oral solution is provided with two syringes for measuring doses. The 1 ml syringe is used to measure out doses ≤ 1 ml (each graduation of 0.05 ml corresponds to 5 mg ciclosporin). The 4 ml syringe is used to measure out doses > 1 ml and ≤ 4 ml (each graduation of 0.1 ml corresponds to 10 mg ciclosporin).

Instructions for first-time use:

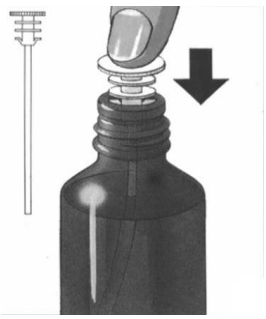
1. Open the plastic cap.



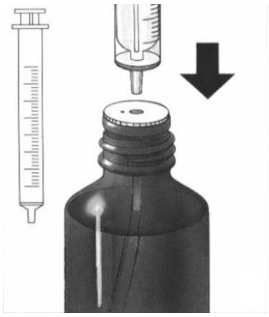
2. Tear off the sealing ring completely.

3. Remove the black stopper and throw it away.

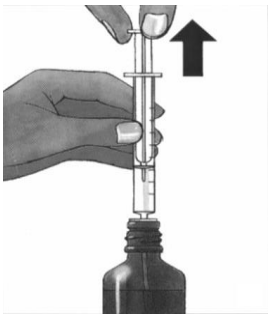
4. Push the tube unit with the white stopper firmly into the neck of the bottle.



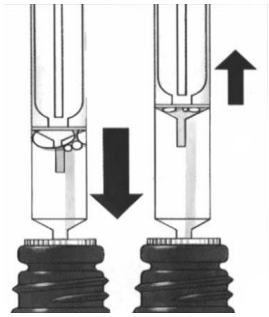
5. Choose the syringe depending on the prescribed volume. For volumes ≤ 1 ml, use the 1 ml syringe. For volumes > 1 ml, use the 4 ml syringe. Insert the syringe into the white stopper.



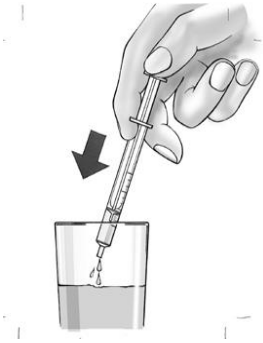
6. Draw up the prescribed volume of solution (position the lower edge of the plunger at the graduation mark corresponding to the prescribed volume).



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



8. Push the solution out of the syringe into a small glass of liquid (not grapefruit juice). Avoid any contact between the syringe and the liquid in the glass. The solution should be mixed immediately before drinking. Stir and drink the entire mixture right away. The mixture must be taken immediately after preparation.



9. After use, wipe the syringe on the outside only with a dry tissue and replace it in its cover. Do not rinse it with water, alcohol or any other liquid. The white stopper and tube should remain in the bottle. Close the bottle using the screw cap provided.

Subsequent use: Repeat from point 5 onwards.

The solution must be diluted in a glass immediately before use. Orange or apple juice are the most suitable diluents. Other non-alcoholic drinks may also be used, depending on individual taste. Grapefruit juice must not be used, however, due to the risk of local interactions involving the intestinal P450-dependent enzyme system. *The syringe must not come into contact with the diluent. Stir well and drink immediately.*

In order to ensure that the whole dose is taken, pour a little more of the diluent into the glass, swirl round, then drink. The same liquid should always be used as the diluent.

For practical recommendations regarding correct use of the capsules/oral solution, see "Dosage/Administration".

Pack sizes

Country specific pack sizes.

Manufacturer

See folding box.

Information last revised

February 2015

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

– The doctor and the pharmacist are experts in medicine, its benefits and risks.

– Do not by yourself interrupt the period of treatment prescribed for you.

– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists