NOVARTIS

Sandimmun® Neoral

Composition

Active substance
Ciclosporin

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).

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 in the form of a concentrate for intravenous 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.
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 7–70 years of age.

Psoriasis

Severe cases in which alternative therapies are ineffective or inappropriate.

Atopic dermatitis

Severe cases in which alternative therapies are ineffective or inappropriate.

Rheumatoid arthritis

Severe cases in which standard specific disease-related 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% of normal.

Induction or maintenance of remission
Maintenance of corticosteroid-induced remission, in order to enable corticosteroids to be withdrawn.

Dosage and 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**.

The total daily requirement of Sandimmun Neoral should always be taken in two divided doses (mornings and evenings).
Practical recommendations for correct use: See section **c) Administration**.

a) Transplantation
The dose 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.

Organ transplantation
The starting dose is 10–15 mg/kg, given in two divided doses a maximum of 12 hours before transplantation. This amount should be maintained as the daily dose for 1–2 weeks post-surgery. The dosage may then be gradually reduced to a maintenance dose of 2–6 mg/kg/

day (depending on blood ciclosporin levels), to be taken in two divided doses.
In renal graft recipients it has been found that doses below 3–4 mg/kg/day, which result in trough blood levels below 50–100 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. 3–6 mg/kg/day orally as a starting dose) may be given.

Dose recommendation in kidney transplantation for oral ciclosporin 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 0–4: 1000–1400 ng/ml; weeks 5–8: 700–900 ng/ml; weeks 9–12: 550–650 ng/ml; weeks 13–52: 350–450 ng/ml.
Prior to dose reduction of ciclosporin, it must be verified 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 minimize the risk of a failure in 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.

Dose recommendation in heart transplantation for oral ciclosporin 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/minute, 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 verified that steady-state everolimus trough blood levels (C_0) are ≥ 3 ng/ml.

Bone-marrow transplantation
The initial dose should be given on the day before transplantation. It is recommended that patients started on oral therapy be given 12.5–15 mg/kg/day initially. The maintenance dose of approx. 12.5 mg/kg/day, administered in two divided doses, should be given for 3–6 (preferably 6) months. It may then be tapered off to zero by 1 year after transplantation.
Higher oral doses or administration by i.v. infusion may be required in patients with absorption-impairing gastrointestinal disorders (see also separate prescribing information for **Sandimmun concentrate for i.v. infusion**).
GVHD may occur in some patients following withdrawal of Sandimmun Neoral, but usually responds to reinstitution. Low doses should be given to treat chronic mild GVHD.

b) Non-transplantation indications
1. Endogenous uveitis
Dosage
5 mg/kg/day in two divided doses is recommended as the starting dose until inflammation subsides and visual acuity improves. In resistant cases, the dosage may be temporarily increased to 7 mg/kg/day.
To achieve particularly rapid remission and thus combat acute inflamma-

tory episodes, and/or if Sandimmun Neoral alone proves insufficiently effective, a systemic corticosteroid – either prednisone (0.2–0.6 mg/kg/day) or an equivalent substance – may be added.
Sandimmun Neoral should be withdrawn if no improvement is evident after three months.
For maintenance therapy, the dose should gradually be reduced to the lowest effective level, which should not exceed 5 mg/kg/day during periods of remission.
The daily dose must be reduced by 25–50% 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 reduction has no effect within one month, Sandimmun Neoral should be withdrawn.

Monitoring of renal function
Sandimmun Neoral may impair renal function, and reliable baseline serum creatinine levels – derived from at least two determinations – should therefore be established prior to the start of treatment. Both determinations should indicate normal renal function. To this end, creatinine clearance may be calculated from serum creatinine levels by means of a suitable formula (e.g. Dettli's). Serum creatinine determinations should be performed at weekly intervals during the first month of treatment and at monthly intervals thereafter, or more frequently if the Sandimmun Neoral dosage is increased. In cases where creatinine exceeds the baseline value by 20–30%, the possibility of transient non-renal increases must be ruled out by means of repeat determinations.

Blood pressure monitoring
If hypertension occurring during Sandimmun Neoral therapy cannot be normalized 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**).

2. Dermatological indications

Special notes

Prior to treatment the patient must be fully informed 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 other than cutaneous (see *Skin tumours* [under Psoriasis] 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**).

Monitoring of renal function / blood pressure: See section ***1. Endogenous uveitis*** above.

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 1 month – by 0.5–1 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, which should not exceed 5 mg/kg/day.

Treatment should be withdrawn if there is insufficient improvement in the psoriatic lesions after 1 month at 5 mg/kg/day or if the effective dose is not compatible with the safety guidelines given above (see *Special notes* in this section [***2. Dermatological indications***]).

Sandimmun Neoral should be tapered off 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 therefore be biopsied before Sandimmun Neoral is given. Patients found to have malignant or premalignant skin changes should only be given Sandimmun Neoral after appropriate treatment has been given 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 2.5–5 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 who do not respond adequately following 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 drug withdrawal 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, however, 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 notes

Prior to treatment the patient must be fully informed 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**).

Blood pressure monitoring: See section ***1. Endogenous uveitis*** above.

Dosage

For the first 6 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.

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 baseline value 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 reduction has no effect within one month, Sandimmun Neoral should be withdrawn.

Monitoring of renal function: See section ***1. Endogenous uveitis*** above.

More frequent serum creatinine determinations are also necessary when an NSAID is introduced or when the dosage 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

Dosage

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 patients with permitted levels of renal impairment, the starting dose should not exceed 2.5 mg/kg/day (N.B.: Serum creatinine levels > 200 µmol/litre in adults and > 140 µmol/litre in children are contraindications [see **Contraindications**]).

The dosage should be individually adjusted as a function of 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 dose should gradually be reduced to the lowest effective level.

The dose should be reduced by 25–50% 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.

Monitoring of renal function: See section ***1. Endogenous uveitis*** above.

Patients in whom renal function is abnormal at baseline (maximum serum creatinine levels of 200 µmol/litre in adults and 140 µmol/litre 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.
Blood pressure monitoring: See section ***1. Endogenous uveitis*** above.

Paediatric use
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 than do 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 of the use of 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 subjects 65 years of age or older to allow any conclusions as to whether their response differs from that of younger subjects. 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.

c) Administration
The total daily requirement of Sandimmun Neoral should always be taken in two divided doses (mornings and evenings).

Capsules
In patients (particularly those with low body weight) for whom the target dose cannot be accurately attained using two identical doses mornings and evenings, the following steps are possible:
Different doses may be given in the morning and evening, or the oral solution may be used.

Contraindications
All indications
Hypersensitivity to ciclosporin or to any of the excipients.

Non-transplantation indications
The following contraindications also hold:

- Renal impairment, except in patients with nephrotic syndrome and with permitted levels of renal impairment, in whom disease-related, moderate increases in baseline serum creatinine values (not more than 200 µmol/litre in adults and not more than 140 µmol/litre in children) improve and cautious therapy (not more than 2.5 mg/kg/day) is thus permitted.
- Inadequately controlled hypertension.
- Inadequately controlled infection.

History of known or diagnosed malignancy of any kind except premalignant or malignant skin changes (see **b) Non-transplantation indications** under **Dosage and Administration** [*Special notes* under ***2. Dermatological indications***; *Skin tumours* under a) Psoriasis] and **Neoplasms** under **Adverse effects**).

Warnings and Precautions

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. Risks associated with 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. This does not apply when switching between Sandimmun Neoral soft gelatin capsules and Sandimmun Neoral oral solution, as these two forms are bioequivalent.

3. Combination with other immunosuppressive agents

Like other immunosuppressive agents, ciclosporin increases the risk

of developing lymphomas and other malignancies, particularly those of the skin.
This increased risk seems to be related more to the degree and duration of immunosuppression than to the use of specific drugs.
In addition, a treatment plan containing several immunosuppressive agents (including ciclosporin) must be used with caution, since it may lead to lymphoproliferative disorders and solid organ tumours that have been reported to 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 jeopardize the graft.

4. Effect on 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, occasionally, liver enzyme levels (see **Adverse effects**).
Regular monitoring of the appropriate hepatic and renal parameters is required, with dose reduction if necessary should results be abnormal.
Renal function should be particularly closely monitored in elderly patients.

5. Determination of blood ciclosporin levels
Blood ciclosporin levels are best determined using a specific monoclonal antibody (determination of unchanged drug). However, HPLC may be used as well (also for the determination of unchanged drug). For assays in plasma or serum, a standard method of separation (time and temperature) should be used.
In liver transplant recipients, initial blood-level monitoring should make use of either the specific monoclonal antibody alone, or of the specific in parallel with the nonspecific monoclonal antibody in order to permit an appropriate degree of immunosuppression.

It must also be remembered that the blood, plasma or serum level of ciclosporin is only one of many factors affecting the patient's clinical status. The results should therefore be viewed only as a guide for treatment in the context of a whole range of other clinical and biochemical parameters (see ***Organ transplantation*** under **Dosage and 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.

7. Biochemical changes
There have been rare reports of treatment with Sandimmun Neoral being associated with a slight, reversible increase in blood lipids; lipid levels should therefore be measured prior to, and one month after, the

start of treatment. In the event of an increase, a reduction in dietary fat intake and, if appropriate, in the dosage should be considered.
Ciclosporin increases the risk of hyperkalaemia, particularly in patients with renal dysfunction. Caution is called for when administering ciclosporin concomitantly with potassium-sparing drugs (e.g. potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists) or drugs containing potassium, or when using it in patients on a potassium-rich diet (see **Interactions**). In such situations, it is advisable to check potassium levels.
Ciclosporin increases magnesium excretion, which can lead to symptomatic hypomagnesaemia, above all in the peri-transplantation period. Monitoring of serum magnesium is recommended during the peri-transplantation period, above all when neurological symptoms occur. If it is deemed necessary, additional magnesium should be administered.
Caution is required in patients with hyperuricaemia.

8. Concomitant medication (see Interactions)
Psoriasis patients should not be given concomitant treatment with beta-blockers or diuretics.
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 blood levels of concomitant medications, such as aliskiren, that are substrates of P-glycoprotein (Pgp; see **Interactions**).

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 malignant 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 of such disorders. 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 be given concomitant UVB radiation or PUVA therapy (see **Interactions**).

Interactions
Food interactions
Concomitant intake of a high-fat meal or of grapefruit juice has been found to increase the bioavailability of ciclosporin.

Drug interactions
Interactions with many different drugs have been reported. 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 controversial reports, is available on request.
A number of drugs are known to increase or reduce the plasma or whole blood level of ciclosporin by competitively inhibiting or inducing the liver enzymes – in particular CYP3A4 – involved in the metabolism and elimination of ciclosporin. Ciclosporin is also an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein (Pgp). It may increase plasma levels of co-medications that are substrates of CYP3A4 or Pgp.

Drugs that cause synergistic nephrotoxicity
Aciclovir, aminoglycosides (including gentamicin and tobramycin), amphotericin B, ciprofloxacin, furosemide, mannitol, melphalan, trimethoprim (+ sulfamethoxazole), vancomycin, NSAIDs (including diclofenac, indometacin, naproxen and sulindac), histamine H_2-receptor antagonists

(e.g. cimetidine, ranitidine), methotrexate (see **Warnings and Precautions**).
Concomitant administration of tacrolimus should be avoided due to the increased risk of nephrotoxicity.

Drugs that reduce ciclosporin levels
Barbiturates, carbamazepine, oxcarbazepine, phenytoin, nafcillin, i.v. sulfadimidine; orlistat, rifampicin, octreotide, probucol, i.v. trimethoprim, St. John's wort preparations, ticlopidine, sulfinpyrazone, terbinafine, bosentan.

Drugs 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
For information regarding vaccines, see ***8. Concomitant medication*** under **Warnings and**

Precautions.
Concomitant 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%. Caution is therefore required when co-administering ciclosporin and lercanidipine (see **Warnings and Precautions**).
Ciclosporin is a highly potent Pgp inhibitor and may increase blood levels of concomitant medications, such as aliskiren, that are substrates of

Pgp. Following concomitant administration of ciclosporin and aliskiren, the C_{max} of aliskiren was approximately 2.5 times higher and the AUC approximately 5 times higher. By contrast, the pharmacokinetic profile of ciclosporin was not significantly altered. Caution is required when co-administering ciclosporin and aliskiren (see **Warnings and Precautions**).

Concomitant administration of diclofenac and ciclosporin has been found to bring about a significant increase in the bioavailability of diclofenac, with the possible complication of reversible renal impairment. The increase is most probably caused by a reduction in the high first-pass effect of diclofenac. Concomitant 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) and etoposide.

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 such toxic effects of colchicine as myopathy and neuropathy, particularly in patients with renal dysfunction. If digoxin or colchicine are given concomitantly with ciclosporin, close clinical monitoring is necessary in order to ensure early detection of toxic manifestations of digoxin or colchicine so that the dose can then be reduced or the drug withdrawn.

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 dosage 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.

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

Caution is called for when administering ciclosporin concomitantly with potassium-sparing drugs (e.g. potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists) or drugs containing potassium, as this may result in a significant increase in serum potassium (see **Warnings and Precautions**).

When used concurrently with bosentan, ciclosporin raises plasma levels of bosentan.

Ciclosporin may raise plasma levels of repaglinide, thereby increasing the risk of hypoglycaemia.

Recommendations

If concomitant administration of drugs 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 concurrently using drugs that may cause synergistic nephrotoxicity. In the event of significant renal impairment, the dosage of the other drug should be reduced or alternative treatment considered.

In graft recipients there have been isolated reports 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 comedication should be withdrawn.

Drugs known to reduce 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 drug, 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 demonstrated. In the case of concomitant administration of drugs 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 drugs is given concomitantly with Sandimmun Neoral, close clinical monitoring is necessary to allow early detection of toxic effects and subsequent dosage reduction or drug withdrawal.
Drug interactions are more likely to occur in elderly patients.

Pregnancy and Lactation
Animal studies have shown reproductive toxicity in rats and rabbits (see **Preclinical data**).
Experience with Sandimmun Neoral in pregnant women is very limited. Pregnant women treated after transplantation with immunosuppressive

agents, including ciclosporin and regimens containing ciclosporin, are at elevated risk of premature delivery (< 37 weeks).
There have been a limited number of observations in children up to 7 years of age who had been exposed to ciclosporin *in utero* (data collected in 12 children). These children had normal renal function and blood pressure.
However, there have been no appropriate, properly controlled studies in pregnant women. Sandimmun Neoral should therefore not be used during pregnancy unless clearly necessary.
Ciclosporin passes into the breast milk. Women being treated with Sandimmun Neoral should therefore not breastfeed.

Effects on ability to drive and 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 and respond to dose reduction.
The range of adverse effects is generally the same in all indications, although there are differences as regards frequency and severity. Due to the higher starting doses and longer maintenance therapy required in the transplantation indications, adverse effects are more frequent and tend to be more severe in graft recipients than in patients being treated for 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 Precau-**

tions). Generalized and localized 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 malignant tumours increases with the intensity and duration of therapy (see **Warnings and Precautions**). Certain malignant tumours 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: ≥ 1/1000 to < 1/100; rare: ≥ 1/10 000 to < 1/1000; very rare: < 1/10 000, including isolated reports.

Neoplasms
Malignant tumours and lymphoproliferative disorders have occurred, but their frequency and distribution in graft recipients appear to be similar to those in patients treated with conventional immunosuppressive agents.

Blood and lymphatic system disorders
Uncommon: Anaemia, thrombocytopenia.
Rare: Thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome.

Metabolism and nutrition disorders
Very common: Hyperlipidaemia.
Common: Loss of appetite, hyperuricaemia, hyperkalaemia, hypomagnesaemia.
Rare: Hyperglycaemia.

Nervous system disorders
Very common: Tremor (10–20%), headache – including migraine (up to about 15%).
Common: Paraesthesia.
Uncommon: Signs of encephalopathy, such as convulsions, mental confusion, disorientation, impaired reactions, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia.
Rare: Motor polyneuropathy.
Very rare: Papilloedema, with possible deterioration of eyesight, due to benign intracranial hypertension.

Vascular disorders
Very common: Hypertension (15–40%).

Gastrointestinal disorders
Common: Nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia.

Hepatobiliary disorders
Common: Abnormal hepatic function (see **Warnings and Precautions**).
Rare: Pancreatitis.

Skin disorders
Common: Hypertrichosis.
Uncommon: Allergic skin reactions.

Musculoskeletal disorders
Common: Muscle cramps, myalgia.
Rare: Muscle weakness, myopathy.

Renal and urinary disorders
Very common: Renal dysfunction (see ***4. Effect on renal and hepatic function*** in **Warnings and Precautions**; incidence 10–50%, depending on indication).

Reproductive system and breast disorders
Rare: Disturbances of menstruation, gynaecomastia.

General disorders and administration-site reactions
Common: Fatigue
Uncommon: Oedema, weight gain.

Other adverse effects, based on post-marketing experience
There have been solicited and spontaneous post-marketing reports of hepatotoxicity and liver damage – including cholestasis, jaundice, hepatitis and hepatic failure – in patients treated with ciclosporin. Most reports included patients with significant co-morbidities, 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
Signs and symptoms
Data are limited on acute ciclosporin overdosage. The clinical consequences of oral doses of up to 10 g (approx. 150 mg/kg) were relatively minor, e.g. vomiting, drowsiness, headache, tachycardia, and, in a few patients, moderate reversible renal impairment. In preterm infants,

however, accidental parenteral overdosage resulted in severe intoxication.

Management
Symptomatic treatment and general supportive measures in all cases. Induced emesis and gastric lavage may be beneficial in the first hour following ingestion.
Neither dialysis nor charcoal haemoperfusion will clear ciclosporin adequately from the system.

Properties and 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 potent 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 lymphokine release by activated T cells in response to antigen contact.
All available evidence suggests that ciclosporin acts specifically and reversibly on lymphocytes. Unlike cytostatic agents, it does not impair haemopoiesis or affect phagocyte function. Transplant patients treated with ciclosporin are thus less prone to infection than those receiving other immunosuppressive agents.
Sandimmun Neoral has been used successfully in the prevention and

management of graft rejection and GVHD in humans undergoing organ and bone-marrow transplantation.
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 drink or gastric juice), 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 constant absorption profile, and is only negligibly affected by concomitant food intake or circadian 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} = 1–2 hours) following administra-

tion of Sandimmun Neoral to organ transplant patients. Absolute bioavailability is 30–60%. In stable renal transplant recipients, mean C_{max} and AUC at steady state (dosage standardized to 100 mg/day) are 793 ng/ml and 2741 hours × ng/ml, respectively.

Distribution
Ciclosporin is distributed largely in the extravascular space, with a mean apparent distribution volume of 3.5 litres/kg. Within the blood, distribution depends on the active substance concentration: 33–47% is found in plasma, 4–9% in lymphocytes, 5–12% in granulocytes and 41–58% in erythrocytes. At high concentrations leukocyte and erythrocyte uptake is saturated. In plasma, approx. 90% of ciclosporin is bound to proteins (primarily lipoproteins).

Metabolism
Ciclosporin is extensively biotransformed, the main site of metabolism being the cytochrome P450 (CYP450 3A4)-dependent monooxygenase system. Over 15 metabolites are known thus far. The major metabolic pathways are monohydroxylation, dihydroxylation and N-demethylation at various molecular sites. Drugs 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 7–16 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 patient 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 elimination of ciclosporin is 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 altered pharmacokinetics. 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 per day in rabbits and 30 mg/kg per 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 body weight per day) was associated with reduced numbers of neph-

rons, renal hypertrophy, systemic hypertension, and progressive renal insufficiency in rabbits up to 35 weeks of age.
Pregnant rats given i.v. doses of 12 mg ciclosporin per kg body weight per day (twice the recommended human intravenous dose) had fetuses with an increased incidence of ventricular septal defect.
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 body weight per day had no adverse effects on fertility in either male or female rats.
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 (see **Warnings and Precautions** for 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 therapy. 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.
Sandimmun Neoral *oral solution* should be stored at 15–30°C, but – as far as possible – should neither be kept at temperatures below 20°C for long periods, nor stored in a refrigerator. The solution contains natural oils which may solidify at low temperatures. At temperatures below 20°C the solution may therefore become gel-like, slight flocculation may occur or a light sediment may form. These effects are reversible at temperatures from 25 to 30°C and do not impair the safety or efficacy of the product. Dosing using the syringe also remains reliable.
Keep out of the reach of children.

Instructions for use and handling
Capsules
The capsules should not be removed from the blisters until immediately before use. The characteristic odour that becomes apparent on opening the blisters is normal and does not indicate 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. Raise the plastic cap.

2. Tear off the sealing ring completely.

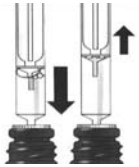
3. Remove the black stopper and throw it away.

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. The 1 ml syringe is used to measure out volumes ≤ 1 ml. The 4 ml syringe is used to measure out volumes > 1 ml. Insert the syringe into the white stopper.

6. Draw up the prescribed amount of solution (with 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 whole 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 case. Do not rinse it with water, alcohol, or any other liquid. The white stopper and tube should remain in the bottle. Close the bottle with the screw cap provided.

Subsequent use

Repeat from point 5 onwards.
Dilute the solution in a glass immediately before use. Orange or apple juice are the most suitable diluents. Other non-alcoholic drinks may, however, be used, depending on individual taste. Grapefruit juice should 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.
Practical recommendations for correct use of the capsules / oral solution: See **c) Administration** under **Dosage and Administration**.

Pack sizes
Country specific pack sizes.

Manufacturer
See folding box

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June 2011

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16 September 2011

® = 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