NOVARTIS

SANDIMMUN® 50 mg per 1 mL Ampoule

SANDIMMUN NEORAL® 100 mg per 1 mL Drink Solution

SANDIMMUN NEORAL® 25 mg Capsule

SANDIMMUN NEORAL® 100 mg Capsule

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1. NAME OF THE MEDICINE

SANDIMMUN ® 50 mg per 1 mL Ampoule

SANDIMMUN NEORAL® 100 mg per 1 mL Drink Solution

SANDIMMUN NEORAL® 25 mg Capsules

SANDIMMUN NEORAL® 100 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ampoule (concentrate for solution for infusion) 50 mg per 1 mL:

Each 1 mL ampoule contains 50 mg ciclosporin.

Drink solution 100 mg per 1 mL:

Each 1 mL of the solution contains 100 mg ciclosporin.

Capsule 25 mg:

Each soft gelatine capsule contains 25 mg ciclosporin.

Capsule 100 mg:

Each soft gelatine capsule contains 100 mg ciclosporin.

For the full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Ampoule (concentrate for solution for infusion) 50 mg per 1 mL:

A clear brown-yellow, oily solution in a 1 mL clear glass ampoule coded with a yellow-coloured ring and a blue-coloured ring on the neck of the ampoule.

Drink solution 100 mg per 1 mL:

A faintly yellow to faintly brownish-yellow liquid, clear or containing small amounts of very fine sediment. A jelly-like formation may occur below 20 °C, which is however reversible at temperatures up to 30 °C. Minor flakes or a slight sediment may still be observed.

Capsule 25 mg:

Blue-grey, oblong, soft gelatine capsule containing a faintly yellow to faintly brownish yellow liquid, which is clear or contains a slight sediment. Length of capsule: 14,0 mm; diameter: 8,2 mm. Imprint: "NVR 25 mg" in red.

Capsule 100 mg:

Blue-grey, oblong, soft gelatine capsule containing a faintly yellow to faintly brownish yellow liquid, which is clear or contains a slight sediment. Length of capsule: 27,7 mm; diameter: 9,5 mm. Imprint: "NVR 100 mg" in red.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Transplantation indications:

Prophylaxis of graft rejection following transplantation of kidney, liver, pancreas, heart, combined heart-lung, lung and bone marrow allogenic transplantation; and for the prevention of graft-versus-host (GVHD) disease following bone marrow transplantation.

It may also be used in the treatment of transplant rejection in patients previously receiving other immunosuppressive agents. SANDIMMUN has also been used, with less effect, in the treatment of established graft-versus-host disease. SANDIMMUN concentrate for solution for infusion/SANDIMMUN NEORAL may be used alone or with corticosteroids.

Psoriasis:

Treatment of patients with severe psoriasis, in whom conventional therapy is ineffective or inappropriate and the risks of treatment are justified.

Rheumatoid arthritis:

Treatment of severe, active rheumatoid arthritis in patients in whom classical slow-acting anti-rheumatic agents are inappropriate or ineffective.

Atopic dermatitis:

Treatment of severe atopic dermatitis where conventional therapy has proved ineffective or is inappropriate.

4.2 Posology and method of administration

Dosage

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

Because of considerable inter- and intra- individual variations in absorption and elimination and the possibility of pharmacokinetic interactions, doses should be titrated individually according to clinical response and tolerability.

In *transplant patients,* routine monitoring of ciclosporin trough blood levels is required to avoid adverse effects due to high levels and to prevent organ rejection due to low levels (see **section 4.5**).

In patients treated for *non-transplant indications*, monitoring of ciclosporin blood levels is of limited value except in the case of unexpected treatment failure or relapse, where it may be appropriate to establish the possibility of very low levels caused by non-compliance, impaired gastrointestinal absorption, or pharmacokinetic interactions (see **section 4.5**).

General target population

Transplantation

Solid organ transplantation

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

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

If the SANDIMMUN concentrate for solution for infusion is used, the recommended dose is approximately one-third of the appropriate SANDIMMUN NEORAL dose, and it is recommended that patients be put on oral therapy as soon as possible.

Treatment with SANDIMMUN concentrate for solution for infusion should be initiated within 12 hours before surgery at a dose of 3 to 5 mg/kg. This dose should be maintained as the daily dose for 1 to 2 weeks post-operatively before being gradually reduced in accordance with blood levels until a maintenance dose of about 0, 7 to 2 mg/kg given in 2 divided doses is reached.

When SANDIMMUN concentrate for solution for infusion is given with other immunosuppressants (e.g., with corticosteroids or as part of a triple or quadruple

medicinal product therapy), lower doses (e.g., 1 to 2 mg/kg given in 2 divided doses for the initial treatment) may be used.

Bone marrow transplantation

The initial dose should be given on the day before transplantation. In most cases, SANDIMMUN intravenous (i.v.) infusion is preferred for this purpose; the recommended i.v. dose is 3 to 5 mg/kg per day. Infusion is continued at this dose level during the immediate post-transplant period of up to 2 weeks, before a change is made to oral maintenance therapy with SANDIMMUN NEORAL at a daily dose of about 12,5 mg/kg given in 2 divided doses.

Maintenance treatment should be continued for at least 3 months (and preferably for 6 months) before the dose is gradually decreased to zero by 1 year after transplantation.
If SANDIMMUN NEORAL is used to initiate therapy, the recommended daily dose is 12, 5 to 15 mg/kg given in 2 divided doses, starting on the day before transplantation.
Higher doses of SANDIMMUN NEORAL, or the use of i.v. therapy, may be necessary in the presence of gastrointestinal disturbances which might decrease absorption.

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

Non-transplant indications:

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

- Before initiation of treatment a reliable baseline level of serum creatinine should be established by at least two measurements, and renal function must be assessed regularly throughout therapy to allow dosage adjustment.
- The only accepted route of administration is by mouth (the CONCENTRATE FOR SOLUTION FOR INFUSION must not be used), and the daily dose should be given in two divided doses.
- For maintenance treatment the lowest effective and well tolerated dosage should be determined individually.
- In patients in whom within a given time (for specific information see below) no adequate response is achieved or the effective dose is not compatible with the established safety guidelines, treatment with SANDIMMUN NEORAL should be discontinued.

Psoriasis:

For inducing remission, the recommended dose is 2,5 mg/kg/day given in two divided oral doses. If there is no improvement after 1 month, the daily dose may be gradually increased but should not exceed 5 mg/kg/day.

Treatment should be discontinued in patients in whom sufficient response of psoriatic lesions cannot be achieved within 6 weeks on 5 mg/kg/day or in whom the effective dose is not compatible with the safety guidelines given below (see **section 4.4**).

An initial dose of 5 mg/kg/day is justified in patients whose condition requires rapid improvement.

For maintenance treatment, the dosage should be titrated individually to the lowest effective level. Dose adjustments should be made in increments of 0, 5 to 1 mg/kg body mass.

Rheumatoid arthritis:

For the first 6 weeks of treatment, the recommended dose is 2,5 mg/kg per day, given orally in two divided doses. If the clinical effect is considered insufficient, the daily dose may then be increased gradually as tolerability permits. The maximum dosage is 5 mg/kg/day, however there is limited experience with dosages above 4 mg/kg/day. If, after 3 months of treatment at the maximum permitted or tolerable dose the response is considered inadequate, treatment should be discontinued.

For maintenance treatment the dose has to be titrated individually according to tolerability. If a patient is on an effective maximum tolerable dose with no further improvements expected, and has been stable for at least 3 months, the dose of

SANDIMMUN NEORAL should be decreased at 0,5 mg/kg per day increments monthly or bi-monthly to the lowest effective dose.

If there is essentially no clinical response by 6 months, and the maximal tolerable dose has been administered for 3 months, SANDIMMUN NEORAL should be discontinued. After 3 months of SANDIMMUN NEORAL therapy without response, blood level monitoring of ciclosporin may be of value to evaluate patient compliance and/or medicine absorption.

SANDIMMUN NEORAL may be given in combination with low-dose corticosteroids and/or non-steroidal anti-inflammatory medicines.

SANDIMMUN NEORAL can also be combined with low-dose weekly methotrexate in patients who have insufficient response to methotrexate alone, by using initially 2,5 mg/kg SANDIMMUN NEORAL in 2 divided doses per day, with the option to increase the dose as tolerability permits.

Atopic dermatitis:

Due to the variability of this condition, treatment must be individualised. The recommended dose range is 2,5 to 5 mg/kg per day given in two divided oral doses. If a starting dose of 2,5 mg/kg per day does not achieve a satisfactory response within 2 weeks of therapy, the daily dose may be rapidly increased to a maximum of 5 mg/kg. In

very severe cases, rapid and adequate control of the disease is more likely to occur with a starting dose of 5 mg/kg per day. Once satisfactory response is achieved, the dose should be reduced gradually and, if possible, SANDIMMUN NEORAL should be discontinued. Subsequent relapse may be managed with a further course of SANDIMMUN NEORAL.

Since there is no experience with long-term treatment, one cure should not exceed 8 weeks.

Special populations

Patients with renal impairment

All indications

Ciclosporin undergoes minimal renal elimination and its pharmacokinetics are not extensively affected by renal impairment. However, due to its nephrotoxic potential (see **section 4.8**), careful monitoring of renal function is recommended (see **section 4.4**).

Non-transplantation indications

Patients with impaired renal function should not receive ciclosporin (see subsection on additional precautions in non-transplantation indications in **section 4.4**).

Patients with hepatic impairment

Ciclosporin is extensively metabolised by the liver. An approximate 2- to 3-fold increase

in ciclosporin exposure may be observed in patients with hepatic impairment. Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see **section 4.4**) and it is recommended that ciclosporin blood levels are monitored until stable levels are reached.

Paediatric population

Clinical studies have included children from 1 year of age. In several studies, paediatric patients required and tolerated higher doses of ciclosporin per kg body weight than those used in adults.

Use of SANDIMMUN in children for non-transplantation indications cannot be recommended (see **section 4.4**).

Elderly population (age 65 years and above)

Experience with SANDIMMUN in the elderly is limited.

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

Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or

cardiac function, and of concomitant disease or medication and increased susceptibility for infections.

Method of administration

Oral administration

SANDIMMUN NEORAL *capsules* should be swallowed whole.

SANDIMMUN NEORAL *oral solution* should be diluted with, preferably, orange or apple juice; however, other drinks such as soft drinks can be used according to individual taste. Immediately before taking the oral solution, it should be stirred well. Owing to its possible interference with the cytochrome P450-dependent enzyme system, grapefruit juice should be avoided for dilution (see **section 4.5**). The syringe should not come in contact with the diluent. If the syringe is to be cleaned, do not rinse it but wipe the outside with a dry tissue (see **section 6.6**).

Intravenous administration

The types of containers suitable for the infusion solution are mentioned in **section 6.6**. Because of the risk of anaphylaxis (see **section 4.4**), the use of the SANDIMMUN concentrate for solution for infusion should be reserved for organ transplant patients who are unable to take the medicine orally (e.g. shortly after surgery) or in whom the absorption of the oral forms might be impaired during episodes of gastrointestinal disorders. In such cases, it is recommended to change to oral administration as soon

as feasible. Another well-established use of the concentrate for solution for infusion consists in the initial treatment of patients with bone marrow transplantation.

The concentrate for solution for infusion should be diluted 1:20 to 1:100 with normal saline or 5 % glucose and given as a slow i.v. infusion over approximately 2 to 6 hours. Once an ampoule is opened, the content should be used immediately. Diluted infusion solutions must be discarded after 24 hours.

4.3 Contraindications

All indications:

Known hypersensitivity to ciclosporin.

When using SANDIMMUN concentrate for solution for infusion: hypersensitivity to *Cremophor*® EL (polyoxyl castor oil). (see **section 4.4**)

For non-transplant indications:

Abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy.

4.4 Special warnings and precautions for use

All indications

Medical supervision

SANDIMMUN NEORAL and SANDIMMUN concentrate for solution for infusion should

be prescribed only by physicians who are experienced in immunosuppressive therapy, and can provide adequate follow-up, including regular full physical examination, measurement of blood pressure, and control of laboratory safety parameters. Transplantation patients receiving the medicine should be managed in facilities with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should receive complete information for the follow-up of the patient.

Polyoxyl castor oil in the i.v. formulation and anaphylactoid reactions

SANDIMMUN concentrate for solution for infusion contains polyoxyl castor oil, which following i.v. administration has been reported to cause anaphylactoid reactions. These reactions can consist of flushing of the face and upper thorax, and non-cardiogenic pulmonary oedema, with acute respiratory distress, dyspnoea, wheezing and blood pressure changes and tachycardia. Special caution is therefore necessary in patients who have previously received, by i.v. injection or infusion, preparations containing polyoxyl castor oil (e.g. a preparation containing Cremophor® EL), and in patients with an allergic predisposition. Thus, patients receiving SANDIMMUN concentrate for solution for infusion should be under continuous observation for at least the first 30 minutes after the start of the infusion and at frequent intervals thereafter. If anaphylaxis occurs, the infusion should be discontinued. An aqueous solution of adrenaline 1:1000 and a source of oxygen should be available at the bedside. Prophylactic administration of an antihistaminic (H1 + H2 blocker) prior to SANDIMMUN concentrate for solution for infusion has also been successfully employed to prevent the occurrence of anaphylactoid reactions.

Lymphomas and other malignancies

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

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

Infections

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

strategies should be employed particularly in patients on multiple long-term immunosuppressive therapy.

Acute and chronic nephrotoxicity

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

Hepatotoxicity and liver injury

Ciclosporin may also cause dose-dependent, reversible increases in serum bilirubin and, in liver enzymes (see **section 4.8**). There have been solicited and spontaneous reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients treated with ciclosporin. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and co-medications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see **section 4.8**). Close monitoring of parameters that assess hepatic function is required. Abnormal values may necessitate dose reduction (see **sections 4.2** and **5.2**).

Elderly population (age 65 years and above)

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

Monitoring ciclosporin levels in transplant patients

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

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

Hypertension

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

Preference should be given to an antihypertensive agent that does not interfere with the pharmacokinetics of ciclosporin, e.g., isradipine (see **section 4.5**).

Blood lipids increased

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

Hyperkalaemia

Ciclosporin enhances the risk of hyperkalaemia, especially in patients with renal dysfunction. Caution is also required when ciclosporin is co-administered with potassium sparing medicines (e.g., potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) and potassium containing medicinal products as well as in patients on a potassium rich diet. Control of potassium levels in these situations is advisable.

Hypomagnesaemia

Ciclosporin enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplant period. Control of serum magnesium levels is therefore recommended in the peri-transplant period, particularly in the

presence of neurological symptoms /signs. If considered necessary, magnesium supplementation should be given.

Hyperuricaemia

Caution is required in treating patients with hyperuricaemia.

Live-attenuated vaccines

During treatment with ciclosporin, vaccination may be less effective; the use of live-attenuated vaccines should be avoided (see **section 4.5**).

Interactions

Caution should be observed while co-administering with drugs that substantially increase or decrease ciclosporin plasma concentrations, through inhibition or induction of CYP3A4 and/or Pglycoprotein. (see **section 4.5**).

Renal toxicity should be monitored when initiating ciclosporin use together with active substances that increase ciclosporin levels or with substances that exhibit nephrotoxic synergy (see **section 4.5**). The clinical condition of the patient should be monitored closely. Monitoring of ciclosporin blood levels and adjustment of the ciclosporin dose may be required.

Caution should be observed while co-administering ciclosporin with lercanidipine.

Ciclosporin may increase blood levels of concomitant medications that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) such as aliskiren, dabigatran or bosentan.

Co-administration of ciclosporin with aliskiren is not recommended. Co-administration of ciclosporin together with dabigatran or bosentan should be avoided. These recommendations are based upon the potential clinical impact of these interactions (see **section 4.5**).

Special Excipients: Ethanol

SANDIMMUN NEORAL contains around 12 % vol. ethanol. A 500 mg dose of SANDIMMUN NEORAL contains 500 mg ethanol, equivalent to nearly 15 mL beer or 5 mL wine. SANDIMMUN concentrate solution for intravenous infusion contains around 34.4 % vol. ethanol. A 100 mg dose of SANDIMMUN concentrate solution contains 556 mg ethanol, equivalent to nearly 15 mL beer or 5 mL wine. This may be harmful in alcoholic patients and should be taken into account in pregnant or breast-feeding women, in patients presenting with liver disease or epilepsy, or if the patient is a child.

Additional precautions in non-transplant indications

Patients with impaired renal function, uncontrolled hypertension, uncontrolled infections, or any kind of malignancy should not receive SANDIMMUN NEORAL.

Additional precautions in rheumatoid arthritis

Since SANDIMMUN NEORAL can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals for the first 3 months of therapy and thereafter once a month. After 6 months of therapy, serum creatinine needs to be measured every 4 to 8 weeks depending on the stability of the disease, its co-medication, and concomitant diseases. More frequent checks are necessary when the SANDIMMUN NEORAL dose is increased, or concomitant treatment with a non-steroidal anti-inflammatory medicine is initiated or its dosage increased.

If the serum creatinine remains increased to more than 30% above baseline at more than one measurement, the dosage of SANDIMMUN NEORAL should be reduced. If the serum creatinine increases by more than 50%, a dosage reduction by 50% is mandatory. These recommendations apply even if the patient's values still lie within the laboratory's normal range. If dose reduction is not successful in reducing levels within one month, SANDIMMUN NEORAL treatment should be discontinued.

Discontinuation of treatment may also become necessary if hypertension developing during SANDIMMUN NEORAL therapy cannot be controlled by appropriate antihypertensive therapy.

As with other long-term immunosuppressive treatments (including ciclosporin), an

increased risk of lymphoproliferative disorders must be borne in mind. Special caution should be observed if SANDIMMUN NEORAL is used in combination with methotrexate.

Additional precautions in psoriasis

Since SANDIMMUN NEORAL can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals for the first 3 months of therapy. Thereafter, if creatinine remains stable, measurements should be made at monthly intervals. If the serum creatinine increases and remains increased to more than 30% above baseline at more than one measurement, the dosage of SANDIMMUN NEORAL must be reduced by 25 to 50%. If the increase from baseline exceeds 50%, further reduction should be considered. These recommendations apply even if the patient's creatinine values still lie within the laboratory's normal range. If dose reduction is not successful in reducing creatinine levels within one month, SANDIMMUN NEORAL treatment should be discontinued.

Discontinuation of SANDIMMUN NEORAL therapy is also recommended if hypertension developing during SANDIMMUN NEORAL treatment cannot be controlled with appropriate therapy.

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

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

In psoriatic patients on ciclosporin, as in those on conventional immunosuppressive therapy, development of malignancies (in particular of the skin) has been reported. Skin lesions not typical for psoriasis, but suspected to be malignant or pre-malignant should be biopsied before SANDIMMUN NEORAL treatment is started. Patients with malignant or pre-malignant alterations of the skin should be treated with SANDIMMUN NEORAL only after appropriate treatment of such lesions, and if no other option for successful therapy exists.

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

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

Additional precautions in atopic dermatitis

Since SANDIMMUN NEORAL can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals for the first 3 months of therapy. Thereafter, if creatinine remains stable, measurements should be made at

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

Discontinuation of SANDIMMUN NEORAL therapy is also recommended if hypertension developing during treatment cannot be controlled with appropriate therapy.

The experience with SANDIMMUN NEORAL in children with atopic dermatitis is limited. Elderly patients should be treated only in the presence of disabling atopic dermatitis and renal function should be monitored with particular care.

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

Active herpes simplex infections should be allowed to clear before treatment with SANDIMMUN NEORAL is initiated, but are not necessarily a reason for treatment 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 controlled with appropriate antibacterial agents. Oral erythromycin, known to have the potential to increase the blood concentration of ciclosporin (see **section 4.5**) should be avoided, or, if there is no alternative, it is recommended to closely monitor blood levels of ciclosporin, renal function, and for side effects of ciclosporin.

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

4.5 Interaction with other medicines and other forms of interaction

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

Interactions resulting in concomitant use not being recommended

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

Interactions to be considered

Caution is required for concomitant use of potassium sparing medicinal products (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) or potassium containing medicinal products since they may lead to significant increases in serum potassium (see **section 4.4**).

Following concomitant administration of ciclosporin and lercanidipine, the AUC of lercanidipine was increased three-fold and the AUC of ciclosporin was increased 21%. Therefore, caution is recommended when co-administering ciclosporin together with lercanidipine (see **section 4.4**).

Care should be taken when using ciclosporin together with methotrexate in rheumatoid arthritis patients due to the risk of nephrotoxic synergy (see **section 4.4**).

Interactions increasing or decreasing ciclosporin levels to be considered

Various agents are known to either increase or decrease plasma or whole blood ciclosporin levels usually by inhibition or induction of enzymes involved in the metabolism of ciclosporin, in particular CYP3A4. Ciclosporin is a substrate of P-gp, hence inhibitors or inducers of P-gp may alter the concentrations of ciclosporin.

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

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

Interactions decreasing ciclosporin levels

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

Interactions increasing ciclosporin levels

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

Cannabidiol (P-gp inhibitor): There have been reports of increased blood levels of another calcineurin inhibitor during concomitant use with cannabidiol. This interaction may occur due to inhibition of intestinal P-glycoprotein efflux, leading to increased bioavailability of the calcineurin inhibitor. Ciclosporin and cannabidiol should therefore be co-administered with caution, closely monitoring for side effects. In transplant recipients, monitor ciclosporin whole blood trough concentrations and adjust the ciclosporin dose if needed. In non-transplant patients, monitoring of ciclosporin blood levels, with dose adjustment if needed, should be considered (see **sections 4.2** and **4.4**).

Other relevant interactions

Food interactions

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

Interactions resulting in a potential increased nephrotoxicity

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

Care should be taken when using ciclosporin together with other medicinal products that

exhibit nephrotoxic synergy such as: aminoglycosides (incl. gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); non-steroidal anti-inflammatory medicines (incl. diclofenac, naproxen, sulindac); melphalan, histamine H2-receptor-antagonists (e.g. cimetidine, ranitidine); methotrexate.

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

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

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

Interaction resulting in an increased rate of gingival hyperplasia

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

Interactions resulting in an increase of other medicine levels

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

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

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

Literature and post marketing cases of myotoxicity, including muscle pain and weakness,

myositis, and rhabdomyolysis, have been reported with concomitant administration of ciclosporin with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely, fluvastatin. When concurrently administered with ciclosporin, the dosage of these statins should be reduced according to label recommendations. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis.

If digoxin, colchicine or HMG-CoA reductase inhibitors (statins) are used concurrently with ciclosporin, close clinical observation is required in order to enable early detection of toxic manifestations of the medicines, followed by reduction of its dosage or its withdrawal. Elevations in serum creatinine were observed in the studies using everolimus or sirolimus in combination with full dose ciclosporin for microemulsion. This effect is often reversible with ciclosporin dose reduction. Everolimus and sirolimus had only a minor influence on ciclosporin pharmacokinetics. Co-administration of ciclosporin significantly increases blood levels of everolimus and sirolimus.

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

Co-administration of bosentan and ciclosporin in healthy volunteers resulted in an approximately 2-fold increase in bosentan exposure and a 35% decrease in ciclosporin

exposure (see above subsection drug interactions decreasing ciclosporin levels and **section 4.4**).

Following concomitant administration of ciclosporin and aliskiren, the Cmax of aliskiren was increased by approximately 2.5-fold and the AUC by approximately 5-fold. However, the pharmacokinetic profile of ciclosporin was not significantly altered (see **section4.4**).
Concomitant administration of dabigatran and ciclosporin leads to increased plasma level of dabigatran due to the P-gp inhibitory activity of ciclosporin (see **section 4.4**).
Dabigatran has a narrow therapeutic index and an increase in plasma level may be associated with an increased risk of bleeding.

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

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

Interactions resulting in decrease of other drug levels

Concomitant administration of ciclosporin and mycophenolate sodium or mofetil in transplant patients may decrease the mean exposure of mycophenolic acid by 20-50%

when compared with other immunosuppressants. This information should be taken into consideration when coadministering these drugs.

The coadministration of a single dose of ciclosporin (200 mg or 600 mg) with a single dose of eltrombopag (50 mg) decreased plasma eltrombopag AUC_{inf} by 18% to 24% and Cmax by 25% to 39%. This decrease in exposure is not considered clinically meaningful.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies have shown reproductive toxicity in rats and rabbits.

There are no adequate or well-controlled clinical studies in pregnant women using ciclosporin.

There is a moderate amount of data on the use of ciclosporin in pregnant patients from post-marketing experience, including published literature. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks). The data have not demonstrated a higher incidence of miscarriages, major birth defects, or maternal events as compared to the rates seen in the general population.

Published data from National Transplantation Pregnancy Registry (NTPR), described pregnancy outcomes in female kidney (482), liver (97), and heart (43) transplant

recipients receiving ciclosporin. The data indicated successful pregnancies with a live birth rate of 76% and 76.9%, and 64% in kidney, liver, and heart transplant recipients, respectively. Premature delivery (<37 weeks) was reported in 52%, 35%, and 35% of kidney, liver, and heart transplant recipients, respectively.

The rates of miscarriages and major birth defects were reported to be comparable to the rates observed in the general population. No direct effect of ciclosporin on maternal hypertension, pre-eclampsia, infections, or diabetes can be established given the limitations inherent to registries and post-marketing safety reporting.

A limited number of observations in children exposed to ciclosporin *in utero* are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal. SANDIMMUN NEORAL should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. The ethanol content of the SANDIMMUN NEORAL formulations should also be taken into account in pregnant women (see **section 4.4**).

Breast-feeding

Ciclosporin passes into breast milk. Mothers receiving treatment with SANDIMMUN should not breast-feed because of the potential of SANDIMMUN to cause serious adverse drug reactions in breast-fed newborns/infants. A decision should be made whether to abstain from breast-feeding or to abstain from using the medicinal product,

taking into account the benefit of breast-feeding for the newborn/infant and the importance of the medicinal product to the mother.

The milk to maternal blood concentration ratio of ciclosporin was in the range of 0.17 to 1.4. Based on the infant milk intake, the highest estimated ciclosporin dose ingested by fully breast-fed infant was approximately 2% of maternal weight adjusted dose**.**

The ethanol content of the SANDIMMUN formulations should also be taken into account in women who are breast-feeding (see **section 4.4**).

Fertility

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

4.7 Effects on ability to drive and use machines

SANDIMMUN NEORAL may cause neurological and visual disturbances (see **section 4.8**). Caution should be exercised when driving a motor vehicle or operating machines. No studies on the effects of SANDIMMUN NEORAL on the ability to drive and use machines have been performed**.**

4.8 Undesirable effects

Summary of the safety profile

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

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

Anaphylactoid reactions have been observed following intravenous administration (see **section 4.4**).

Infections and infestations

Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic) (see section 4.4). Both generalised and localised infections can occur. Pre-existing infections may also be aggravated and reactivation of polyomavirus infections may lead to polyomavirus-associated nephropathy (PVAN) or to JC virus associated progressive multifocal leukopathy (PML). Serious and/or fatal outcomes have been reported.

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

Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin containing regimens, are at increased risk of developing lymphomas or lymphoproliferative disorders and other malignancies, particularly of the skin.

The frequency of malignancies increases with the intensity and duration of therapy (see section 4.4). Some malignancies may be fatal.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1: Adverse drug reactions from clinical trials

Blood and lymphatic system disorders	
Common	Leucopenia
Uncommon	Thrombocytopenia, anaemia

Rare	Haemolytic uraemic syndrome, microangiopathic haemolytic anaemia
Not known*	Thrombotic microangiopathy, thrombotic thrombocytopenic purpura
Metabolism and nutrition disorders	
Very common	Hyperlipidaemia
Common	Hyperglycaemia, anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia
Nervous system disorders	
Very common	Tremor, headache
Common	Convulsions, paraesthesia
Uncommon	Encephalopathy including Posterior Reversible Encephalopathy Syndrome (PRES), signs and symptoms such as convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis and cerebellar ataxia
Rare	Motor polyneuropathy
Very rare	Optic disc oedema, including papilloedema, with possible visual impairment secondary to benign intracranial hypertension
Not known*	Migraine
Vascular disorders	
Very common	Hypertension

Common	Flushing
Gastrointestinal disorders	
Common	Nausea, vomiting, abdominal discomfort/pain, diarrhoea, gingival hyperplasia, peptic ulcer
Rare	Pancreatitis
Hepatobiliary disorders	
Common	Hepatic function abnormal (see **section 4.4**)
Not known*	Hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure with some fatal outcome (see **section 4.4**)
Skin and subcutaneous tissue disorders	
Very common	Hirsutism
Common	Acne, hypertrichosis
Uncommon	Allergic rashes
Musculoskeletal and connective tissue disorders	
Common	Myalgia, muscle cramps
Rare	Muscle weakness, myopathy
Not known*	Pain of lower extremities
Renal and urinary disorders	
Very common	Renal dysfunction (see **section 4.4**)
Reproductive system and breast disorders	
Rare	Menstrual disturbances, gynaecomastia

General disorders and administration site conditions	
Common	Pyrexia, fatigue
Uncommon	Oedema, weight increase

* Adverse events reported from post marketing experience where the ADR frequency is not known due to the lack of a real denominator.

Other adverse drug reactions from post-marketing experience

There have been solicited and spontaneous reports of hepatotoxicity and liver injury including cholestasis, jaundice hepatitis and liver 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 **section 4.4**).

Acute and chronic nephrotoxicity

Patients receiving calcineurin inhibitor (CNI) therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of acute or chronic nephrotoxicity. There have been reports from clinical trials and from the post-marketing setting associated with the use of SANDIMMUN. Cases of acute nephrotoxicity reported disorders of ion homeostasis, such as hyperkalaemia, hypomagnesaemia, and hyperuricaemia. Cases reporting chronic morphological changes included arteriolar hyalinosis, tubular atrophy and interstitial fibrosis (see **section 4.4)**.

Pain of lower extremities

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

Paediatric population

Clinical studies have included children from 1 year of age using standard ciclosporin dosage with a comparable safety profile to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Little experience is available with acute overdosage. Signs of nephrotoxicity might occur. 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 intoxications have been reported following accidental parenteral overdosage in premature neonates.

Treatment:

Symptomatic treatment and general supportive measures should be followed in all cases of overdosage. Forced emesis and gastric lavage could be of value within the first few hours after intake of the oral dosage forms. SANDIMMUN concentrate for solution for infusion /SANDIMMUN NEORAL is not dialysable to any great extent, nor is it effectively cleared with charcoal haemoperfusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 34 Other

Ciclosporin, a cyclic polypeptide consisting of 11 amino acids, is a potent immunosuppressive agent. The exact mechanism of action of ciclosporin is not yet known. Animal studies suggest that ciclosporin inhibits the development of cell-mediated reactions, including allograft immunity, delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund’s adjuvant arthritis, graft-versus-host disease (GVHD) and also T-cell dependent antibody production.

Experimental evidence suggests that the effectiveness of ciclosporin is due to a specific and reversible inhibition of immunocompetent lymphocytes in the G_0 and G_1 phase of the cell cycle, with preference for T-lymphocytes among which the T-helper cells are the main target. Thereby ciclosporin inhibits the production and release of lymphokines including interleukin 2 (IL-2, T-cell growth factor). Ciclosporin does not depress haematopoiesis and does not impair the function of phagocytic cells.

5.2 Pharmacokinetic properties

In patients with renal failure the intravenous infusion of 3,5 mg/kg over 4 hours resulted in a mean peak blood level of 1 800 ng/mL (range 1 536 to 2 331 ng/mL).

Within the blood, distribution is concentration dependent, with 33 to 47 % present in plasma, 4 to 9 % in lymphocytes, 5 to 12 % in granulocytes, and 41 to 58 % in erythrocytes. At high concentrations the uptake by leucocytes and erythrocytes becomes saturated.

Ciclosporin is extensively metabolised to more than 15 metabolites. The main site of metabolism is the cytochrome P450-dependent mono-oxygenase system in the liver, and the main pathways of metabolism consist of mono- and dihydroxylation and N-demethylation at various positions of the molecule.

Agents known to inhibit or induce the cytochrome P450-dependent enzyme system have

been found to increase or decrease ciclosporin levels (see section 4.5). All metabolites identified so far contain the intact peptide structure of the parent compound; some possess weak immunosuppressive activity (up to one-tenth that of the unchanged medicine).

There is a high variability in the data reported on the terminal half-life of ciclosporin depending on the assay applied and on the target population. The terminal half-life ranged from 6,3 hours in healthy volunteers to 20,4 hours in patients with severe liver disease.

Parent compound and metabolites are excreted mainly via the bile, with only 6 % of the oral dose excreted in the urine and with less than 1 % in the unchanged form.
Within the plasma, ciclosporin is 90 % bound to proteins, mostly lipoproteins.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SANDIMMUN concentrate for solution for infusion

Ethanol anhydrous, polyoxyl 35 castor oil. SANDIMMUN concentrate for solution for infusion contains 34.4 % v/v ethanol (27.8 % w/v)

SANDIMMUN NEORAL Oral solution

alpha–tocopherol, ethanol anhydrous, propylene glycol, corn oil-mono–di–triglycerides,

polyoxyl 40 hydrogenated castor oil. SANDIMMUN NEORAL oral solution contains 12 % v/v ethanol (9.5 % w/v)

SANDIMMUN NEORAL Capsules

Capsule content:

alpha–tocopherol, ethanol anhydrous, propylene glycol, corn oil–mono–di–triglycerides, 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)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

SANDIMMUN Ampoule 50 mg per 1 mL: 4 years

SANDIMMUN NEORAL Drink Solution 100 mg per 1 mL: 3 years

SANDIMMUN NEORAL Capsule 25 mg: 2 years

SANDIMMUN NEORAL Capsule 100 mg: 2 years

6.4 Special precautions for storage

Ampoules and capsules*:* Store below 25 °C. Protect from light.

Drink solution: Store between 15 and 30 °C. Use contents within two months after opening the bottle. Protect from light.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

Ampoule (concentrate for solution for infusion) 50 mg per 1 mL: Carton of 10 ampoules of 1 mL each.

Drink Solution 100 mg per 1 mL: Amber bottle of 50 mL with a rubber stopper and a grey screw aluminium cap. Each bottle is supplied with a 1 mL and 4 mL pipette and plunger.

Capsule 25 mg: Carton containing 50 blister-packed capsules.

Capsule 100 mg: Carton containing 50 blister-packed capsules.

6.6 Special precautions for disposal and other handling

Capsules:

Capsules should be swallowed whole. Leave capsules in blister pack until required for use. Capsules should not be stored above 25 °C.

Occasional increases in temperatures up to 30 °C do not affect the quality of the product.

When a blister pack is opened, a characteristic smell is noticeable. This is normal and does not mean that there is anything wrong with the capsules.

Concentrate for infusion:

Polyoxyl castor oil contained in the concentrate can cause phthalate stripping from PVC. If available, glass containers should be used. Plastic bottles should only be used if they conform to the requirements for "Sterile plastic containers for human blood and blood components", or "Empty sterile containers of plasticised polyvinylchloride for human blood and blood components" of the current European Pharmacopoeia. Containers and stoppers should be free of silicone oil and fatty substances.

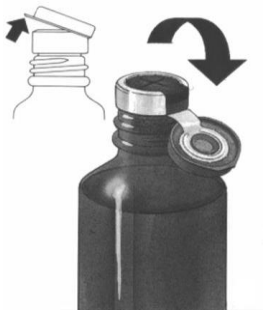
Oral drink solution:

SANDIMMUN NEORAL drink solution is provided with two syringes for measuring the doses. The 1-mL syringe is used to measure doses less than or equal to 1 mL (each graduation of 0,05 mL corresponds to 5 mg of ciclosporin). The 4-mL syringe is used to

measure doses greater than 1 mL and up to 4 mL (each graduation of 0,1 mL corresponds to 10 mg of ciclosporin).

Initial use of SANDIMMUN NEORAL drink solution:

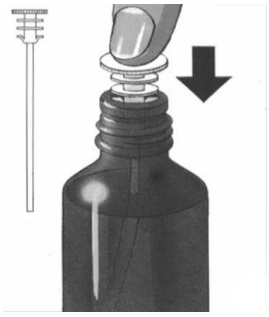
1. Raise flap in centre of the metal sealing ring.



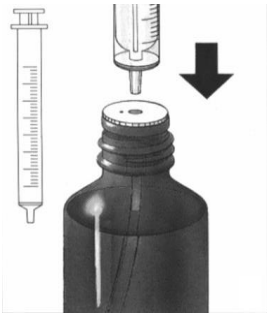
2. Tear off the sealing ring completely.

3. Remove the grey stopper and throw it away.

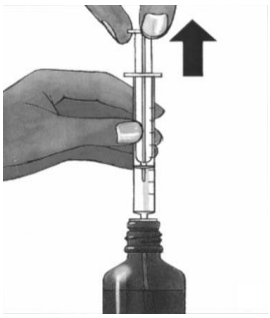
4. Push the tube unit with the white stopper firmly into the neck of the bottle.



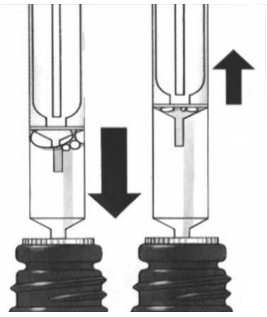
5. Choose the syringe depending on the prescribed volume. For volume less than 1 mL or equal to 1 mL, use the 1 mL syringe. For volume greater than 1 mL, use the 4 mL syringe. Insert the nozzle of the syringe into the white stopper.



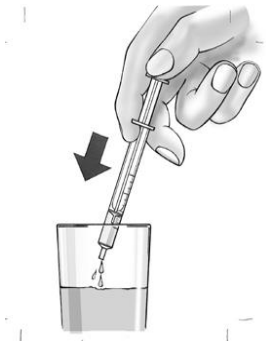
6. Draw up prescribed volume of solution (position the lower part of the plunger ring in front of the graduation corresponding to the prescribed volume).



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



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



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

The syringe should not come in contact with the diluent. The glass must be rinsed well

with some diluent to ensure that all the dose is taken. If the syringe is to be cleaned, do not rinse it but wipe the outside with a dry tissue.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

Magwa Crescent West,

Waterfall City,

Jukskei view,

Johannesburg,

2090

Tel. (011) 347 6600

8. REGISTRATION NUMBERS

SANDIMMUN ® Ampoule 50 mg per 1 mL: R/34/267

SANDIMMUN NEORAL® Drink Solution 100 mg per 1 mL: 29/34/0059

SANDIMMUN NEORAL® Capsule 25 mg: 29/34/0056

SANDIMMUN NEORAL® Capsule 100 mg: 29/34/0058

9. DATE OF FIRST AUTHORISATION

09 December 2008

10. DATE OF REVISION OF THE TEXT

13 January 2025

Namibia		
SANDIMMUN NEORAL® 25 mg Capsules	04/34/0543	NS2
SANDIMMUN NEORAL® 100 mg Capsules	04/34/0545	NS2
Botswana		
SANDIMMUN NEORAL® 25 mg Capsules	B9310640	S2
SANDIMMUN NEORAL® 100 mg Capsules	B9310645	S2

Namibia		
SANDIMMUN NEORAL® 100 mg/mL Solution	04/34/0542	NS2
Botswana		
SANDIMMUN NEORAL® 100 mg/mL Solution	B9310635	S2

Namibia		
SANDIMMUN® Ampoules 50 mg/mL	90/34/00719	NS2
Botswana		
SANDIMMUN® Ampoules 50 mg/mL	B9310625	S2