NOVARTIS

Drug Regulatory Affairs

SANDIMMUN®

(ciclosporin)

25 mg, 50 mg or 100 mg soft gelatine capsules
100 mg/mL oral solution
50 mg/mL concentrate for solution for infusion

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Trade name of the medicinal product

SANDIMMUN®

2 Qualitative and quantitative composition

Soft gelatine capsules containing 25 mg, 50 mg or 100 mg ciclosporin.

Oral solution containing 100 mg ciclosporin per mL.

Concentrate for solution for infusion containing 50 mg ciclosporin per mL.

For a full list of excipients see section 6.1 List of excipients.

3 Pharmaceutical form

Soft gelatine capsules and oral solution for oral administration.

Concentrate for solution for infusion.

4 Clinical particulars

4.1 Therapeutic indications

Solid organ transplantation

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

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

Bone marrow transplantation

Prevention of graft rejection and of graft-versus-host disease (GVHD) following bone marrow transplantation.

Treatment of established graft-versus-host disease (GVHD).

Endogenous uveitis

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

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

Nephrotic syndrome

Induction and maintenance of remission in patients with steroid-dependent or steroid-resistant nephrotic syndrome caused by glomerular diseases such as minimal change nephropathy, focal or segmental glomerulosclerosis, or membranous glomerulonephritis.

Maintenance of steroid-induced remission, allowing dose reduction or withdrawal of steroids.

Rheumatoid arthritis

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

Psoriasis

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

Atopic dermatitis

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

4.2 Posology and method of administration

General remarks, instructions, and practical recommendations

For most clinical conditions the recommended route of Sandimmun administration is by oral intake. For exceptions see below: *Sandimmun concentrate for solution for infusion*.

When *oral forms (oral solution, capsules)* are used, the daily dose is preferably given in two divided doses. In transplant patients a single daily dose may be used, although in kidney transplantation the change from twice- to once-a-day administration has been associated with an increased risk of organ rejection.

Sandimmun oral solution should be diluted in a glass (not plastic) container with cold chocolate drink, milk, fruit juice or cola immediately before being taken, stirred well and drunk at once. Owing to its possible interference with the cytochrome P450 enzyme system, grapefruit juice should be avoided for dilution. The syringe should not come in contact with the diluent. The glass must be rinsed well with some more diluent to ensure that all of the dose is taken. The syringe should not be rinsed, but wiped outside with a dry tissue to remove remaining drops of the solution (see section 6.6 Instructions for use/handling).

Sandimmun capsules should be swallowed whole.

Conversion between oral ciclosporin formulations: Switching from one oral ciclosporin formulation to another should be made with caution and under physician supervision. The introduction of the new formulation must be made with monitoring of blood levels of ciclosporin to ensure that pre-conversion levels are attained [57].

Sandimmun concentrate for solution for infusion: Because of the risk of anaphylaxis (see section 4.4 Special warnings and precautions for use) the use of this preparation should be reserved for organ transplant patients who are unable to take the drug 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 2 to 6 hours. Once an ampoule is opened, the contents should be used immediately. Diluted infusion solutions must be discarded after 24 hours.

Because of considerable inter- and intraindividual variations in absorption and elimination and the possibility of pharmacokinetic drug interactions (see section 4.5 Interaction with other medicinal products and other forms of interaction), 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. This can best be carried out in whole blood by radioimmunoassay with the use of one of the commercially available specific monoclonal antibodies (measuring parent drug concentrations), although the HPLC method can be used. If plasma or serum are used, a standard separation protocol (related to time and temperature) should be followed. It must be remembered that ciclosporin concentration is only one of many factors contributing to the clinical status of the patient. Results should therefore serve only as a guide to dosing in the context of other clinical and laboratory parameters.

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.

Use in children

In paediatric usage, the same Sandimmun dose and dosing regimen may generally be used as in adults, although in several studies children have required and tolerated higher doses than those used in adults.

Use in the elderly

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

In rheumatoid arthritis clinical trials with ciclosporin, 17.5% of patients were aged 65 or older. These patients were more likely to develop systolic hypertension on therapy, and more likely to show serum creatinine rises ≥50% above the baseline after 3 to 4 months of therapy [29].

Clinical studies of Neoral in transplant and psoriasis patients did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from

younger subjects. Other reported clinical experiences have not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [29].

Indication-specific dosage recommendations

Transplantation

Solid organ transplantation

To initiate treatment, a single oral dose of 10 to 15 mg/kg may be given 4 to 12 hours prior to surgery. This dose is continued as the daily dose for one to two weeks post-operatively. It should then be gradually reduced until in the individual patient the target blood concentration and the most appropriate maintenance dose, usually in the range of 2 to 6 mg/kg per day, are attained. In renal transplant patients, doses from the lower end of this range, i.e. below 3 to 4 mg/kg per day, resulting in trough blood levels below 50 to 100 ng/mL, have been found to be associated with an increased risk of rejection episodes.

More recently, many transplant centres prefer, for the initial phase of treatment, the use of lower doses of Sandimmun (e.g. oral doses of 3 to 6 mg/kg per day) in combination with corticosteroids and other immunosuppressants, as part of a triple or quadruple drug therapy.

Patients in whom the use of Sandimmun concentrate for solution for infusion is indicated should receive about one-third of the recommended oral dose.

Bone marrow transplantation

For the *initiation of Sandimmun therapy* the preferred route of administration is by intravenous infusion. The recommended i.v. dosage is 3 to 5 mg/kg per day, starting on the day before transplantation and continuing for up to 2 weeks before a change to oral maintenance treatment is made (longer periods of i.v. infusion treatment may be required in patients unable to take the drug orally or in the presence of impaired gastrointestinal absorption). If additional immunosuppressant agents are used, the Sandimmun dosage regimen for initial treatment should not be reduced.

For oral *maintenance therapy* the recommended starting dose is 10 to 12.5 mg/kg per day. This dose should then be adjusted according to ciclosporin blood levels, clinical effectiveness and tolerability. Maintenance treatment should be continued for at least three, preferably six months. Thereafter the dose should be gradually reduced, and treatment may be withdrawn one year after transplantation. If during the dose-reduction period signs of graft-versus-host disease (GVHD) occur, the Sandimmun dose should be increased to the level found to be effective during the foregoing maintenance therapy.

In some patients GVHD occurs after withdrawal of Sandimmun. 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 Sandimmun may be used to treat mild, chronic GVHD.

Non-transplant indications

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

Before initiation of treatment a reliable baseline level of serum creatinine should be established by at least two measurements, and renal function must be assessed regularly throughout therapy to allow dosage adjustment (see `Additional precautions in non-transplant indications' in section 4.4 Special warnings and precautions for use).

The only accepted route of administration is by mouth (the concentrate for intravenous infusion must not be used), and the daily dose should be given in two divided doses.

Except in patients with sight-threatening endogenous uveitis and in children with nephrotic syndrome, the total daily dose must never exceed 5 mg/kg.

For maintenance treatment the lowest effective and well tolerated dosage should be determined individually.

In patients in whom within a given time (for specific information see below) no adequate response is achieved or the effective dose is not compatible with the established safety guidelines (see `Additional precautions in non-transplant indications' in section 4.4 Special warnings and precautions for use), treatment with Sandimmun should be discontinued.

Endogenous uveitis

For *inducing remission*, the recommended dose is 5 mg/kg per day, given in two divided oral doses, until control of active uveal inflammation and improvement in visual acuity are achieved. In refractory cases, the dose may be increased to 7 mg/kg per day for a limited period. If Sandimmun alone does not control the situation sufficiently, oral corticosteroid treatment with daily doses of 0.2 to 0.6 mg/kg prednisone (or an equivalent) may be added. If no apparent benefit occurs within 3 months of treatment, Sandimmun should be discontinued.

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

Nephrotic syndrome

For *inducing remission*, the recommended daily dose, given in two divided oral doses, is 5 mg/kg for adults and 6 mg/kg for children, except in patients with a permissible degree of renal function impairment (maximal serum creatinine levels of 200 micro mol/L in adults and 140 micro mol/L in children), in whom the initial dose should not exceed 2.5 mg/kg per day.

The combination of Sandimmun with low doses of oral corticosteroids is recommended if the efficacy of Sandimmun alone is not satisfactory. The doses of Sandimmun need to be individually adjusted according to efficacy (proteinuria) and safety (primarily serum creatinine), but should not exceed 5 mg/kg per day in adults and 6 mg/kg per day in children.

In the absence of effectiveness after 3 months' treatment, Sandimmun should be discontinued.

For *maintenance treatment*, the dosage should be titrated individually to the lowest effective level.

Rheumatoid arthritis

For the *first 6 weeks of treatment* the recommended dose is 3 mg/kg per day given in two divided oral doses. If within this period no satisfactory effect occurs, the daily dose may be increased gradually as tolerability permits, but should not exceed 5 mg/kg.

Sandimmun may be given in combination with low-dose corticosteroids and/or non-steroidal anti-inflammatory drugs (see ‘Additional precautions in non-transplant indications' in section 4.4 Special warnings and precautions for use).

If no apparent benefit is seen by 3 months of treatment, Sandimmun should be discontinued.

For *maintenance treatment* the dosage should be titrated individually to the lowest effective level.

Psoriasis

For *inducing remission*, the recommended dose is 2.5 mg/kg per day given in two divided oral doses. If there is no improvement after one month of therapy, the daily dose may be gradually increased, but should not exceed 5 mg/kg. Initial doses of 5 mg/kg per day are permissible in patients whose condition requires rapid improvement. Treatment should be discontinued in patients in whom sufficient response cannot be achieved within 6 weeks on 5 mg/kg per day, or in whom the effective dose is not compatible with the safety guidelines given below (see ‘Additional precautions in non-transplant indications’ in section 4.4 Special warnings and precautions for use).

For *maintenance treatment*, the dosage should be titrated individually to the lowest effective level.

Atopic dermatitis

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 two weeks of therapy, the daily dose may be rapidly increased to a maximum of 5 mg/kg. In very severe cases, rapid and adequate control of the disease is more likely to occur with a starting dose of 5 mg/kg per day.

Since the experience with long-term use of Sandimmun in atopic dermatitis is still limited, it is recommended that the duration of a single treatment course should not exceed 8 weeks.

4.3 Contraindications

Known hypersensitivity to ciclosporin or to any of the excipients of Sandimmun.

When using Sandimmun concentrate for solution for infusion: hypersensitivity to polyethoxylated castor oil (see section 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

All indications

Sandimmun should be prescribed only by physicians who are experienced in immunosuppressive therapy and in the management of the condition for which the drug is being used.

Patients receiving Sandimmun should be managed in facilities equipped with adequate laboratory and medical resources. Provision should also be made for an adequate follow-up, including regular full physical examination, measurement of blood pressure and control of safety parameters, in particular serum creatinine (see below). The physician responsible for maintenance therapy should receive complete information for the follow-up of the patient.

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, in particular those treated for psoriasis or atopic dermatitis, should be warned to avoid excess unprotected sun exposure and should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy [48].

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) [56], or to JC virus associated progressive multifocal leukoencephalopathy (PML) have been observed in patients receiving ciclosporin [55]. 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 [56]**.** Serious and/or fatal outcome**s** have been reported**.** Effective pre-emptive and therapeutic strategies should be employed particularly in patients on multiple long-term immunosuppressive therapy.

As a frequent and potentially serious complication, increases in serum creatinine and urea may occur during the first few weeks of Sandimmun therapy. These functional changes are dose-dependent and reversible, usually responding to dose reduction. During long-term treatment structural changes in the kidney (e.g. interstitial fibrosis) may develop in some patients; in renal transplant patients these changes must be differentiated from changes associated with chronic rejection. Sandimmun may also cause dose-dependent, reversible increases in serum bilirubin and, occasionally, in liver enzymes (see section 4.8 Undesirable effects). There have been solicited and spontaneous postmarketing reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients treated with ciclosporin. Most reports included patients with significant co-morbidities, underlying

conditions and other confounding factors including infectious complications and comedications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see section 4.8 Undesirable effects) [59]. Close monitoring of parameters that assess renal and hepatic function is required. Abnormal values may necessitate dose reduction.

In elderly patients, renal function should be monitored with particular care [48].

When Sandimmun is used in transplant patients, routine monitoring of ciclosporin blood levels is an important safety measure (see `General remarks, instructions, and practical recommendations' in section 4.2 Posology and method of administration).

Regular monitoring of blood pressure is required during Sandimmun 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 Interaction with other medicinal products and other forms of interaction).

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

Ciclosporin enhances the risk of hyperkalaemia, especially in patients with renal dysfunction. Caution is also required when ciclosporin is co-administered with potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors [1], angiotensin II receptor antagonists [2]) and potassium containing drugs as well as in patients on a potassium rich diet (see section 4.5 Interaction with other medicinal products and other forms of interaction). Control of potassium levels in these situations is advisable.

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 symptom/signs. If considered necessary, magnesium supplementation should be given [3].

Caution is required in patients with hyperuricaemia.

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

Caution should be observed while co-administering lercanidipine with ciclosporin (see section 4.5 Interaction with other medicinal products and other forms of interaction) [49].

Ciclosporin may increase blood levels of concomitant medications that are substrates of P-glycoprotein (Pgp) such as aliskiren (see Section 4.5 Interaction other medicinal products and other forms of interaction) [60].

The concentrate for solution for infusion contains polyethoxylated castor oil (see section 6.1 List of excipients), which has been reported to cause anaphylactoid reactions. These reactions can consist of flushing of the face and upper thorax, and non-cardiogenic pulmonary oedema

[24], 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 polyethoxylated castor oil (e.g. a preparation containing Cremophor® EL), and in patients with an allergic predisposition. Thus, patients receiving Sandimmun i.v. should be under continuous observation for at least the first 30 minutes after the start of the infusion and at frequent intervals thereafter. If anaphylactoid reactions occur, the infusion should be discontinued. An aqueous solution of adrenaline 1:1000 and a source of oxygen should be available at the bedside [48]. Pre-treatment with an antihistamine may prevent anaphylactoid reactions.

Additional precautions in non-transplant indications

(Consult also `4.2 Posology and method of administration')

Patients with impaired renal function (except in nephrotic syndrome patients with a permissible degree of renal impairment), uncontrolled hypertension, uncontrolled infections, or any kind of malignancy should not receive ciclosporin.

Monitoring of renal function

Since Sandimmun 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 (Note: very careful monitoring at weekly intervals is required during the initial treatment phase in patients with nephrotic syndrome presenting with a permissible degree of renal function impairment). Thereafter, if the creatinine levels are within acceptable values (see next paragraph) and remain stable, longer monitoring intervals may be appropriate. In the treatment of patients with rheumatoid arthritis, the intervals should, however, not exceed 4 weeks; more frequent measurements are necessary when the Sandimmun dose is increased or concomitant treatment with a non-steroidal anti-inflammatory drug is initiated or its dosage increased. In the treatment of psoriasis, the monitoring intervals may be prolonged to a maximum of 8 weeks in patients who are on 2.5 mg/kg per day, but should not exceed 4 weeks if higher doses are used.

Dose adjustment based on creatinine value

If serum creatinine increases and remains increased by more than 30% above baseline at more than one measurement, the Sandimmun dose must be reduced by 25 to 50%. If the increase from baseline exceeds 50%, the dose must be reduced by at least 50%. These recommendations apply even if the patient's creatinine values still lie within the laboratory's normal range. In patients in whom dose reduction is not successful in reducing creatinine levels within 4 weeks, Sandimmun treatment should be discontinued.

Elderly patients

For psoriasis and atopic dermatitis, elderly patients should be treated only in the presence of disabling pathology [48].

Renal biopsy in patients with nephrotic syndrome

In some patients it may be difficult to detect Sandimmun-induced renal dysfunction because of changes in renal function related to the nephrotic syndrome itself. This explains why, in rare cases, Sandimmun-associated structural kidney alterations have been observed without increases in serum creatinine. Therefore, renal biopsy should be considered for patients with steroid-dependent minimal change nephropathy in whom Sandimmun therapy has been maintained over more than one year.

Hypertension during Sandimmun therapy

If hypertension develops, which cannot be controlled by appropriate antihypertensive therapy, dose reduction or discontinuation of Sandimmun treatment is recommended.

Surveillance for early detection of lymphoproliferative disorders and solid malignancies

As with other immunosuppressive treatments, an increased risk for the development of lymphoproliferative disorders and of solid malignancies, particularly of the skin, must be considered. For early detection of such disorders, patients on long-term Sandimmun therapy should be closely observed. If any premalignant or malignant condition is detected, treatment should be discontinued.

Skin lesions in psoriatic patients

In psoriatic patients on Sandimmun as in those on conventional therapy, development of skin cancer has been reported. Skin lesions not typical for psoriasis but suspected to be malignant or premalignant should be biopsied before Sandimmun treatment is initiated. Patients with malignant or premalignant alterations of the skin should be treated with Sandimmun only after appropriate treatment of such lesions and if no other option for successful therapy exists.

Skin infections in patients with atopic dermatitis

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

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

Lymphadenopathy in patients with atopic dermatitis

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 [48].

Paediatric use in non-transplant indications

Except for the treatment of nephrotic syndrome, there is no adequate experience available with Sandimmun; its use in children under 16 years of age for non-transplant indications other than nephrotic syndrome cannot be recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Food interactions

The concomitant intake of a fat-rich meal or grapefruit juice has been reported to increase the bioavailability of ciclosporin.

Drug interactions

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

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 also an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein and may increase plasma levels of comedications that are substrates of this enzyme and/or transporter [51].

Drugs that decrease ciclosporin levels

Barbiturates, carbamazepine, oxcarbazepine [49], phenytoin; nafcillin, sulfadimidine i.v., rifampicin, octreotide, probucol, orlistat [4-6]; *hypericum perforatum* (St. John's wort) [5-9], ticlopidine [26], sulfinpyrazone [30], terbinafine [30], bosentan [49].

Drugs that increase ciclosporin levels

Macrolide antibiotics (e.g. erythromycin, azithromycin [30] and clarithromycin [5,6,14-19]); ketoconazole, fluconazole, itraconazole, voriconazole [49]; diltiazem, nicardipine, verapamil; metoclopramide; oral contraceptives; danazol; methylprednisolone (high dose); allopurinol; amiodarone; cholic acid and derivatives; protease inhibitors [28], imatinib [31], colchicine [49]; nefazodone [53].

Other relevant drug interactions

Care should be taken when using ciclosporin together with other drugs that exhibit nephrotoxic synergy such as: aminoglycosides (incl. gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); non-steroidal anti-inflammatory drugs (incl. diclofenac, naproxen, sulindac); melphalan, histamine H2 receptor

antagonists (e.g. cimetidine, ranitidine) [30]; methotrexate (see section 4.4 Special warnings and precautions for use) [49].

Concomitant use with tacrolimus should be avoided due to increased potential for nephrotoxicity [30].

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.Following concomitant administration of ciclosporin and lercanidipine, the AUC of lercanidipine was increased threefold and the AUC of ciclosporin was increased 21%. Therefore caution is recommended when co-administering ciclosporin together with lercanidipine (see section 4.4 Special warnings and precautions for use) [49].

Ciclosporin is a highly potent Pgp inhibitor and may increase blood levels of concomitant medications that are substrates of Pgp such as aliskiren. Following concomitant administration of 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. Caution is recommended when co-administering ciclosporin together with aliskiren (see section 4.4 Special warnings and precautions for use) [60].

The concomitant use of diclofenac and ciclosporin has been found to result in a significant increase in the bioavailability of diclofenac, with the possible consequence of reversible renal function impairment. The increase in the bioavailability of diclofenac is most probably caused by a reduction of its high first-pass effect. If non-steroidal anti-inflammatory drugs with a low first-pass effect (e.g. acetylsalicylic acid) are given together with ciclosporin, no increase in their bioavailability is to be expected.

Ciclosporin may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins) [30] and etoposide [52].

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 are used concurrently with ciclosporin, close clinical observation is required in order to enable early detection of toxic manifestations of digoxin or colchicine, followed by reduction of dosage or its withdrawal.

Literature and postmarketing cases of myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of ciclosporin with lovastatin, simvastatin [21-23], atorvastatin [27], pravastatin [20-22], 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 [27,30].

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 [32].

Caution is required for concomitant use of potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors [1], angiotensin II receptor antagonists [2]) or potassium containing drugs since they may lead to significant increases in serum potassium (see section 4.4 Special warnings and precautions for use) [49].

Ciclosporin may increase the plasma concentrations of repaglinide and thereby increase the risk of hypoglycaemia [54].

Recommendations

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

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

In graft recipients there have been isolated reports of considerable but reversible impairment of kidney function (with corresponding increase in serum creatinine) following concomitant administration of fibric acid derivatives (e.g. bezafibrate, fenofibrate). Kidney function must therefore be closely monitored in these patients. In the event of significant impairment of kidney function the comedication should be withdrawn [30].

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

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

Non-steroidal anti-inflammatory drugs known to undergo strong first-pass metabolism (e.g. diclofenac) should be given at doses lower than those that would be used in patients not receiving ciclosporin [47].

If *digoxin*, *colchicine* or HMG-CoA reductase inhibitors (statins) [30], are used concurrently with ciclosporin, close clinical observation is required in order to enable early detection of toxic manifestations of the drugs, followed by reduction of its dosage or its withdrawal.

4.6 Pregnancy and lactation

Pregnancy

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

Experience with Sandimmun in pregnant women is limited. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks) [50].

A limited number of observations in children exposed to ciclosporin in utero is available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal [34].

However there are no adequate and well-controlled studies in pregnant women and, therefore, Sandimmun should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

Lactation

Ciclosporin passes into breast milk. Mothers receiving treatment with Sandimmun should not breast-feed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 i.v. administration (see section 4.4 ‘Special warnings and precautions for use’) [50].

Infections and Infestations

Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic) (see section 4.4 'Special warnings and precautions for use'). Both generalised and localised infections can occur. Pre-existing infections may also be aggravated and reactivation of Polyomavirus infections may lead to Polyomavirus associated nephropathy (PVAN) [56] or to JC virus associated progressive multifocal leukoencephalopathy (PML) [55]**.** Serious and/or fatal outcomes have been reported [50].

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

Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of developing lymphomas or lymphoproliferative disorders and other malignancies, particularly of the skin. The frequency of malignancies increases with the intensity and duration of therapy (see section 4.4 'Special warnings and precautions for use'). Some malignancies may be fatal [50].

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: 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), including isolated reports.

Table 1 [50]

Blood and lymphatic system disorders	
Uncommon	Anaemia, thrombocytopenia.
Rare	Microangiopathic haemolytic anaemia, haemolytic uraemic syndrome.
Metabolism and nutrition disorders	
Very common	Hyperlipidaemia.
Common	Anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia.
Rare	Hyperglycaemia.
Nervous system disorders	
Very common	Tremor, headache including migraine [61].
Common	Paraesthesia.
Uncommon	Signs of encephalopathy such as convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia.
Rare	Motor polyneuropathy.
Very rare	Optic disc oedema [6] including papilloedema, with possible visual impairment secondary to benign intracranial hypertension [25].
Vascular disorders	
Very common	Hypertension.
Gastrointestinal disorders	
Common	Nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia
Rare	Pancreatitis.
Hepatobiliary disorders	
Common	Hepatic function abnormal (see section 4.4 Special warnings and precautions for use).

Skin and subcutaneous tissue disorders	
Common	Hypertrichosis.
Uncommon	Allergic rashes.
Musculoskeletal and connective tissue disorders	
Common	Muscle cramps, myalgia.
Rare	Muscle weakness, myopathy.
Renal and urinary disorders	
Very common	Renal dysfunction (see section 4.4 Special warnings and precautions for use).
Reproductive system and breast disorders	
Rare	Menstrual disturbances, gynecomastia.
General disorders and administration site conditions	
Common	Fatigue.
Uncommon	Oedema, weight increase.

Other adverse drug reactions from post-marketing experience

There have been solicited and spontaneous postmarketing reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients treated with ciclosporin. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and comedications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see section 4.4 Special warnings and precautions for use) [59].

4.9 Overdose

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

Symptoms

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

Treatment

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

5 Pharmacological properties

5.1 Pharmacodynamic properties

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

Ciclosporin, a cyclic polypeptide consisting of 11 amino acids, is a potent immunosuppressive agent.

In animals, ciclosporin has been shown to prolong the survival of allogeneic transplants of skin, cornea, kidney, liver, heart, lung, pancreas, small intestine, and bone marrow. It also inhibits the development of cell-mediated reactions involved in delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, graft-versus-host disease (GVHD), and 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 or 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).

In man, successful solid organ and bone marrow transplantations have been performed using Sandimmun to prevent and treat rejection and GVHD. Ciclosporin has been used successfully both in Hepatitis C Virus (HCV) positive and HCV negative liver transplant recipients [58]. Marked beneficial effects of Sandimmun therapy have also been shown in a variety of conditions that are known or may be considered to have an immunological mechanism.

Since ciclosporin does not depress haematopoiesis and does not impair the function of phagocytic cells, patients treated with Sandimmun are less prone to infections than those receiving cytostatic agents for immunosuppression.

5.2 Pharmacokinetics properties

The absorption of ciclosporin from the gastrointestinal tract is variable and may be influenced by the intake of food. Compared to the fasted state, the intake of a fat-rich meal concomitantly with the oral administration of Sandimmun was found to markedly prolong the absorption of ciclosporin and to increase the total exposure to the drug (AUC) by 37%.

Following oral administration peak blood concentrations are reached within 1 to 6 hours. The absolute bioavailability is 20 to 50%; the capsules and the oral solution have been found to be bioequivalent. Within the therapeutic dose range the peak plasma concentration and the area under the plasma concentration/time curve are proportional to the dose; for whole blood, however, the relationship is non-linear. Following single oral doses of 300 mg given to healthy volunteers, the average maximum blood concentration was 1,042 ng/mL (range 719 to 1,655 ng/mL). 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).

Ciclosporin is distributed largely outside the blood volume with an apparent volume of distribution of 3.5 L/kg on average. 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. In plasma, approximately 90% is bound to proteins, mostly lipoproteins.

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 Interaction with other medicinal products and other forms of interaction). 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 drug).

There is a high variability in the data reported on the terminal elimination half-life of ciclosporin, depending on the assay applied and 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. Elimination is primarily biliary, with only 6% of an oral dose excreted in the urine, and with less than 1% in the unchanged form.

5.3 Preclinical safety data

Ciclosporin gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally). At toxic doses (rats at 30 mg/kg and rabbits at 100 mg/kg per day orally), ciclosporin was embryo- and fetotoxic as indicated by increased prenatal and postnatal mortality, and reduced fetal weight together with related skeletal retardations [38-39].

In two published research studies, rabbits exposed to ciclosporin in utero (10 mg/kg/day subcutaneously) demonstrated reduced numbers of nephrons, renal hypertrophy, systemic hypertension, and progressive renal insufficiency up to 35 weeks of age [34].

Pregnant rats which received 12 mg/kg/day of ciclosporin intravenously (twice the recommended human intravenous dose) had foetuses with an increased incidence of ventricular septal defect [34].

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

Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg per day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value [36]. In the 24-month rat study conducted at 0.5, 2, and 8 mg/kg per day, pancreatic islet cell adenomas significantly exceeded the control rate at the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related [37].

No impairment in fertility was demonstrated in studies in male and female rats [35].

Ciclosporin has not been found mutagenic/genotoxic in the Ames test [43], the v79–hgprt test [44], the micronucleus test in mice and Chinese hamsters [40,42], the chromosome-aberration

tests in Chinese hamster bone marrow [40], the mouse dominant lethal assay [41], and the DNA repair test in sperm from treated mice [45]. A study analyzing sister chromatid exchange (SCE) induction by ciclosporin using human lymphocytes *in vitro* gave indication of a positive effect (i.e. induction of SCE) at high concentrations in this system [46].

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

6 Pharmaceutical particulars

6.1 List of excipients

Soft gelatine capsules

Capsule content: ethanol anhydrous, maize oil interesterified , refined maize oil.

Capsule shell: Iron oxide red (E172) (25- and 100-mg capsules), iron oxide yellow (50-mg capsule) (E172), titanium dioxide, glycerol 85%, sorbitol syrup special (anidrisorb 85/70), gelatine.

Oral solution

Ethanol anhydrous, maize oil interesterified, maize oil refined (for USA: absolute ethanol, labrafil M 1944 CS, olive oil).

Sandimmun concentrate for solution for infusion

Ethanol anhydrous, macrogolglycerol ricinoleate (Ph.Eur)/ polyethoxylated castor oil (NF) (see section 4.4 Special warnings and precautions for use).

6.2 Incompatibilities

Sandimmun concentrate for solution for infusion contains polyethoxylated castor oil, which can cause phathalate stripping from PVC. If available, glass containers should be used for infusion. Plastic bottles should be used only if they conform to the requirements for “Sterile plastic containers for human blood and blood components” respectively to “Empty sterile containers of plasticised poly(vinyl chloride) for human blood and blood components” of the current European Pharmacopoeia. Containers and stoppers should be free of silicone oil and fatty substances.

6.3 Shelf life

Soft gelatine capsules: 3,5 years [33].

Oral solution: 3 years.

Concentrate for solution for infusion: 4 years.

6.4 Special precautions for storage

Soft gelatine capsules: The capsules should be left in the blister pack until required for use and stored at temperatures not exceeding 30°C. When a blister is opened, a characteristic smell is noticeable; this is normal and does not mean that there is anything wrong with the capsule.

Oral solution: The oral solution should not be refrigerated. It may be stored at room temperature not exceeding 30°C. A slight precipitate that may occur during storage does not affect the efficacy and safety of the drug. Once the bottle has been opened, the content must be used within two months.

6.5 Nature and contents of container

Soft gelatine capsules: Blister packs of double-sided aluminium.

Oral solution: 50-mL amber glass bottles with rubber stopper and aluminium flip tear-up seal.

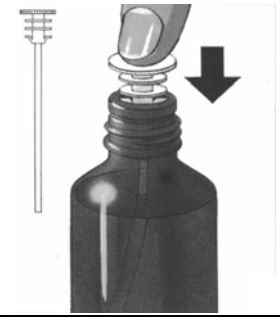
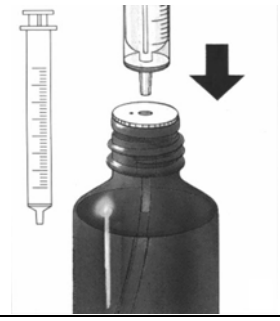
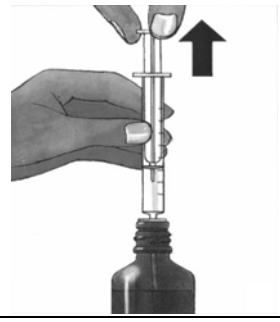
Concentrate for solution for infusion: 1-mL and 5-mL uncoloured glass ampoules.

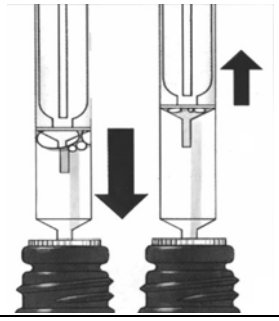
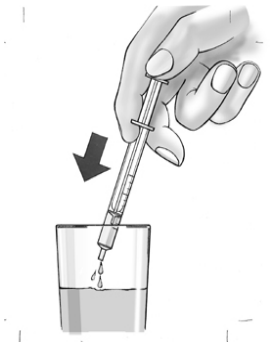
6.6 Instructions for use/handling of Sandimmun oral solution

Sandimmun oral 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 oral solution

1.	Raise flap in centre of the metal sealing ring.	
2.	Tear off the sealing ring completely.	

3.	Remove the black stopper and throw it away.	
4.	Push the tube unit with the white stopper firmly into the neck of the bottle.	
5.	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.	

Subsequent use

Commence at point 5.

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

This is a non-referenced document.