NEW ZEALAND DATA SHEET

1 PRODUCT NAME

SANDIMMUN® 50 mg/mL concentrate for solution for infusion
(ciclosporin)

2 QUALITY AND QUANTITATIVE COMPOSITION

Sandimmun® concentrate for solution for infusion containing 50 mg ciclosporin per mL. Each ampoule of 1 mL contains 50 mg of ciclosporin. Each ampoule of 5 mL contains 250 mg ciclosporin.

For a full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Sandimmun concentrate for solution for infusion is a clear, brown-yellow, oleaginous concentrate to be diluted before parenteral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Solid organ transplantation

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

Treatment of transplant rejection in patients previously receiving other immunosuppressive agents.

Bone marrow transplantation

Prevention of graft rejection following bone marrow transplantation.

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

4.2 Dose and method of administration

Dosage

The daily doses of Sandimmun oral formulations should always be given in 2 divided doses. The dose ranges given are intended to serve as guidelines only. The recommended dose of Sandimmun concentrate for solution for infusion is approximately one third of the appropriate oral dose.

Because of considerable inter- and intra-individual variations in absorption and elimination and the possibility of pharmacokinetic drug interactions (see Section 4.5 Interaction with other medicines and other forms of interaction), doses should be titrated individually according to clinical response and tolerability.

In transplant patients, routine monitoring of ciclosporin blood levels is required to avoid adverse effects due to high levels and to prevent organ rejection due to low levels (see Section 4.4 Special warnings and precautions for use); this can be carried out by means of a radioimmunoassay (RIA) method based on monoclonal antibodies. The results obtained will serve, as a guide for determining the actual dosage required to achieve the desired target concentrations in individual patients.

Because of the risk of anaphylaxis, Sandimmun concentrate for solution for infusion should be reserved for patients who are unable to take the drug orally (e.g. shortly after surgery) or in whom the absorption of the oral form might be impaired during episodes of gastrointestinal disorders. In such cases, it is recommended to change to oral administration as soon as feasible.

Method of administration

The types of container suitable for the infusion solution are mentioned in 'Incompatibilities'.

The concentrate should be diluted 1:20 to 1:100 with normal saline or 5 % glucose, using appropriate aseptic technique, and given as a slow i.v. infusion over approximately 2 to 6 hours.

For instructions on preparation and handling of Sandimmun concentrate for solution for infusion, (see Section 6.6 Special precautions for use/handling of the product).

General target population

Transplantation

Solid organ transplantation

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 is reached, given in 2 divided doses.

When Sandimmun concentrate for solution for infusion is given with other immunosuppressants (e.g. with corticosteroids or as part of a triple or quadruple drug therapy), lower doses (e.g. 1 to 2 mg/kg, given in 2 divided doses, for the initial treatment) may be used.

The recommended dose of Sandimmun concentrate for solution for infusion is approximately one third of the appropriate oral dose. It is recommended that patients be put on oral therapy as soon as possible.

Bone marrow transplantation

The initial dose should be given on the day before transplantation. For the initiation of Sandimmun therapy the preferred route of administration is by intravenous infusion. In most cases the recommended dose is 3 to 5 mg/kg per day. Infusion is continued at this dose level during the immediate post-transplant period of up to 2 weeks, before a change is made to oral maintenance therapy.

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. Continuation of ciclosporin treatment via i.v. therapy may be necessary in the presence of oral ciclosporin induced gastrointestinal disturbances which might decrease drug absorption.

In some patients, GVHD occurs after discontinuation of ciclosporin treatment, but usually responds favourably 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.

Special population

Renal impairment

Ciclosporin undergoes minimal renal elimination and its pharmacokinetics is not affected by renal impairment (see Section 5 Pharmacological properties). However, due to its nephrotoxic potential (see Section 4.8 Undesirables effects), a careful monitoring of the renal function is recommended (see Section 4.4 Special warnings and precautions for use, subsection all indications).

Hepatic impairment

Ciclosporin is extensively metabolized by the liver. The terminal half-life varied between 6.3 hours in healthy volunteers to 20.4 hours in severe liver disease patients (see Section 5 Pharmacological properties). Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see Section 4.4 Special warnings and precautions for use and Section 5 Pharmacological properties).

Geriatrics (65 years old and above)

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

In rheumatoid arthritis clinical trials with oral 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.

Clinical studies of Neoral in transplant and psoriasis patients did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experiences have not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Use in children

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

4.3 Contraindications

Hypersensitivity to ciclosporin or to any of the excipients of Sandimmun concentrate for solution for infusion including polyethoxylated castor oil.

4.4 Special warnings and precautions for use

All indications

Medical supervision

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

For monitoring ciclosporin levels in whole blood, radioimmunoassay (RIA) with the use of a specific monoclonal antibody (measurement of parent drug) is preferred; a HPLC method, which also measures the parent drug, can be used as well. If plasma or serum are used, a standard separation protocol (time and temperature) should be followed. For the initial monitoring of liver transplant patients, either the specific monoclonal antibody should be used, or parallel measurements using both the specific

monoclonal antibody and the non-specific 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.

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

Sandimmun concentrate for solution for infusion contains polyethoxylated castor oil (see Section 6.1 List of excipients), 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 polyethoxylated 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 (H_1 + H_2 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 (see Section 4.8 Undesirable effects).

In view of the potential risk of skin malignancy, patients on Sandimmun concentrate for solution for infusion 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 (see Section 4.8 Undesirable effects).

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 Sandimmun 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. arteriolar hyalinosis, tubular atrophy and interstitial fibrosis) which, in renal transplant patients, must be differentiated from changes due to chronic rejection (see Section 4.8 Undesirable effects). Close monitoring of parameters that assess renal function is

required. Abnormal values may necessitate dose reduction (see Section 4.2 Dose and method of administration and Section 5 Pharmacological properties).

Hepatotoxicity and liver injury

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). Close monitoring of parameters that assess renal and hepatic function is required. Abnormal values may necessitate dose reduction (see Section 4.2 Dose and method of administration and Section 5 Pharmacological properties).

Geriatrics

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 (see Section 4.2 Dose and method of administration).

For monitoring ciclosporin levels in whole blood, a specific monoclonal antibody (measurement of parent drug) is preferred; a HPLC method, which also measures the parent drug, can be used as well. If plasma or serum 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 (see Section 4.2 Dose and method of administration).

Hypertension

Regular monitoring of blood pressure is required during Sandimmun therapy; if hypertension develops, appropriate antihypertensive treatment must be instituted (see Section 4.8 Undesirable effects). 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 medicines and other forms of interaction).

Blood lipid increased

Since 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 (see Section 4.8 Undesirable effects).

Hyperkalaemia

Ciclosporin enhances the risk of hyperkalaemia, especially in patients with renal dysfunction (see Section 4.8 Undesirable effects). Caution is also required when ciclosporin is co-administered with

potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and potassium containing drugs as well as in patients on a potassium rich diet (see Section 4.5 Interaction with other medicinal products and other forms of interaction). Control of potassium levels in these situations is advisable.

Hypomagnesemia

Ciclosporin enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplant period (see Section 4.8 Undesirable effects). 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.

Hyperuricemia

Caution is required in treating patients with hyperuricaemia (see Section 4.8 Undesirable effects).

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 Interaction with other medicines and other forms of interaction).

Interactions

Caution should be observed while co-administering lercanidipine with ciclosporin (see Section 4.5 Interaction with other medicines and other forms of interaction).

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 Interaction with other medicines and other forms of interaction).

Co-administration of ciclosporin with St. John's wort (Hypericum perforatum) may lead to a decrease in ciclosporin blood levels, thus potentially impacting the clinical efficacy of ciclosporin. Therefore, concomitant use of ciclosporin and herbal preparations containing St. John's wort (Hypericum perforatum) should be avoided (see Section 4.5 Interaction with other medicines and other forms of interaction).

Special excipient: ethanol

The ethanol (alcohol) content (see Section 6.1 List of excipients) should be taken into account when given to pregnant or breast feeding women, in patients presenting with liver disease or epilepsy, in alcoholic patients or if Sandimmun is given to a child.

4.5 Interactions with other medicines and other forms of interaction

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.

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 (see Section 4.4 Special warnings and precautions for use).

Interactions to be considered

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

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).

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 Special warnings and precautions for use).

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 drugs known to interact with ciclosporin cannot be avoided, the following basic recommendation should be observed in transplant patients. Frequent measurement of ciclosporin levels and, if necessary, ciclosporin dosage adjustment is required, particularly during the introduction or withdrawal of the co-administered drug.

Interactions decreasing ciclosporin levels

Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, sulfadimidine i.v., rifampicin, octreotide, probucol, orlistat; hypericum perforatum (St. John's wort, see section 4.4 special warnings and precautions for use); ticlopidine, sulfinpyrazone, terbinafine, and bosentan.

Interactions increasing ciclosporin levels

Macrolide antibiotics (e.g. erythromycin [see Section 4.4 Special warnings and precautions for use in atopic dermatitis], 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, colchicines; and nefazodone.

Other relevant interactions

Drug-food/drink interactions

The concomitant intake of grapefruit juice has been reported to increase the bioavailability of ciclosporin (see Section 4.2 Dose and method of administration).

Interactions resulting in a potential increased nephrotoxicity

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.

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), and methotrexate (see Section 4.4 Special warnings and precautions for use).

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 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. 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.

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.

Interactions 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 (see Section 4.8 Undesirable effects).

Interactions resulting in an increase of other drug 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, and prednisolone, HMG-CoA reductase inhibitors (statins), etoposide, aliskiren, bosentan and 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 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, 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 drugs, 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 hypoglycaemia.

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).

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 AUCinf 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

Women of child-bearing potential

There are no special recommendations for women of child-bearing potential.

Fertility

There is limited data on the effect of Sandimmun on human fertility. No impairment in fertility was demonstrated in studies in male and female rats (see Section 5.3 Preclinical safety data).

Pregnancy

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

There is moderate amount of data on the use of Sandimmun in pregnant patients. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks).

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

However there are no adequate data in pregnant women and, therefore, Sandimmun should not be used during pregnancy unless the expected benefit to the mother outweighs the potential risk to the foetus. The ethanol content of the Sandimmun formulations should also be taken into account in pregnant women (see Section 4.4 Special warnings and precautions for use).

Lactation

Ciclosporin passes into breast milk. The ethanol content of the Sandimmun should also be taken into account in breastfeeding mothers (see Section 4.4 Special warnings and precautions for use). 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 drug, taking into account the importance of the medicinal product to the mother.

4.7 Effects on ability to drive and use machines

Sandimmun may cause neurological and visual disturbances (see Section 4.8 Undesirable effects). Caution should be exercised when driving a motor vehicle or operating machines. No studies on the effects of Sandimmun 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, hirsutism, hypertension, diarrhea, 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 i.v. administration (see Section 4.4 Special warnings and precautions for use).

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) or to JC virus associated progressive multifocal leukoencephalopathy (PML). Serious and/or fatal outcomes have been reported.

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

Patients receiving immunosuppressive therapies, including 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.

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 group, 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), including isolated reports.

Table 1 Adverse reactions from clinical trials

Blood and lymphatic system disorders

Common	Leucopenia

Metabolism and nutrition disorders

Very common	Anorexia, hyperglycaemia

Nervous system disorders

Very common	Tremor, headache
Common	Convulsions, paraesthesia

Vascular disorders

Very common	Hypertension (see Section 4.4 Special warnings and precautions for use)
Common	Flushing

Gastrointestinal disorders

Very common	Nausea, vomiting, abdominal discomfort, diarrhoea, gingival hyperplasia
Common	Peptic ulcer

Hepatobiliary disorders

Common	Hepatotoxicity (see Section 4.4 Special warnings and precautions for use).

Skin and subcutaneous tissue disorders

Very common	Hirsutism
Common	Acne, rash

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

General disorders and administration site conditions

Common Pyrexia, oedema

Adverse drug reactions from post-marketing experience (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Sandimmun via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drugs reactions are listed according to system organ classes in MedDRA. Within each organ class, ADRs are presented below in Table 2 in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Blood and lymphatic system disorders	Thrombotic microangiopathy, haemolytic uremic syndrome, thrombotic thrombocytopenic purpura; anaemia; thrombocytopenia
Metabolism and nutrition disorders	Hyperlipidemia; hyperuricemia; hyperkalemia; hypomagnesemia
Nervous system disorders	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, cerebellar ataxia; optic disc oedema including papilledema, with possible visual impairment secondary to benign intracranial hypertension; peripheral neuropathy; migraine
Gastrointestinal disorders	Pancreatitis acute
Hepatobiliary disorders	Hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure with some fatal outcome (see Section 4.4 Special warnings and precautions for use)
Skin and subcutaneous tissue disorders	Hypertrichosis
Musculoskeletal and connective tissue disorders	Myopathy; muscle spasm; myalgia; muscular weakness, pain of lower extremities
Reproductive system and breast disorders	Gynecomastia
General disorders and administration site conditions	Fatigue; weight increase

Description of selected adverse drug reactions

Hepatotoxicity and liver injury

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

Acute and chronic nephrotoxicity

Patients receiving calcineurin inhibitors (CNIs) 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 homestasis, such as hyperkalemia, hypomagnesemia, hyperuricemia. Cases reporting chronic morphological changes included arteriolar hyalinosis, tubular atrophy and interstitial fibrosis (see Section 4.4 Special warnings and precautions for use).

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) as described in the literature [80].

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions - Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

The oral LD_{50} 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. LD_{50} 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 ciclosporin of up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia and, in a few patients, moderately severe, reversible impairment of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with ciclosporin 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.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Ciclosporin (also known as ciclosporin A) is a cyclic polypeptide consisting of 11 amino acids. It is a potent immunosuppressive agent, which in animals prolongs survival of allogeneic transplants of skin, heart, kidney, pancreas, bone marrow, small intestine or lung. Studies suggest that 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. At the cellular level it inhibits production and release of lymphokines including interleukin 2 (T-cell growth factor, TCGF). Ciclosporin appears to block the resting lymphocytes in the G0 or G1 phase of the cell cycle, and inhibits the antigen-triggered release of lymphokines by activated T cells.

All available evidence suggests that ciclosporin acts specifically and reversibly on lymphocytes. Unlike cytostatic agents, it does not depress haemopoiesis and has no effect on the function of phagocytic cells. Patients treated with Sandimmun are less prone to infection than those receiving other immunosuppressive therapy.

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

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. In the blood, 33 to 47% is present in plasma, 4 to 9% in lymphocytes, 5 to 12% in granulocytes, and 41 to 58% in erythrocytes. In plasma, approximately 90% is bound to proteins, mostly lipoproteins.

Ciclosporin is extensively biotransformed to approximately 15 metabolites. There is no single major metabolic pathway. 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 Interactions with other medicines 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 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. Elimination is primarily biliary, with only 6% of the oral dose excreted in the urine; only 0.1% is excreted in the urine as unchanged drug (see Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use).

Special Populations

Renal impairment

In a study performed in patients with terminal renal failure, following an intravenous infusion of 3.5 mg/kg over 4 hours mean peak blood levels of 1,800 ng/mL (range 1,536 to 2,331 ng/mL) resulted. The mean volume of distribution (Vdss) was 3.49 L/kg and systemic clearance (CL) was 0.369 L/hr/kg. This systemic CL (0.369 L/hr/kg) was approximately two thirds of the mean systemic CL (0.56 L/hr/kg) in patients with normally functioning kidneys. Renal impairment had no significant effect on the elimination of ciclosporin.

Hepatic impairment

In a study performed in severe liver disease patients with biopsy-proven cirrhosis, the terminal half-life was 20.4 hours (range between 10.8 to 48.0 hours compared to 7.4 to 11.0 hours in healthy subjects.

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.

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.

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.

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

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

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

Ciclosporin has not been found mutagenic/genotoxic in the Ames test, the v79–hgprt test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone marrow, the mouse dominant lethal assay, and the DNA repair test in sperm from treated mice. A

study analyzing sister chromatid exchange (SCE) induction by ciclosporin using human lymphocytes in vitro gave indication of a positive effect (i.e. induction of SCE) at high concentrations in this system.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies during 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

Ethanol 94% (w/w)(34.4% v/v ethanol or 27.8% w/v), 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 phthalate 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

4 years.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Packs containing 10 x 5-mL uncoloured glass ampoules.

6.6 Special precautions for use/handling

Sandimmun concentrate for solution for infusion should be kept out of the reach and sight of children.

Sandimmun concentrate for solution for infusion should be visually inspected for particulate matter and discoloration before dilution.

Sandimmun concentrate for solution for infusion does not contain preservatives or bacteriostatic agents, therefore, the product should be diluted immediately after opening the ampoule. The diluted solution for infusion should be prepared by a healthcare professional using appropriate aseptic technique and administered as soon as possible.

Based on the chemical and physical in-use stability data, the infusion should be completed within 6 hours at room temperature. Discard any unused diluted solution. If not administered immediately, the diluted solution can be stored at 2° C to 8° C (under refrigeration), provided that the total duration for both storage and infusion is less than 24 hours.

NEW ZEALAND DATA SHEET

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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Telephone: 0800 354 335

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9 DATE OF FIRST APPROVAL

15 December 1983

10 DATE OF REVISION OF THE TEXT

01 May 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Addition of method of administration heading and corresponding cross-reference to section 6.6. for instructions on preparation and handling of Sandimmun.
4.4, 4.5	Revised wording on the drug interaction with St John's wort.
6.6	Addition of instructions on preparation and handling after opening and dilution of Sandimmun.

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