NOVARTIS

Sandimmun®

Immunosuppressive agents, calcineurin inhibitors

DESCRIPTION AND COMPOSITION

Pharmaceutical form

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

Active substance

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

Not all presentations may be available locally.

Excipients

Ethanol anhydrous, macrogolglycerol ricinoleate (Ph.Eur)/polyoxyl 35 castor oil (NF) (see section WARNINGS AND PRECAUTIONS). Sandimmun concentrate for solution for infusion contains 34.4% v/v ethanol (27.8% w/v).

Pharmaceutical formulations may vary between countries.

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).

DOSAGE REGIMEN AND ADMINISTRATION

Dosage Regimen

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.

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 WARNINGS AND PRECAUTIONS). 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 asfeasible.

General target population

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.

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 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 The recommended i.v. dose is 3 to 5 mg/kg per day. Infusion is continued at this dose level during the immediate post-transplant period of up to 2 weeks, before a change is made to oral maintenance therapy.

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 favorably to re-introduction of therapy. Low doses of ciclosporin should be used to treat mild, chronic GVHD.

Special populations

Renal impairment

Ciclosporin undergoes minimal renal elimination, and its pharmacokinetics is not significantly affected by renal impairment (see section CLINICAL PHARMACOLOGY). However, due to its nephrotoxic potential (see section ADVERSE DRUG REACTIONS), a careful monitoring of the renal function is recommended (see section WARNINGS AND PRECAUTIONS 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 CLINICAL PHARMACOLOGY). Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see section WARNINGS AND PRECAUTIONS and section CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

Experience with ciclosporin 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 ciclosporin per kg body weight than those used in adults.

Geriatrics (65 years of age or above)

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

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.

Method of administration

The types of container suitable for the infusion solution are mentioned in section INSTRUCTIONS FOR USE AND HANDLING.

The concentrate for solution for infusion 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 PHARMACEUTICAL INFORMATION.

CONTRAINDICATIONS

Hypersensitivity to ciclosporin or to any of the excipients of Sandimmun concentrate for solution for infusion including polyoxyl castor oil (see section WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

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.

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

Sandimmun concentrate for solution for infusion contains polyoxyl castor oil (see DESCRIPTION AND COMPOSITION), which following i.v. administration has been reported to cause anaphylactoid reactions. These reactions can consist of flushing of the face and upper thorax, and non-cardiogenic pulmonary oedema, with acute respiratory distress, dyspnoea, wheezing and blood pressure changes and tachycardia. Special caution is therefore necessary in patients who have previously received, by i.v. injection or infusion, preparations containing polyoxyl castor oil (e.g., a preparation containing Cremophor® EL), and inpatients 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, theinfusion should be discontinued. An aqueous solution of adrenaline 1:1000 and a source ofoxygen 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 beensuccessfully 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 tumors, some with reported fatalities (see section ADVERSE DRUG REACTIONS).

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 outcome havebeen reported. Effective pre-emptive and therapeutic strategies should be employedparticularly in patients on multiple long-term immunosuppressive therapy (see section ADVERSE DRUG REACTIONS).

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 ciclosporin 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 ADVERSE DRUG REACTIONS). Close monitoring of parameters that assess renal function is required. Abnormal values may necessitate dose reduction (see section DOSAGE REGIMEN AND ADMINISTRATION and section CLINICAL PHARMACOLOGY

Hepatotoxicity and liver injury

Ciclosporin may also cause dose-dependent, reversible increases in serum bilirubin and in liver enzymes. (see section ADVERSE DRUG REACTIONS). 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 ADVERSE DRUG REACTIONS).

Close monitoring of parameters that assess hepatic function is required. Abnormal values may necessitate dose reduction (see section DOSAGE REGIMEN AND ADMINISTRATION and section CLINICAL PHARMACOLOGY).

Geriatric patients (65 years of age or above)

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

Monitoring ciclosporin levels in transplant patients

Routine monitoring of ciclosporin blood levels is an important safety measures (see section DOSAGE REGIMEN AND ADMINISTRATION).

It must be remembered that the ciclosporin blood concentration 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 DOSAGE REGIMEN AND ADMINISTRATION).

Hypertension

Regular monitoring of blood pressure is required during ciclosporin therapy; if hypertension develops, appropriate antihypertensive treatment must be instituted (see section ADVERSE DRUG REACTIONS). Preference should be given to an antihypertensive agent that does not interfere with the pharmacokinetics of ciclosporin (see section INTERACTIONS).

Blood lipids increased

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

Hyperkalaemia

Ciclosporin enhances the risk of hyperkalaemia, especially in patients with renal dysfunction (see section ADVERSE DRUG REACTIONS).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 INTERACTIONS). 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 ADVERSE DRUG REACTIONS). 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 hyperuricemia (see section ADVERSE DRUG REACTIONS).

Live-attenuated vaccines

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

Interactions

Caution should be observed while co-administering lercanidipine with ciclosporin (see section INTERACTIONS).

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

Special excipients: Ethanol

The ethanol content (see section DESCRIPTION AND COMPOSITION) should be takeninto account when given to pregnant or breast- feeding women, in patients presenting withliver disease or epilepsy, in alcoholic patients or if Sandimmun is given to a child.

Driving and using machines

Sandimmun may cause neurological and visual disturbance (see section ADVERSE DRUG REACTIONS). 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.

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.

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 WARNINGS AND PRECAUTIONS).

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 WARNINGS AND PRECAUTIONS).

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 WARNINGS AND PRECAUTIONS).

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, 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); ticlopidine, sulfinpyrazone, terbinafine, bosentan.

Interactions increasing ciclosporin levels

Macrolide antibiotics (e.g. erythromycin, azithromycin and clarithromycin); ketoconazole, fluconazole, itraconazole, voriconazole; diltiazem, nicardipine, verapamil; metoclopramide; oral

contraceptives; danazol; methylprednisolone (high dose); allopurinol; amiodarone; cholic acid and derivatives; protease inhibitors, imatinib, colchicines; nefazodone.

Other relevant interactions

Drug-food/drink interactions

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

Interactions resulting in a potential increased nephrotoxicity

During the concomitant use of a *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 H_2-receptor-antagonists (e.g. cimetidine, ranitidine), methotrexate. Concomitant use with tacrolimus should be avoided due to increased potential for nephrotoxicity.
The concomitant use of diclofenac and ciclosporin has been found to result in a significant increase in the bioavailability of diclofenac, with the possible consequence of reversible renal function impairment. The increase in the bioavailability of diclofenac is most probably caused by a reduction of its high first-pass effect. If non-steroidal anti-inflammatory 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.

Interaction resulting in an increased rate of gingival hyperplasia

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

Interactions resulting in an increase of other drugs

Ciclosporin is also an inhibitor of CYP3A4 and of the multidrug efflux transporter P-gp 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 and HMG-CoA reductase inhibitors (statins), etoposide, aliskiren, bosentan or dabigatran.

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

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

If digoxin, colchicine, or HMG-CoA reductase inhibitors (statins) are used concurrently with ciclosporin, close clinical observation is required in order to enable early detection of toxic manifestations of the 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 and section WARNINGS AND PRECAUTIONS).

Following concomitant administration of ciclosporin and aliskiren, the Cmax of aliskiren was increased by approximately 2.5 fold and the AUC by approximately 5 fold. However, the pharmacokinetic profile of ciclosporin was not significantly altered (see section WARNINGS AND PRECAUTIONS).

Concomitant administration of dabigatran and ciclosporin leads to increased plasma level of dabigatran due to the P-gp inhibitory activity of ciclosporin (see section WARNINGS AND PRECAUTIONS). Dabigatran has a narrow therapeutic index and an increase in plasma level may be associated with an increased risk of bleeding.

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

A significant increased exposure in anthracycline antibiotics (e.g doxorubicin, mitoxanthrone, daunorubicin) 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.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no adequate or well-controlled clinical studies in pregnant women using ciclosporin. There is a moderate amount of data on the use of ciclosporin in pregnant patients from post-marketing experience, including published literature. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks). The data have not demonstrated a higher incidence of miscarriages, congenital anomalies, or maternal events as compared to the rates seen in the general population (see Human Data)

Embryo-fetal developmental (EFD) studies in rats and rabbits with ciclosporin have shown embryo-fetal toxicity at dose levels below the maximum recommended human dose (MRHD) based on body surface area (BSA) (see Animal data).

Sandimmun should not be used during pregnancy unless the expected benefit to the mother outweighs the potential risk to the fetus. The ethanol content should also be taken into account in pregnant women (see section WARNINGS AND PRECAUTIONS).

Data

Human data

Published data from National Transplantation Pregnancy Registry (NTPR), described pregnancy outcomes in female kidney (482), liver (97), and heart (43) transplant recipients receiving ciclosporin. The data indicated successful pregnancies with a live birth rate of 76% and 76.9%, and 64% in kidney, liver, and heart transplant recipients, respectively. Premature delivery (<37 weeks) was reported in 52%, 35%, and 35% of kidney, liver, and heart transplant recipients, respectively.

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

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

Animal data

Three EFD studies (two oral and one intravenous) are available in rats. In oral EFD studies, pregnant rats were administered with ciclosporin either at doses of 10, 17, 30, 100 and 300 mg/kg/day or 4, 10 and 25 mg/kg/day from gestation day (GD) 6 to 15 or from GD 7 to 17, respectively. Maternal toxicity characterized by mortality, clinical signs of toxicity and impaired body weight gain were observed at 30 mg/kg/day and above. Ciclosporin was embryo- and fetotoxic as indicated by increased embryonic mortality and reduced fetal weight together with skeletal retardations in rats at 25 mg/kg/day and above. In addition, ventricular septal defect was observed at 25 mg/kg/day in fetuses. The no observed effect level (NOEL) for both dams and fetus was 17 mg/kg/day (below the MRHD based on BSA) after oral administration. In the other oral study, the NOEL for dams and fetuses were 10 and 4 mg/kg/day (below the MRHD based on BSA), respectively. In the IV EFD study, rats were administered with 3, 6 and 12 mg/kg/day of ciclosporin from GD 7 to 17. An increase in post implantation loss was observed at 12 mg/kg/day; ventricular septal defect was observed at 6 mg/kg/day and above in fetuses. The NOEL for dams and fetus were 6 and 3 mg/kg/day (below the MRHD based on BSA), respectively, after IV administration.

In rabbits, ciclosporin was orally administered at dose levels of 10, 30, 100 or 300 mg/kg/day from GD 6 to 18. At 100 mg/kg/day and above, reduction in body weight gain of dams and at 300

mg/kg/day abortions were observed. Maternal toxicity, embryo-fetotoxicity as indicated by increased pre- and postnatal mortality, reduced fetal weight together with skeletal retardations were observed at 100 mg/kg/day and above. The NOEL for dams and fetuses was 30 mg/kg/day (below the MRHD based on BSA).

In two published research studies, pregnant rabbits exposed to ciclosporin (10 mg/kg/day subcutaneously) during gestation demonstrated maternal toxicity (reduced body weight gain) and kidney changes in pups and adults (reduced numbers of nephrons, renal hypertrophy, systemic hypertension, and progressive renal insufficiency)An increase in fetal resorptions and a decrease in live pups and pup body weight were observed.

In a peri-and postnatal development study in rats, pregnant rats were orally administered with ciclosporin (5, 15 or 45 mg/kg/day) from GD 15 until end of lactation. At 45 mg/kg/day (below the MRHD based on BSA), increased pre and postnatal mortality of offspring and reduced body weight gain of surviving pups were observed. Ciclosporin up to 15 mg/kg/day (below the MRHD based on BSA) had no effect on pregnancy, pre and postnatal development of offspring.

Lactation

Risk summary

Ciclosporin is transferred into breast milk. Mothers receiving treatment with Sandimmun should not breast-feed. Because of the potential of Sandimmun to cause serious adverse drug reactions in breastfed newborns/infants, a decision should be made whether to abstain from breast-feeding or to abstain from using the medicinal drug, takinginto account the benefit of breast-feeding for the newborn/infant and the importance of the medicinal product to the mother.

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

The ethanol content of the Sandimmun formulations should also be taken into account (see section WARNINGS AND PRECAUTIONS)

Females and males of reproductive potential

Female

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

Infertility

There is limited data on the effect of ciclosporin on human fertility. No impairment in fertility was demonstrated in male and female rats up to 5mg/kg/day (below MRHD based on BSA) (see section NON-CLINICAL SAFETY DATA).

ADVERSE DRUG REACTIONS

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, diarrhoea, anorexia, nausea and vomiting. Many side effects associated with ciclosporin therapy are dose-dependent and responsive to dose reduction. In the various indications the overall spectrum of side effects is essentially the same; there are, however, differences in incidence and severity. As a consequence of the higher initial doses and longer maintenance therapy required after

transplantation, side effects are more frequent and usually more severe in transplant patients than in patients treated for other indications.

Anaphylactoid reactions have been observed following i.v. administration (see section WARNINGS AND PRECAUTIONS).

Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic) (see section WARNINGS AND PRECAUTIONS). 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.

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 WARNINGS AND PRECAUTIONS). Some malignancies may be fatal.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), including isolated reports.

Table 1 Adverse drug reaction from clinical trials

Blood and lymphatic system disorders	
Common	Leucopenia
Metabolism and nutrition disorders	
Very common	Anorexia, hyperglycaaemia
Nervous system disorders	
Very common	Tremor, headache
Common	Convulsions, paraesthesia
Vascular disorders	
Very common	Hypertension (see section WARNINGS AND PRECAUTIONS)
Common	Flushing
Gastrointestinal disorders	
Very common	Nausea, vomiting, abdominal discomfort, diarrhoea, gingival hyperplasia
Common	Peptic ulcer
Hepatobiliary disorders	
Common	Hepatotoxicity (see section WARNINGS AND PRECAUTIONS)
Skin and subcutaneous tissue disorders	
Very common	Hirsutism
Common	Acne, rash
Renal and urinary disorders	
Very common	Renal dysfunction (see section WARNINGS AND PRECAUTIONS).
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 drug 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 uraemic syndrome, thrombotic thrombocytopenic purpura;anaemia; thrombocytopenia, microangiopathic hemolytic anemia
Metabolism and nutrition disorders
Hyperlipidaemia; hyperuricemia; hyperkalaemia; hypomagnesaemia
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 papilloedema, 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 WARNINGS AND PRECAUTIONS)
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
Gynaecomastia
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 post-marketing 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, underlyingconditions 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 WARNINGS AND PRECAUTIONS)**.**

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 useof ciclosporin. Cases of acute nephrotoxicity reported disorders of ion homeostasis, such as hyperkalaemia, hypomagnesaemia, and hyperuricaemia. Cases reporting chronic morphological changes included arteriolar hyalinosis, tubular atrophy and interstitial fibrosis (see section WARNINGS AND PRECAUTIONS).

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.

OVERDOSAGE

The oral LD_{50} of ciclosporin is 2329 mg/kg in mice, 1480 mg/kg in rats and > 1000 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, suchas vomiting, drowsiness, headache, tachycardia and, in a few patients, moderately severe,reversible impairment of renal function. However, serious symptoms of intoxication havebeen reported following accidental parenteral overdosage with ciclosporin in prematureneonates.

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.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

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

Mechanism of action/PHARMACODYNAMICS (PD)

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 G_0 or G_1 phase of the cell cycle, and inhibits the antigen- triggered release of lymphokines by activated T cells.

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

Successful solid organ and bone marrow transplantations have been performed in man using ciclosporin to prevent and treat rejection and GVHD. 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.

PHARMACOKINETICS (PK)

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. 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.

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 rangedfrom 6.3 hours in healthy volunteers to 20.4 hours in patients with severe liver disease (see sections DOSAGE REGIMEN AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Special Population

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 themean systemic CL (0.56 L/hr/kg) in patients with normally functioning kidneys. Renalimpairment 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).

NON-CLINICAL SAFETY DATA

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/day, evidence of a statistically significanttrend 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/ 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.

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.

In a fertility study in rats, increased perinatal mortality and impaired postnatal development of F1 pups were observed at 15 mg/kg/day (below the MRHD based on BSA). No adverse effects on fertility and reproduction were observed up to 5 mg/kg/day (below the MRHD based on BSA) in male and female rats.

For reproductive toxicity, see Section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

PHARMACEUTICAL INFORMATION
Special precautions for storage

See folding box.

Sandimmun concentrate for solution for infusion should not be used after the date marked "EXP" on the pack.

Unopened ampoule does not require any special temperature storage conditions. For storage conditions after opening and dilution, see Instructions for use and handling of Sandimmun concentrate for solution for infusion.

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

Instructions for Use and handling

Sandimmun concentrate for solution for infusion should be inspected visually for particulate matter and discoloration prior to 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 below 25°C. 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.

Sandimmun concentrate for solution for infusion contains polyoxyl 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.

Manufacturer:

See folding box.

Package Leaflet

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