

DATA SHEET

SANDIMMUN® cyclosporin

50mg concentrate for solution for infusion

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Qualitative and quantitative composition

Sandimmun® concentrate for solution for infusion containing 50 mg cyclosporin per mL.

For a full list of excipients see List of excipients.

Pharmaceutical form

Sandimmun concentrate for solution for infusion.

Clinical particulars

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).

Dosage and method of administration

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.

Routine monitoring of cyclosporin blood levels is required to avoid adverse effects due to high levels and to prevent organ rejection due to low levels (see 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.

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, and given as a slow i.v. infusion over approximately 2 to 6 hours. Diluted infusion solutions must be discarded after 24 hours.

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.

It is recommended that patients be put on oral therapy as soon as possible.

Bone marrow transplantation

For the initiation of Sandimmun therapy the preferred route of administration is by intravenous infusion.

The initial dose should be given on the day before transplantation. 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 cyclosporin treatment via i.v. therapy may be necessary in the presence of oral cyclosporin induced gastrointestinal disturbances which might decrease drug absorption.

In some patients, GVHD occurs after discontinuation of cyclosporin treatment, but usually responds favourably to re-introduction of therapy. Low doses of cyclosporin should be used to treat mild, chronic GVHD.

Use in the elderly

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

In rheumatoid arthritis clinical trials with oral cyclosporin, 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 $\geq 50\%$ 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.

Contraindications

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

Special warnings and precautions for use

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 cyclosporin 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 cyclosporin 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.

Sandimmun concentrate for solution for infusion contains polyethoxylated castor oil (see 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 (H1 + H2 blocker) prior to Sandimmun concentrate for solution for infusion has also been successfully employed to prevent the occurrence of anaphylactoid reactions.

Like other immunosuppressants, cyclosporin 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 cyclosporin) should be used with caution as this could lead to lymphoproliferative disorders and solid organ tumours, some with reported fatalities.

In view of the potential risk of skin malignancy, patients on Sandimmun concentrate for solution for infusion should be warned to avoid excess ultraviolet light exposure.

Like other immunosuppressants, cyclosporin 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 cyclosporin. 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.

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. interstitial fibrosis) which, in renal transplant patients, must be differentiated from changes due to chronic rejection. Sandimmun may also cause dose-dependent, reversible increases in serum bilirubin and, occasionally, in liver enzymes (see ADVERSE 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 cyclosporin. 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 ADVERSE EFFECTS). Close monitoring of parameters that assess renal and hepatic function is required. Abnormal values may necessitate dose reduction.

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

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

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

Cyclosporin enhances the risk of hyperkalaemia, especially in patients with renal dysfunction. Caution is also required when cyclosporin 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 Interaction with other medicinal products and other forms of interaction). Control of potassium levels in these situations is advisable.

Cyclosporin enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplant period. Control of serum magnesium levels is therefore recommended in the peri-transplant period, particularly in the presence of neurological symptom/signs. If considered necessary, magnesium supplementation should be given.

Caution is required in treating patients with hyperuricaemia.

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

Caution should be observed while co-administering lercanidipine with cyclosporin (see Interaction with other medicinal products and other forms of interaction).

Cyclosporin may increase blood levels of concomitant medications that are substrates of Pgp such as aliskiren (see Interaction with other medicinal products and other forms of interaction).

Interaction with other medicinal products and other forms of interaction

Food interactions

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

Drug interactions

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

Various agents are known to either increase or decrease plasma or whole blood cyclosporin levels usually by inhibition or induction of enzymes involved in the metabolism of cyclosporin, in particular CYP3A4. Cyclosporin is

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

Drugs that decrease cyclosporin levels

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

Drugs that increase cyclosporin levels

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

Other relevant drug interactions

Care should be taken when using cyclosporin 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), methotrexate (see Special warnings and precautions for use).

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

The concurrent administration of nifedipine with cyclosporin may result in an increased rate of gingival hyperplasia compared with that observed when cyclosporin is given alone.

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

Cyclosporin is a highly potent Pgp inhibitor and may increase blood levels of concomitant medications that are substrates of Pgp such as aliskiren. Following concomitant administration of cyclosporin and aliskiren, the C_{max} of aliskiren was increased by approximately 2.5 fold and the AUC by approximately 5 fold. However, the pharmacokinetic profile of cyclosporin was not significantly altered. Caution is recommended when co-administering cyclosporin together with aliskiren (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The concomitant use of diclofenac and cyclosporin 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 cyclosporin, no increase in their bioavailability is to be expected.

Cyclosporin may reduce the clearance of digoxin, colchicine, and prednisolone, HMG-CoA reductase inhibitors (statins) and etoposide.

Severe digitalis toxicity has been seen within days of starting cyclosporin in several patients taking digoxin. There are also reports on the potential of cyclosporin 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 cyclosporin, 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 cyclosporin with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely, fluvastatin. When concurrently administered with cyclosporin, 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.

Elevations in serum creatinine were observed in the studies using everolimus or sirolimus in combination with full-dose cyclosporin for microemulsion. This effect is often reversible with cyclosporin dose reduction.

Everolimus and sirolimus had only a minor influence on cyclosporin pharmacokinetics. Co-administration of cyclosporin significantly increases blood levels of everolimus and sirolimus.

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 Special warnings and precautions for use).

Cyclosporin may increase the plasma concentrations of repaglinide and thereby increase the risk of hypoglycaemia.

Recommendations

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

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

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

Drugs known to reduce or increase the bioavailability of cyclosporin: in *transplant patients* frequent measurement of cyclosporin levels and, if necessary, cyclosporin dosage adjustment are required, particularly during the introduction or withdrawal of the co-administered drug.

If drugs known to increase cyclosporin levels are given concomitantly, frequent assessment of renal function and careful monitoring for cyclosporin-related side effects may be more appropriate than blood level measurement.

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

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 cyclosporin.

If digoxin, colchicines, or HMG-CoA reductase inhibitors (statins) are used concurrently with cyclosporin, 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.

Pregnancy and lactation

Pregnancy

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

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

A limited number of observations in children exposed to cyclosporin 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 and well-controlled studies in pregnant women and, therefore, Sandimmun should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

Lactation

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

Effects on ability to drive and use machines

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

Adverse effects

Many side effects associated with cyclosporin 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 'Special warnings and precautions for use').

Infections and Infestations

Patients receiving immunosuppressive therapies, including cyclosporin and cyclosporin-containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic) (see '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 cyclosporin and cyclosporin-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 'Special warnings and precautions for use'). Some malignancies may be fatal.

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100, < 1/10$); uncommon ($\geq 1/1,000, < 1/100$); rare ($\geq 1/10,000, < 1/1,000$) very rare ($< 1/10,000$), including isolated reports.

Table 1

Blood and lymphatic system disorders

Uncommon Anaemia, thrombocytopenia.

Rare Microangiopathic haemolytic anaemia, haemolytic uraemic syndrome.

Metabolism and nutrition disorders

Very common Hyperlipidaemia.

Common

Common Anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia.

Rare Hyperglycaemia.

Nervous system disorders

Very common Tremor, headache, including migraine.

Common

Common Paraesthesia.

Uncommon Signs of encephalopathy such as convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia.

Rare Motor polyneuropathy.

Very rare Optic disc oedema including papilloedema, with possible visual impairment secondary to benign intracranial hypertension.

Vascular disorders

Very common Hypertension.

Common

Gastrointestinal disorders

Common Nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia

Rare Pancreatitis.

Hepatobiliary disorders

Common Hepatic function abnormal (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Skin and subcutaneous tissue disorders

Common Hypertrichosis.

Uncommon Allergic rashes.

Musculoskeletal and connective tissue disorders

Common Muscle cramps, myalgia.

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|---|---|
| Rare | Muscle weakness, myopathy. |
| Renal and urinary disorders | |
| Very common | Renal dysfunction (see Special warnings and precautions for use). |
| Reproductive system and breast disorders | |
| Rare | Menstrual disturbances, gynecomastia. |
| General disorders and administration site conditions | |
| Common | Fatigue. |
| Uncommon | Oedema, weight increase. |

Other adverse drug reactions from post-marketing experience

There have been solicited and spontaneous postmarketing reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients with cyclosporin. 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Overdose

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

Symptoms

Experience with acute overdosage of cyclosporin is limited. Oral doses of cyclosporin 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 cyclosporin 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. Cyclosporin is not dialysable to any great extent, nor is it well cleared by charcoal haemoperfusion.

Pharmacological properties

Pharmacodynamic properties

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

Cyclosporin (also known as cyclosporin 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 cyclosporin 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). Cyclosporin 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 cyclosporin 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. Cyclosporin 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.

Pharmacokinetics properties

Cyclosporin 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.

Cyclosporin 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 cyclosporin 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.

Preclinical safety data

Cyclosporin 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), cyclosporin 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 cyclosporin 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 cyclosporin intravenously (twice the recommended human intravenous dose) had fetuses with an increased incidence of ventricular septal defect.

These findings have not been demonstrated in other species and their relevance 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.

Cyclosporin has not been found mutagenic/genotoxic in the Ames test, the v79–hprt 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 cyclosporin 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 cyclosporin 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.

Pharmaceutical particulars

List of excipients

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

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.

Shelf life

4 years.

Special precautions for storage

Store below 30°C

Nature and contents of container

Packs containing 10 x 5-mL uncoloured glass ampoules.

Instructions for use/handling

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

Medicine classification

Prescription Medicine

Name and address

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Date of preparation

2 September 2010