

SANDIMMUN[®] Concentrate for infusion

1. Trade name of the medicinal product

SANDIMMUN[®]

2. Qualitative and quantitative composition

Sandimmun[®] concentrate for intravenous infusion containing 50 mg ciclosporin per mL.

3. Pharmaceutical form

Sandimmun concentrate for i.v. infusion.

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. Posology and method of administration

The dose ranges given are intended to serve as guidelines only. The recommended dose of Sandimmun concentrate for i.v. infusion is approximately one third of the appropriate oral dose.

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 4.4. Special warnings and special 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 i.v. 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 section '6.2. 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 i.v. 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 i.v. 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 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. Low doses of ciclosporin 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.

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 and/or polyoxyethylated castor oil.

4.4. Special warnings and special precautions for use

Sandimmun concentrate for i.v. 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.

Sandimmun concentrate for i.v. infusion contains polyoxyethylated castor oil, which following i.v. administration has been reported to cause anaphylactoid reactions. These reactions consist of flushing of the face and upper thorax, acute respiratory distress with dyspnoea and wheezing, blood pressure changes and tachycardia. Special caution is therefore necessary in patients who have previously received, by i.v. injection or infusion, preparations containing polyoxyethylated castor oil (e.g. a preparation containing Cremophor[®] EL), and in patients with an allergic predisposition. Thus, patients receiving Sandimmun concentrate for i.v. 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 i.v. infusion has also been successfully employed to prevent the occurrence of anaphylactoid reactions.

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

Like other immunosuppressants, ciclosporin predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections, often with opportunistic pathogens. As this can lead to a fatal outcome, 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. Close monitoring of parameters that assess renal and hepatic function is required. Abnormal values may necessitate dose reduction.

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.

Ciclosporin enhances the risk of hyperkalaemia, especially in patients with renal dysfunction. Caution is also required when ciclosporin is co-administered with potassium sparing diuretics, angiotensin converting enzyme inhibitors [1], angiotensin II receptor antagonists [2] and potassium containing drugs as well as in patients on a potassium rich diet. Control of potassium levels in these situations is advisable.

Ciclosporin enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplant period. Control of serum magnesium levels is therefore recommended in the peri-transplant period, particularly in the presence of neurological symptom/signs. If considered necessary, magnesium supplementation should be given [3].

Caution is required in treating patients with hyperuricaemia.

4.5. Interaction with other medicaments and other forms of interaction

Food interactions

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

Drug interactions

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

Various agents are known to either increase or decrease plasma or whole blood ciclosporin levels usually by inhibition or induction of enzymes involved in the metabolism of ciclosporin, in particular cytochrome P450 enzymes.

Drugs that decrease ciclosporin levels

Barbiturates, carbamazepine, phenytoin; nafcillin, sulfadimidine i.v.; rifampicin; octreotide; probucol; orlistat [4-6]; *hypericum perforatum* (St. John's wort) [5-9]; troglitazone [5,6,10-13].

Drugs that increase ciclosporin levels

Macrolide antibiotics (mainly erythromycin and clarithromycin [5,6,14-19]); ketoconazole, fluconazole, itraconazole; diltiazem, nifedipine, verapamil; metoclopramide; oral contraceptives; danazol; methylprednisolone (high dose); allopurinol; amiodarone; cholic acid and derivatives.

Other relevant drug interactions

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

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

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

Ciclosporin may also reduce the clearance of digoxin, colchicine, lovastatin, pravastatin, simvastatin and prednisolone, thereby causing digoxin toxicity or enhancing the potential of colchicine, lovastatin, pravastatin [20-22] and simvastatin [21,23] to induce muscular toxicity, including muscle pain and weakness, myositis and, occasionally, rhabdomyolysis.

Recommendations

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

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

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

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

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

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

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

4.6. Pregnancy and lactation

Ciclosporin is not teratogenic in animals. Experience with Sandimmun in pregnant women, however, is still limited. Data available from organ transplant recipients indicate that, compared with other immunosuppressive therapy, Sandimmun treatment imposes no increased risk of adverse effects on the course and outcome of pregnancy. However, there are no adequate and well-controlled studies in pregnant women and, therefore, Sandimmun should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

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

Frequency estimate: very common $\geq 10\%$, common $\geq 1\%$ to $< 10\%$; uncommon $\geq 0.1\%$ to $< 1\%$; rare $\geq 0.01\%$ to $< 0.1\%$; very rare $< 0.01\%$.

Renal

Very common: renal dysfunction (see 4.4. Special warnings and special precautions for use).

Cardiovascular

Very common: hypertension.

Nervous system

Very common: tremor, headache.

Common: paraesthesia

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

Rare: motor polyneuropathy.

Very rare: optic disc oedema.[6]

Gastrointestinal tract and liver

Common: anorexia, nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia, hepatic dysfunction.

Rare: pancreatitis.

Metabolic

Very common: hyperlipidaemia.

Common: hyperuricaemia, hyperkalaemia, hypomagnesaemia.

Rare: hyperglycaemia.

Muskuloskeletal

Common: muscle cramps, myalgia.

Rare: muscle weakness, myopathy.

Haemopoietic

Uncommon: anaemia, thrombocytopenia.

Rare: micro-angiopathic haemolytic anaemia, haemolytic uraemic syndrome.

Skin and appendages

Common: hypertrichosis.

Uncommon: allergic rashes.

Body as a whole

Common: fatigue.

Uncommon: oedema, weight increase.

Endocrine

Rare: menstrual disturbances, gynecomastia.

4.9. Overdose

The oral LD₅₀ of ciclosporin is 2329 mg/kg in mice, 1480 mg/kg in rats and > 1000 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.

No experience of acute overdosage of Sandimmun is available. Renal dysfunction, which would be expected to resolve following drug withdrawal, may occur. If indicated, general supportive measures should follow. Ciclosporin is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressive agents (ATC code L04A A01)

Ciclosporin (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 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. 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

Ciclosporin is distributed largely outside the blood volume. In the blood, 33-47% is present in plasma, 4-9% in lymphocytes, 5-12% in granulocytes, and 41-58% 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 ranged from 6.3 hours in healthy volunteers to 20.4 hours in patients with severe liver disease.

5.3. Preclinical safety data

Ciclosporin gave no evidence of mutagenic or teratogenic effects in appropriate test systems. Only at dose levels toxic to dams were adverse effects seen in reproduction studies in rats. 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 the well-tolerated dose range (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally), ciclosporin proved to be without any embryolethal or teratogenic effects.

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

Absolute ethanol, polyoxyethylated castor oil.

6.2. Incompatibilities

Sandimmun concentrate for i.v. infusion contains polyoxyethylated 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 plastic containers for blood of the European Pharmacopoeia. Containers and stoppers should be free of silicon oil and fatty substances.

6.3. Shelf life

48 months.

6.4. Nature and contents of container

1-mL and 5-mL uncolored glass ampoules.

6.5. Instructions for use/handling

Sandimmun concentrate for i.v. infusion should be kept out of the reach of children.

Manufacturer:

Novartis Pharma AG, Basel, Switzerland

License holder:

Promedico Ltd.

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