

Ciclosporin

Proposed Core Safety Profile

4.3 Contraindications

Hypersensitivity to ciclosporin or to any of the excipients of Sandimmun/ Sandimmun Neoral.

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

4.4 Special warnings and precautions for use

Sandimmun Neoral and 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.

Sandimmun concentrate for solution for infusion contains polyethoxylated castor oil, 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, 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.

In view of the potential risk of skin malignancy, patients on Sandimmun/ Sandimmun Neoral, in particular those treated for psoriasis or atopic dermatitis, should be warned to avoid excess unprotected sun exposure and should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

Like other immunosuppressants, ciclosporin predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections, often with opportunistic pathogens.

Activation of latent Polyomavirus infections that may lead to Polyomavirus associated nephropathy (PVAN), especially to BK virus nephropathy (BKVN), or to JC virus associated progressive multifocal leukoencephalopathy (PML) have been observed in patients receiving ciclosporin. These conditions are often related to a high total immunosuppressive burden and should be considered in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Serious and/or fatal outcomes have been reported. Effective pre-emptive and therapeutic strategies should be employed particularly in patients on multiple long-term immunosuppressive therapy.

A frequent and potentially serious complication, an increase in serum creatinine and urea, may occur during the first few weeks of Sandimmun/ Sandimmun Neoral 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/ Sandimmun Neoral may also cause dose-dependent, reversible increases in serum bilirubin and, occasionally, in liver enzymes (see section 4.8 Undesirable effects). There have been solicited and spontaneous reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients treated with ciclosporin. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and comedications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see section 4.8 Undesirable effects). Close monitoring of parameters that assess renal and hepatic function is required. Abnormal values may necessitate dose reduction.

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

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

monoclonal antibody should be performed, to ensure a dosage that provides adequate immunosuppression.

It must be remembered that the ciclosporin concentration in blood, plasma, or serum is only one of many factors contributing to the clinical status of the patient. Results should therefore serve only as a guide to dosage in relationship to other clinical and laboratory parameters.

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

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

Ciclosporin enhances the risk of hyperkalaemia, especially in patients with renal dysfunction. Caution is also required when ciclosporin is co-administered with potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) 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.

Caution is required in treating patients with hyperuricaemia.

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

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

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

Sandimmun/ Sandimmun Neoral contain Polyoxyl 40 hydrogenated castor oil which may cause stomach upsets and diarrhoea.

Sandimmun/Sandimmun oral formulations contain around 12% vol. ethanol. A 500 mg dose of Sandimmun/Sandimmun Neoral contains 500 mg of ethanol equivalent to nearly 15 ml of beer or 5 ml of wine. Sandimmun IV formulation contains 34.4% ethanol. A 100 mg dose of Sandimmun concentrate contains 556 mg of ethanol, also

equivalent to nearly 15 ml of beer or 5 ml of wine. This may be harmful in alcoholic patients and should be taken into account in pregnant or breast feeding women, in patients presenting with liver disease or epilepsy, or if the medicine is being given to a child. Patients with rare hereditary problems of fructose intolerance should not take Sandimmun capsules due to the presence of sorbitol.

Additional precautions in non-transplant indications

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

Additional precautions in endogenous uveitis

Since Sandimmun/ Sandimmun Neoral can impair renal function, it is necessary to assess renal function frequently, and if serum creatinine remains increased to more than 30% above baseline at more than one measurement, to reduce the dosage of Sandimmun/ Sandimmun Neoral by 25 to 50%. These recommendations apply even if the patient's values still lie within the laboratory's normal range.

There is only limited experience with the use of Sandimmun/ Sandimmun Neoral in children with endogenous uveitis.

Additional precautions in nephrotic syndrome

Since Sandimmun/ Sandimmun Neoral can impair renal function, it is necessary to assess renal function frequently, and if the serum creatinine remains increased to more than 30% above baseline at more than one measurement, to reduce the dosage of Sandimmun/ Sandimmun Neoral by 25 to 50 %.

Patients with abnormal baseline renal function should initially be treated with 2.5 mg/kg per day and must be monitored very carefully.

In some patients, it may be difficult to detect Sandimmun/ Sandimmun Neoral - induced renal dysfunction because of changes in renal function related to the nephrotic syndrome itself. This explains why, in rare cases, Sandimmun Neoral-associated structural kidney alterations have been observed without increases in serum creatinine. Renal biopsy should be considered for patients with steroid-dependent minimal-change nephropathy, in whom Sandimmun/ Sandimmun Neoral therapy has been maintained for more than 1 year.

In patients with nephrotic syndrome treated with immunosuppressants (including ciclosporin), the occurrence of malignancies (including Hodgkin's lymphoma) has occasionally been reported.

Additional precautions in rheumatoid arthritis

Since Sandimmun/ Sandimmun Neoral can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals during the

first 3 months of therapy and thereafter once a month. After 6 months of therapy, serum creatinine needs to be measured every 4 to 8 weeks depending on the stability of the disease, its co medication, and concomitant diseases. More frequent checks are necessary when the Sandimmun/ Sandimmun Neoral dose is increased, or concomitant treatment with a non-steroidal anti-inflammatory drug is initiated or its dosage increased.

If the serum creatinine remains increased to more than 30% above baseline at more than one measurement, the dosage of Sandimmun/ Sandimmun Neoral should be reduced. If the serum creatinine increases by more than 50%, a dosage reduction by 50% is mandatory. These recommendations apply even if the patient's values still lie within the laboratory's normal range. If dose reduction is not successful in reducing levels within one month, Sandimmun/ Sandimmun Neoral treatment should be discontinued.

Discontinuation of the drug may also become necessary if hypertension developing during Sandimmun/ Sandimmun Neoral therapy cannot be controlled by appropriate antihypertensive therapy.

As with other long-term immunosuppressive treatments (including ciclosporin), an increased risk of lymphoproliferative disorders must be borne in mind. Special caution should be observed if Sandimmun/ Sandimmun Neoral is used in combination with methotrexate.

Additional precautions in psoriasis

Since Sandimmun/ Sandimmun Neoral can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals for the first 3 months of therapy.

Thereafter, if creatinine remains stable, measurements should be made at monthly intervals. If the serum creatinine increases and remains increased to more than 30% above baseline at more than one measurement, the dosage of Sandimmun/ Sandimmun Neoral must be reduced by 25 to 50%. These recommendations apply even if the patient's values still lie within the laboratory's normal range. If dose reduction is not successful in reducing levels within one month, Sandimmun/ Sandimmun Neoral treatment should be discontinued.

Discontinuation of Sandimmun/ Sandimmun Neoral therapy is also recommended if hypertension developing during Sandimmun/ Sandimmun Neoral treatment cannot be controlled with appropriate therapy.

Elderly patients should be treated only in the presence of disabling psoriasis, and renal function should be monitored with particular care.

There is only limited experience with the use of Sandimmun/ Sandimmun Neoral in children with psoriasis.

In psoriatic patients on ciclosporin, as in those on conventional immunosuppressive therapy, development of malignancies (in particular of the skin) has been reported. Skin lesions not typical for psoriasis, but suspected to be malignant or pre-malignant should be biopsied before Sandimmun/ Sandimmun Neoral treatment is started. Patients with malignant or pre-malignant alterations of the skin should be treated with Sandimmun Neoral only after appropriate treatment of such lesions, and if no other option for successful therapy exists.

In a few psoriatic patients treated with Sandimmun/ Sandimmun Neoral, lymphoproliferative disorders have occurred. These were responsive to prompt drug discontinuation.

Patients on Sandimmun/ Sandimmun Neoral should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

Additional precautions in atopic dermatitis

Since Sandimmun/ Sandimmun Neoral can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals for the first 3 months of therapy.

Thereafter, if creatinine remains stable, measurements should be made at monthly intervals. If the serum creatinine increases and remains increased to more than 30% above baseline at more than one measurement, the dosage of Sandimmun/ Sandimmun Neoral must be reduced by 25 to 50%. These recommendations apply even if the patient's values still lie within the laboratory's normal range. If dose reduction is not successful in reducing levels within 1 month, Sandimmun/ Sandimmun Neoral treatment should be discontinued.

Discontinuation of Sandimmun/ Sandimmun Neoral therapy is also recommended if hypertension developing during Sandimmun/ Sandimmun Neoral treatment cannot be controlled with appropriate therapy.

The experience with Sandimmun/ Sandimmun Neoral in children with atopic dermatitis is limited.

Elderly patients should be treated only in the presence of disabling atopic dermatitis and renal function should be monitored with particular care.

Benign lymphadenopathy is commonly associated with flares in atopic dermatitis, and invariably disappears spontaneously or with general improvement in the disease.

Lymphadenopathy observed on treatment with ciclosporin should be regularly monitored.

Lymphadenopathy which persists despite improvement in disease activity should be examined by biopsy as a precautionary measure to ensure the absence of lymphoma.

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

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

Patients on Sandimmun/ Sandimmun Neoral should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

Paediatric use in non-transplant indications

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

4.5 Interaction with other medicinal products and other forms of interaction

Food interactions

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

The concomitant intake of fat-rich meal has been reported to increase the bioavailability of Sandimmun oral formulations.

Drug interactions

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

Various agents are known to either increase or decrease plasma or whole blood ciclosporin levels usually by inhibition or induction of enzymes involved in the metabolism of ciclosporin, in particular CYP3A4. Ciclosporin is also an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein and may increase plasma levels of co medications that are substrates of this enzyme and/or transporter.

Drugs that decrease ciclosporin levels

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

Drugs that increase ciclosporin 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 ciclosporin together with other drugs that exhibit nephrotoxic synergy such as: aminoglycosides (incl. gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); non-steroidal antiinflammatory drugs (incl. diclofenac, naproxen, sulindac); melphalan histamine H₂-receptor antagonists (e.g. cimetidine, ranitidine); methotrexate (see section 4.4 Special warnings and precautions for use).

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

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

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

Ciclosporin is a highly potent Pgp inhibitor and may increase blood levels of concomitant medications that are substrates of Pgp such as aliskiren. Following concomitant administration of ciclosporin and aliskiren, the C_{max} of aliskiren was increased by approximately 2.5 fold and the AUC by approximately 5 fold. However, the pharmacokinetic profile of ciclosporin was not significantly altered. Caution is recommended when co-administering ciclosporin together with aliskiren (see section 4.4 Special warnings and precautions for use).

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

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

Severe digitalis toxicity has been seen within days of starting ciclosporin in several patients taking digoxin. There are also reports on the potential of ciclosporin to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. If digoxin or colchicine 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.

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. Coadministration of ciclosporin 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 section 4.4 Special warnings and precautions for use).

Ciclosporin 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 ciclosporin cannot be avoided, the following basic recommendations should be observed:

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

In graft recipients there have been isolated reports of considerable but reversible impairment of kidney function (with corresponding increase in serum creatinine) following concomitant administration of fibric acid derivatives (e.g. bezafibrate, fenofibrate).

Kidney function must therefore be closely monitored in these patients. In the event of significant impairment of kidney function the co-medication should be withdrawn.

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

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

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

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.

4.6 Pregnancy and lactation

Pregnancy

Animal studies have shown reproductive toxicity in rats and rabbits.

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

A limited number of observations in children exposed to ciclosporin in utero are 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/ Sandimmun Neoral should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Anaphylactoid reactions have been observed following i.v. administration (see section 4.4 'Special warnings and precautions for use').

Infections and Infestations

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

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

Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of developing lymphomas or lymphoproliferative disorders and other malignancies, particularly of the skin. The frequency of malignancies increases with the intensity and duration of therapy (see section 4.4). 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 Anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia (see section 4.4).

Rare Hyperglycemia.

Nervous system disorders

Very
common Tremor, headache including migraine.

Common Paraesthesia.

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

Gastrointestinal disorders

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

Rare Pancreatitis.

Hepatobiliary disorders

Common Hepatic function abnormal (see section 4.4 Special warnings and precautions for use).

Skin and subcutaneous tissue disorders

Common Hypertrichosis.

Uncommon Allergic rashes.

Musculoskeletal and connective tissue disorders

Common Muscle cramps, myalgia.

Rare Muscle weakness, myopathy.

Renal and urinary disorders

Very
Common Renal impairment (see section 4.4 Special warnings and precautions for use).

Reproductive system and breast disorders

Rare Menstrual disturbances, gynecomastia.

General disorders and administration site conditions

Common Fatigue.

Uncommon Oedema, weight increase.

Other adverse drug reactions from post-marketing experience

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

4.9 Overdose

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

Symptoms

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

Treatment

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