

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ciclosporin Genfarma 50 mg Soft Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg ciclosporin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft

Ciclosporin Genfarma 50 mg Capsules are grey soft gelatin capsules with imprinting "DX 50 mg".

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Organ Transplantation

Prevention of graft rejection following kidney, liver, heart, combined heart-lung, lung or pancreas transplants.
Treatment of transplant rejection in patients previously receiving other immunosuppressive agents.

Bone Marrow Transplantation

Prevention of graft rejection following bone marrow transplantation and prophylaxis of graft-versus-host disease (GVHD).

Treatment of established graft-versus-host disease (GVHD).

Psoriasis

Ciclosporin Genfarma are indicated in patients with severe psoriasis in whom conventional therapy is ineffective or inappropriate.

Atopic Dermatitis

Ciclosporin Genfarma are indicated for short term treatment (8 weeks) of patients with severe atopic dermatitis in whom conventional therapy is ineffective or inappropriate.

Nephrotic Syndrome

Ciclosporin Genfarma are indicated in the treatment of adults and children with steroid-dependent and steroid-resistant nephrotic syndrome owing to glomerular diseases such as minimal change nephropathy, focal segmental glomerulosclerosis or membranous glomerulonephritis.

Ciclosporin Genfarma can be used to induce remissions and for maintenance treatment.

Rheumatoid Arthritis

Ciclosporin Genfarma are indicated for the treatment of severe, active rheumatoid arthritis in patients in whom classical slow-acting anti-rheumatic agents are inappropriate or ineffective.

4.2 Posology and method of administration

Route of Administration

Oral. Ciclosporin should not be taken with grapefruit juice.

Recommended Dosage Schedule

Due to differences in bioavailability between different oral formulations of ciclosporin it is important that health professionals and patients be aware that substitution of Ciclosporin Genfarma Capsules for other formulations may lead to alterations in ciclosporin blood levels.

Therefore patients should not be transferred to or from other oral formulations of ciclosporin without appropriate close monitoring of ciclosporin blood concentrations, serum creatinine levels and blood pressure.

Organ Transplantation

Initially, a dose of 10 to 15 mg/kg body weight in two divided doses should be given within twelve hours before transplantation. As a general rule, treatment should continue at a dose of 10 to 15 mg/kg/day in two divided doses for one to two weeks post-operatively. Dosage should then be gradually reduced until a maintenance dose of 2 to 6 mg/kg/day is reached. This total daily dose should be given in two divided doses. Dosage should be adjusted by monitoring ciclosporin blood levels and kidney function. When Ciclosporin Genfarma are given with other immunosuppressants (e.g. with corticosteroids or as part of a triple or quadruple drug therapy) lower doses (e.g. 3 to 6 mg/kg/day in two divided doses orally initially) may be used.

Bone Marrow Transplantation/Prevention and Treatment of Graft-Versus-Host Disease (GVHD)

Maintenance treatment with Ciclosporin Genfarma should continue using the oral forms at a dosage of 12.5 mg/kg/day in two divided doses for at least three and preferably six months before tailing off to zero.

In some cases, it may not be possible to withdraw Ciclosporin Genfarma until a year after bone marrow transplantation. Higher oral doses or the use of I.V. ciclosporin therapy may be necessary in the presence of gastrointestinal disturbances which might decrease absorption.

If oral treatment is used to initiate therapy, the recommended dose is 12.5 to 15 mg/kg/day in two divided doses starting on the day before transplantation.

If GVHD develops after Ciclosporin Genfarma are withdrawn, it should respond to re-institution of therapy. Low doses should be used for mild, chronic GVHD.

Psoriasis

Refer also to "Additional Precautions in Psoriasis" section.

To induce remission, the recommended initial dose is 2.5 mg/kg/day given orally in two divided doses. If there is no improvement after one month, the daily dose may be gradually increased, but should not exceed 5 mg/kg/day orally. Treatment should be discontinued if sufficient response is not achieved within six weeks on 5 mg/kg/day orally, or if the effective dose is not compatible with the safety guidelines given below (see Precautions). Initial doses of 5 mg/kg/day orally are justified in patients whose condition requires rapid improvement.

For maintenance treatment, dosage must be individually titrated to the lowest effective level, and should not exceed 5 mg/kg/day orally in two divided doses.

Some clinical data are available which provide evidence that once satisfactory response is achieved, ciclosporin may be discontinued and subsequent relapse managed with reintroduction of ciclosporin at the previous effective dose. In some patients continuous maintenance therapy may be necessary.

Atopic Dermatitis

Refer also to "Additional Precautions in Atopic Dermatitis" section.

The recommended dose range is 2.5 – 5 mg/kg/day orally in two divided doses for a maximum of eight weeks. If a starting dose of 2.5 mg/kg/day does not achieve a good initial response within two weeks the dose may be rapidly increased to a maximum of 5 mg/kg/day. In very severe cases, rapid and adequate control of disease is more likely with a starting dose of 5 mg/kg/day, given orally in two divided doses.

Nephrotic Syndrome

Refer to "Additional Precautions in Nephrotic Syndrome" section.

To induce remission, the recommended dose is 5 mg/kg/day given orally in two divided doses for adults, and 6 mg/kg/day given orally in two divided doses for children, if, with the exception of proteinuria, renal function is normal. In patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day orally.

In focal segmental glomerulosclerosis, the combination of ciclosporin and corticosteroids may be of benefit.

In the absence of efficacy after 3 months treatment for minimal change and focal segmental glomerulosclerosis or 6 months treatment for membranous glomerulonephritis, ciclosporin therapy should be discontinued.

The doses need to be adjusted individually according to efficacy (proteinuria) and safety (primarily serum creatinine), but should not exceed 5 mg/kg/day orally in adults or 6 mg/kg/day orally in children.

For maintenance treatment, the dose should be slowly reduced to the lowest effective level.

Long-term data of ciclosporin in the treatment of nephrotic syndrome are limited. However, in clinical trials patients have received treatment for 1 to 2 years. Long-term treatment may be considered if there has been a significant reduction in proteinuria with preservation of creatinine clearance and provided adequate precautions are taken.

Rheumatoid Arthritis

Refer also to "Additional Precautions in Rheumatoid Arthritis" section.

It is recommended that initiation of Ciclosporin Genfarma therapy should take place over a period of 12 weeks.

For the first 6 weeks of treatment, the recommended dose is 2.5 mg/kg/day given orally in two divided doses. If the effect is insufficient, the daily dose may then be increased gradually as tolerability permits, but should not exceed 4 mg/kg/day orally.

If, after 3 months of treatment at the maximum permitted or tolerable dose the response is considered inadequate, treatment should be discontinued.

For maintenance treatment the dose has to be titrated individually according to tolerability.

Ciclosporin Genfarma can be given in combination with low-dose corticosteroids and/or non-steroidal anti-inflammatory drugs. Pharmacodynamic interactions can occur between ciclosporin and NSAIDs and therefore this combination should be used with care (*see section 4.5, Interaction with other medicinal products and other forms of interaction*).

Long-term data on the use of ciclosporin in the treatment of rheumatoid arthritis are still limited. Therefore, it is recommended that patients are re-evaluated after 6 months of maintenance treatment and therapy only continued if the benefits of treatment outweigh the risks.

Administration

The total daily dosage of Ciclosporin Genfarma should always be given in two divided doses.

Ciclosporin should not be taken with grapefruit or grapefruit juice for 1 hour prior to dose administration (*see section 4.5, Interaction with other medicinal products and other forms of interaction*).

Use in the Elderly

Experience in the elderly is limited but no particular problems have been reported following the use of the drug at the recommended dose. However, factors sometimes associated with ageing, in particular impaired renal function, make careful supervision essential and may necessitate dosage adjustment.

Use in Children

Experience with ciclosporin in young children is still limited. Transplant recipients from three months of age have

received ciclosporin at the recommended dosage with no particular problems, although, at dosages above the upper end of the recommended range, children seem to be more susceptible to fluid retention, convulsions and hypertension. This responds to dosage reduction.

4.3 Contraindications

Known hypersensitivity to ciclosporin or to any of the excipients.

Ciclosporin Genfarma are also contraindicated in psoriatic patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy other than of the skin (see Precautions).

Ciclosporin Genfarma are contraindicated in rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy.

Ciclosporin Genfarma should not be used to treat rheumatoid arthritis in patients under the age of 18 years.

Ciclosporin Genfarma are contra-indicated in nephrotic syndrome patients with uncontrolled hypertension, uncontrolled infections, or any kind of malignancy.

Concomitant use of tacrolimus is specifically contraindicated.

4.4 Special warnings and precautions for use

Precautions

Ciclosporin Genfarma can impair renal function. Close monitoring of serum creatinine and urea is required and dosage adjustment may be necessary. Increases in serum creatinine and urea occurring during the first few weeks of Ciclosporin Genfarma therapy are generally dose-dependent and reversible and usually respond to dosage reduction. During long-term treatment, some patients may develop structural changes in the kidney (eg. interstitial fibrosis) which, in renal transplant recipients, must be distinguished from chronic rejection.

Ciclosporin Genfarma may also affect liver function and dosage adjustment, based on the results of bilirubin and liver enzyme monitoring, may be necessary.

Regular monitoring of blood pressure is required during Ciclosporin Genfarma therapy. If hypertension develops, appropriate antihypertensive treatment must be instituted.

Since, on rare occasions, 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.

Since ciclosporin occasionally causes hyperkalaemia or may aggravate pre-existing hyperkalaemia, monitoring of serum potassium is recommended, especially in patients with marked renal dysfunction. Patients receiving Ciclosporin Genfarma should avoid a high dietary potassium intake. Caution is also required when ciclosporin is co-administered with potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and potassium containing drugs. Refer also to Drug Interactions.

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.

Ciclosporin increases the risk of malignancies including lymphomas, skin and other tumours. The increased risk appears to be related to the degree and duration of immunosuppression rather than to the specific use of ciclosporin. Hence a treatment regimen containing immunosuppressants should be used with caution as this could lead to lymphoproliferative disorders and solid organ tumours, some with reported fatalities.

Ciclosporin predisposes patients to infection with a variety of pathogens including bacteria, parasites, viruses and other opportunistic pathogens. This appears to be related to the degree and duration of immunosuppression rather than to the specific use of ciclosporin. 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.

There are differences in bioavailability between different oral formulations of ciclosporin.

Ciclosporin may increase the risk of Benign Intracranial Hypertension. Patients presenting with signs of raised

intracranial pressure should be investigated and if Benign Intracranial Hypertension is diagnosed, ciclosporin should be withdrawn due to the possible risk of permanent visual loss.

Caution is required in treating patients with hyperuricaemia.

Ciclosporin should preferably not be administered with other immunosuppressive agents except corticosteroids. However, some transplant centres use ciclosporin together with azathioprine and corticosteroids or other immunosuppressive agents (all in low doses) with the aim of reducing the risk of ciclosporin-induced renal dysfunction or renal structural changes. When ciclosporin is used with other immunosuppressive agents, there is a risk of over-immunosuppression, which can lead to increased susceptibility to infection and to possible development of lymphoma.

In ciclosporin-treated renal transplant recipients, a machine perfusion time of more than 24 hours and a reanastomosis time of more than 45 minutes can have a significant effect on graft function. Both factors appear to increase the incidence of acute tubular necrosis.

Additional Precautions in Psoriasis and Atopic Dermatitis

Only the oral forms of ciclosporin are recommended for the treatment of patients with psoriasis or atopic dermatitis. Treatment and its monitoring should be carried out under the supervision of a dermatologist experienced in the management of severe skin diseases.

Careful dermatological and physical examinations, including measurements of blood pressure and renal function on at least two occasions prior to starting therapy should be performed to establish an accurate baseline status.

Development of malignancies (particularly of the skin) have been reported in psoriatic patients treated with ciclosporin as well as during treatment with conventional therapy. A search for all forms of pre-existing tumours, including those of the skin and cervix, should be carried out. Skin lesions which are not typical for psoriasis should be biopsied before starting Ciclosporin Genfarma treatment to exclude skin cancers, mycosis fungoides or other pre-malignant disorders. Patients with malignant or pre-malignant alterations of the skin should be treated with Ciclosporin Genfarma only after appropriate treatment of such lesions and only if no other option for successful therapy exists.

Because of the possibility of renal dysfunction or renal structural changes, serum creatinine should be measured at two-weekly intervals during the first three months of therapy. Thereafter, if creatinine remains stable, measurements should be repeated at monthly intervals in patients who require higher doses. If serum creatinine increases to more than 30% above baseline, even if the values are still within the normal range, Ciclosporin Genfarma dosage must be reduced by 25 to 50%. If dosage reduction is not successful within one month, treatment should be discontinued.

In atopic dermatitis patients, serum creatinine should be measured at two weekly intervals throughout the treatment period.

If hypertension develops which cannot be controlled by Ciclosporin Genfarma dosage reduction or appropriate antihypertensive therapy, discontinuation of the drug is recommended.

In view of the potential risk of skin malignancy, patients on Ciclosporin Genfarma should be warned to avoid excess unprotected sun exposure and should not receive concomitant therapeutic ultraviolet B irradiation or PUVA photochemotherapy.

Additional precautions in Atopic Dermatitis

Active herpes simplex infections should be allowed to clear before initiating treatment with Ciclosporin Genfarma but are 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 Ciclosporin Genfarma therapy but should be controlled with appropriate antibacterial agents. Orally erythromycin, known to have the potential to increase the blood concentration of ciclosporin (see Interactions) should be avoided or, if there is no alternative, its concomitant use must be accompanied by close monitoring of the blood levels of ciclosporin.

As experience with ciclosporin in children with atopic dermatitis is still limited, its use in children under 16 years of age cannot be recommended.

Additional Precautions in Nephrotic Syndrome

Only the oral forms of ciclosporin are recommended for the treatment of patients with nephrotic syndrome.

Development of malignancies (including Hodgkin's lymphoma) has occasionally been reported in nephrotic syndrome patients treated with ciclosporin, as well as during treatment with other immunosuppressive agents.

Since ciclosporin can impair renal function, it is necessary to assess renal function frequently and if the serum creatinine remains increased by more than 30% above baseline at more than one measurement, to reduce the dose by 25-50%. Patients with abnormal baseline renal function are at higher risk, they should initially be treated with 2.5mg/kg/day orally and must be controlled very carefully.

In some patients it may be difficult to detect ciclosporin induced renal dysfunction because of changes in renal function related to the underlying renal disease. If Ciclosporin Genfarma is indicated for more than one year in the long term management, the serial renal biopsies should be performed at yearly intervals to assess the progression of the renal disease and the extent of any ciclosporin-associated changes in the renal morphology that may co-exist.

Additional Precautions in Rheumatoid Arthritis

Only the oral forms of ciclosporin are recommended for the treatment of patients with rheumatoid arthritis.

Since ciclosporin 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. Thereafter, measurements can be made every 4 weeks, but more frequent checks are necessary when the Ciclosporin Genfarma dose is increased or concomitant treatment with a non-steroidal anti-inflammatory drug is initiated or its dosage increased. Because the pharmacodynamic interaction between ciclosporin and NSAIDs may adversely affect renal function, caution should be exercised if NSAID therapy is to be continued.

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

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

As hepatotoxicity is a potential side effect of non-steroidal anti-inflammatory drugs, regular monitoring of hepatic function is advised when Ciclosporin Genfarma are co-administered with these drugs in rheumatoid arthritis patients.

As with other long-term immunosuppressive treatments, an increased risk of lymphoproliferative disorders must be considered.

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.

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.

Drugs that decrease ciclosporin levels:

Barbiturates, carbamazepine, phenytoin; rifampicin; octreotide; orlistat; hypericum; perforatum (St. John's Wort); ticlopidine and intravenous sulphadimidine.

Drugs that increase ciclosporin levels:

Macrolide antibiotics (mainly erythromycin and clarithromycin); ketoconazole, fluconazole, itraconazole; diltiazem, nicardipine, verapamil; metoclopramide; oral contraceptives; danazol; methylprednisolone (high dose); allopurinol;

amiodarone; ursodeoxycholic acid; protease inhibitors.

Other relevant drug interactions

Care should be taken when using ciclosporin together with other drugs that exhibit nephrotoxic synergy: aminoglycosides (including gentamicin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); non-steroidal anti-inflammatory drugs (including 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 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 thereby causing digoxin toxicity.

Ciclosporin has also been reported to reduce the clearance of prednisolone.

Administration of ciclosporin may enhance the potential of HMG-CoA reductase inhibitors and colchicine to induce muscular toxicity eg muscle pain and weakness, myositis and occasionally rhabdomyolysis.

Recommendations

If the concomitant use of drug 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. In non-transplant patients the value of ciclosporin blood level monitoring is questionable, as in these patients the relationship between blood level and clinical effect 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, as the concomitant use of diclofenac and ciclosporin has been found to result in a significant increase in the bioavailability of diclofenac, most probably caused by a reduction of its first-pass effect. When diclofenac is given concomitantly with ciclosporin the dose of diclofenac should be reduced by approximately half(see section 4.2 Posology & Administration).

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.

If digoxin, colchicine or HMG-CoA reductase inhibitors 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 Fertility, pregnancy and lactation

Ciclosporin is not teratogenic in animals. Limited data available from organ transplant recipients using earlier formulations of ciclosporin indicate that, compared with other immunosuppressive agents, ciclosporin 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. As the safety of ciclosporin in human pregnancy has not been fully

established, it should only be used in pregnancy if the benefit outweighs any potential risks.

Ciclosporin passes into the breast milk and mothers receiving treatment with ciclosporin should therefore not breast feed their infants.

4.7 Effects on ability to drive and use machines

No data exists on the effects of ciclosporin 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 $<0.01\%$.

Blood and the lymphatic system disorders:

Uncommon: anaemia, thrombocytopenia

Rare: micro-angiopathic haemolytic anaemia, haemolytic uraemic syndrome

Endocrine disorders:

Rare: menstrual disturbances, gynaecomastia

Metabolism and nutrition disorders:

Very common : hyperlipidaemia

Common: hyperuricaemia, hyperkalaemia, hypomagnesaemia

Rare: hyperglycaemia

Nervous system disorders:

Very common: tremor, headache

Common: paraesthesia

Uncommon: signs of encephalopathy or demyelination, especially in liver transplant patients, 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.

Cardiovascular disorders:

Very common: hypertension

Gastrointestinal disorders:

Common: anorexia, nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia,

Hepato-biliary disorders:

Common: hepatic dysfunction

Rare: pancreatitis.

Skin and subcutaneous tissue disorders:

Common: hypertrichosis

Uncommon: allergic rashes

Musculoskeletal, connective tissue and bone disorders:

Common: muscle cramps, myalgia

Rare: muscle weakness, myopathy

Renal and urinary disorders:

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

General disorders and administration site conditions:

Common: fatigue

Uncommon: oedema, weight increase

The increased risk of developing malignancies and lymphoproliferative disorders appears to be related to the degree and duration of immunosuppression rather than to the use of specific agents (refer to Section 4.4 'Special warnings and special precautions').

4.9 Overdose

Little experience is available with overdosage. Symptomatic treatment and general supportive measures should be followed in all cases of overdosage. Forced emesis could be of value within the first few hours after intake. Signs of nephrotoxicity might occur which would be expected to resolve following drug withdrawal. Ciclosporin is not dialysable to any great extent nor is it well cleared by charcoal haemoperfusion. Hypertension and convulsions have been reported in some patients receiving ciclosporin therapy at doses above the recommended range and in others with high trough blood levels of ciclosporin. This might therefore be expected as a feature of overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotheapeutic group: Selective immunosuppressive agents (ATC code L04A D01).

Ciclosporin A is a cyclic undecapeptide with immunosuppressant properties. Studies suggest that ciclosporin A inhibits the development of cell-mediated reactions, including allograft immunity, delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, graft-versus-host disease and also T-cell dependent antibody production. It also inhibits lymphokine production and release, including interleukin 2 or T-cell growth factor (TCGF). Ciclosporin appears to block the resting lymphocytes in the G0 or G1 phase of the cell cycle.

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.

5.2 Pharmacokinetic properties

The maximal blood concentration (C_{max}) is achieved within 1-2 hours (T_{max}). The absolute bioavailability is ~30%. The inter- and intra-individual pharmacokinetic variability is 10-20% for AUC and C_{max} in healthy volunteers. Bioequivalence studies under both fasting and fed conditions were performed to compare the pharmacokinetic parameters of Ciclosporin and the originator product, as follows:

1. A randomised, two-way cross-over study in 24 healthy male volunteers under fasting conditions. The results of the study are presented in Table 1 below:

Table 1 Pharmacokinetic parameters - fasting conditions

	Ciclosporin 2x100 mg (Test)	Originator product 2x100 mg (Reference)	Test/Reference 90% CI
(n=24)			
AUC inf (ng*h*ml ⁻¹)	4930 (1283)	4866 (1107)	1.01 (0.93 – 1.09) ¹
C _{max} (ng/ml)	1184 (215)	1203 (231)	0.99 (0.90 – 1.09) ¹
T _{max} (h)	1.65 (0.48)	1.63 (0.52)	0 (-0.25 – 0.25) ²

All pharmacokinetic parameters presented are mean (SD) values

¹ Geometric means of the individual ratios and 90% parametric CI

² Median Difference and 90% non parametric CI

2. A randomised, two-way cross-over study in 39 healthy male volunteers under fed conditions. The volunteers were fed with a standard high-fat high-calorie breakfast before administration of ciclosporin. The results of the study are presented in Table 2 below:

Table 2 Pharmacokinetic parameters - fed conditions

	Ciclosporin 2x100 mg (Test)	Originator product 2x100 mg (Reference)	Test/Reference 90% CI
(n=39)			
AUC inf (ng*h*ml ⁻¹)	4323 (883)	4098 (934)	1.06 (1.03 – 1.10) ¹
Cmax (ng/ml)	1076 (294)	958 (311)	1.13 (1.05 – 1.22) ¹
Tmax (h)	1.68 (0.65)	1.75 (0.71)	0.00 (-0.25 ; 0.13) ²

All pharmacokinetic parameters presented are mean (SD) values

¹ Geometric means of the individual ratios and 90% parametric CI

² Median Difference and 90% non parametric CI

A self-reference study was also conducted, as follows:

3. A randomised, two-way cross-over, food effect study in which 16 healthy male volunteers received a standard high-fat high-calorie breakfast before administration of ciclosporin.

The results of the study are presented in Table 3 below:

Table 3 Pharmacokinetic parameters - fasting versus fed conditions

	Ciclosporin 2x100 mg Fed conditions (Test Fed)	Ciclosporin 2x100 mg Fasting conditions (Test Fasting)	Test Fed/ Test Fasting 90% CI
(n=16)			
AUC inf (ng*h*ml ⁻¹)	4992 (1237)	5359 (1073)	0.93 (0.86 ; 1.01) ¹
Cmax (ng/ml)	1109 (191)	1308 (299)	0.85 (0.76 ; 0.96) ¹
Tmax (h)	1.81 (0.63)	1.31 (0.31)	0.50 (0.25 ; 0.75) ²

All pharmacokinetic parameters presented are mean (SD) values

¹ Geometric means of the individual ratios and 90% parametric CI

² Median Difference and 90% non parametric CI

The results show that food intake decreases AUC and Cmax by 7% and 15%, respectively, compared to the values obtained under fasting conditions.

The reduction in AUC and Cmax are not significant and Ciclosporin can be administered with or without food.

Ciclosporin is distributed largely outside the blood volume. Within 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 in proteins, mainly lipoproteins.

Ciclosporin is extensively biotransformed to approximately 15 metabolites, there being 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 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 30mg/kg and rabbits at 100mg/kg a day orally), ciclosporin was embryo- and foetotoxic as indicated by increased prenatal and post-natal mortality and reduced fetal weight together with related skeletal retardation. In the well-tolerated dose range (rats up to 17mg/kg and rabbits up to 30mg/kg a 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 16mg/kg a 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 8mg/kg a 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 analysing 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 recognised 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 lesions to regress.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
 Sorbitan oleate
 Lecithin
 Triglyceride
 Macroglycerol hydroxystearate
 Ethyl lactate
Ingredients of the capsule shell
 Gelatin
 Glycerol
 Ferric oxide black (E172)
 Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
 Do not refrigerate and/or freeze.

Genfarma Capsules should be left in the blister pack until required for use. When a blister is opened, a characteristic smell is noticeable.

6.5 Nature and contents of container

The capsules are available in blister packs of double-sided aluminium consisting of an aluminium bottom foil and an aluminium covering foil, which are contained within a printed cardboard carton. Ciclosporin Genfarma 50 mg Capsules are available in 30, 50 or 60 capsules in each carton. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/030/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 January 2008

Date of last renewal: 27 January 2010

10 DATE OF REVISION OF THE TEXT

March 2010