IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1380/028/002
Case No: 2057297

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Ciclosporin Dumex, 50 Milligram

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **05/11/2008** until .

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ciclosporin Dumex 50 mg Capsule.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg Ciclosporin.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

Ciclosporin Dumex 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 Dumex 50mg Capsules are indicated in patients with severe psoriasis in whom conventional therapy is ineffective or inappropriate.

Atopic Dermatitis
Ciclosporin Dumex 50mg Capsules 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 Dumex 50mg Capsules 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 Dumex 50mg Capsules can be used to induce remissions and for maintenance treatment. It can also be used for the maintenance of steroid-induced remission, allowing withdrawal of steroids.

Rheumatoid Arthritis
Ciclosporin Dumex 50mg Capsules 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

For all indications, ciclosporin blood levels must be monitored on a routine basis. These measurements should be used as guidance to determine the dose of Ciclosporin Dumex 50mg Capsules required to obtain the desired blood levels of ciclosporin (See section 4.4).

Organ Transplantation
Initially, a dose of 10 to15 mg/kg body weight in two divided doses, should be given four to 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 6mg/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 Dumex 50mg Capsules 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 Dumex 50mg Capsules should continue using the oral forms at a dosage of 12.5 mg/kg/day for at least three and preferably six months before tailing off to zero.
In some cases, it may not be possible to withdraw Ciclosporin Dumex 50mg Capsules until a year after bone marrow transplantation. Higher oral doses or the use of I.V. 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 starting on the day before transplantation.

If GVHD develops after Ciclosporin Dumex 50mg Capsules 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.

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 5mg/kg/day. In very severe cases, rapid and adequate control of disease is more likely with a starting dose of 5 mg/kg/day.

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.

The combination of Ciclosporin Dumex 50mg Capsules with low doses of oral corticosteroids is recommended if the effect of Ciclosporin Dumex 50mg Capsules alone is not satisfactory, especially in steroid-resistant patients.

In the absence of efficacy after 3 months' treatment, Ciclosporin Dumex 50mg Capsules 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.

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

For the first 6 weeks of treatment, the recommended dose is 3 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 5 mg/kg/day orally. To achieve full effectiveness, up to 12 weeks of Ciclosporin Dumex 50mg Capsules therapy may be required.

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

Ciclosporin Dumex 50mg Capsules can be given in combination with low-dose corticosteroids and/or non-steroidal anti-inflammatory drugs.

Administration
The total daily dosage of Ciclosporin Dumex 50mg Capsules should always be given in two divided doses.

Ciclosporin should not be taken with grapefruit juice (see interactions).

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 Dumex 50mg Capsules in young children is still limited. Transplant recipients from three months of age have received the drug 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 Dumex 50mg Capsules are contraindicated in psoriatic and atopic dermatitis patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy other than of the skin (see

Precautions).

Ciclosporin Dumex 50mg Capsules are contraindicated in rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy.

Herbal preparations containing Hypericum perforatum (St. John's Wort) are contra-indicated during treatment with Ciclosporin Dumex 50mg Capsules, as concomitant use may lead to decreased plasma concentrations and reduced efficacy of ciclosporin.

4.4 Special warnings and precautions for use

Precautions
Ciclosporin Dumex 50mg Capsules 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 Dumex 50mg Capsules 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 Dumex 50mg Capsules 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 Dumex 50mg Capsules therapy. If hypertension develops, appropriate antihypertensive treatment must be instituted.

Since, on rare occasions, Ciclosporin Dumex 50mg Capsules have 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 Dumex 50mg Capsules 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 Dumex 50mg Capsules should avoid a high dietary potassium intake. 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 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.

Caution is required in treating patients with hyperuricaemia.

Ciclosporin Dumex 50mg Capsules should preferably not be administered with other immunosuppressive agents except corticosteroids. However, some transplant centres use Ciclosporin Dumex 50mg Capsules together with azathioprine and corticosteroids or other immunosuppressive agents (all in low doses) with the aim of reducing the risk of Ciclosporin Dumex 50mg Capsules-induced renal dysfunction or renal structural changes. When Ciclosporin Dumex 50mg Capsules are 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 Dumex 50mg Capsules-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.

Occurrence of non-cardiogenic pulmonary oedema (indicated by wheezing) as a result of capillary leak syndrome is possible.

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.

There are numerous methods of measuring ciclosporin levels. Comparing patient levels to literature references should only be carried out when detailed information on the method used is available. Methods by which unaltered ciclosporin is measured (HPLC, monoclonal radio immuno assay) are available, as well as non-specific methods that also measure several metabolites. The results from different methods are therefore not interchangeable. When using plasma, levels will partially depend on the temperature used during separation of the plasma from whole blood. Plasma levels vary, ranging from 20% to 50% of whole blood. Ciclosporin levels in blood, plasma or urine are only one of many factors determining the clinical state of the patient. Measurements are therefore only to be regarded as a guideline on treatment, in combination with other laboratory values and clinical parameters. In kidney transplant patients exhibiting deterioration of kidney function parameters in conjunction with excessively high blood levels of ciclosporin, which does not respond to dose reduction, further diagnostics are required. Renal biopsy could be considered.

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.

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 Dumex 50mg Capsules 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 Dumex 50mg Capsules 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 two-month intervals in patients receiving doses of 2.5m g/kg/day and 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 Dumex 50mg Capsules 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 Dumex 50mg Capsules dosage reduction or appropriate antihypertensive therapy, discontinuation of the drug is recommended.

In view of the potential risk of skin malignancy, patients on Ciclosporin Dumex 50mg Capsules should be warned to avoid excess unprotected sun exposure and should not receive concomitant therapeutic ultraviolet B irradiation or PUVA photochemotherapy. After completion of ciclosporin treatment, a 2 to 3 day treatment-free period should be observed before commencing PUVA or B therapy.

Additional precautions in Atopic Dermatitis
Active herpes simplex infections should be allowed to clear before initiating treatment with Ciclosporin Dumex 50mg Capsules 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 Dumex 50mg Capsules therapy but should be controlled with appropriate antibacterial agents. Orally erythromycin, known to have the potential to increase the blood concentration of Ciclosporin Dumex 50mg Capsules (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 Dumex 50mg Capsules.

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 Dumex 50mg Capsules are indicated for more than one year in the long term management, the serial renal biopsies should be performed at 1 to 2-yearly intervals to assess the progression of the renal disease and the extent of any Ciclosporin Dumex 50mg Capsules-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 Dumex 50mg Capsules 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 Dumex 50mg Capsules 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 by more than 30% above baseline at more than one measurement, the dosage of Ciclosporin Dumex 50mg Capsules 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 Dumex 50mg Capsules treatment should be discontinued.

Discontinuation of the drug may also become necessary if hypertension developing during Ciclosporin Dumex 50mg Capsules therapy cannot be controlled by appropriate antihypertensive therapy.

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

Care should be taken when using Ciclosporin Dumex 50mg Capsules in combination with systemic antibiotics or other compounds known to have nephrotoxic effects, eg.
Aminoglycosides, amphoteracin B, ciprofloxacin, melphalan and trimethorpim.

Various agents are known to either increase or decrease the plasma or whole blood concentrations of ciclosporin by competitive inhibition or induction of hepatic enzymes involved in the metabolism and excretion of Ciclosporin Dumex 50mg Capsules, in particular cytochrome P450.

Agents known to increase the plasma or whole blood concentration include ketoconazole, fluconazole, itraconazole, erythromycin, clarithromycin, oral contraceptives, diltiazem, nicardipine, verapamil, metoclopromide, danazol, methylprednisolone (high dose), allopurinol, amiodarone, bile acid and derivatives.

Agents known to decrease plasma or whole blood ciclosporin concentrations include phenytoin, nafcillin, sulphadimidine (intravenous administration), octreotide, probucol, orlistat, Hypericum perforatum, troglitazone, ticlopidine, terbinafine, carbamazepine, barbiturates and rifampicin.
In transplant patients, frequent measurements of ciclosporin levels and, if necessary, Ciclosporin Dumex 50mg Capsules 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 levels 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 Dumex 50mg Capsules-related side-effects may be more appropriate than blood level measurement.

Intravenous (but not oral) administration of sulphadimidine and trimethprim has also resulted in a marked reduction of plasma or whole blood levels. Concomitant administration of such drugs with Ciclosporin Dumex 50mg Capsules should therefore be avoided. Where combined administration is unavoidable, careful monitoring of ciclosporin blood levels and adjustment of Ciclosporin Dumex 50mg Capsules dosage are essential.

In addition, it has been noted that ciclosporin reduces the clearance of prednisolone and conversely, high-dose therapy with methylprednisolone can increase the blood concentration of ciclosporin.

As non-steroidal anti-inflammatory drugs alone can have an adverse effect on renal function, addition of these drugs to Ciclosporin Dumex 50mg Capsules therapy or an increase in their dosage should initially be accompanied by particularly close monitoring of renal function.

Ciclosporin Dumex 50mg Capsules may enhance the potential of the HMG-CoA reductase inhibitor lovastatin to induce rhabdomyolysis. The potential for interaction with other drugs in this class should be considered.

Muscular toxicity, including muscle pains and weakness, has also been reported in patients receiving colchicine concurrently with ciclosporin.
The concurrent administration of nifedipine and ciclosporin has resulted in an increased rate of gingival hyperplasia when compared with that for ciclosporin alone.

Where there is a risk of hyperkalaemia, potassium-sparing diuretics should be avoided and care should be taken when prescribing potassium supplements or potassium-containing medications.

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

Ciclosporin should not be taken with grapefruit juice because its metabolism may be inhibited.

4.6 Pregnancy and lactation

Pregnancy
Limited experience with ciclosporin in pregnant women does not indicate an increased risk of congenital malformations. Animal studies have shown reproductive toxicity in rats and rabbits (see section 5.3). Ciclosporin crosses the placenta. In transplantation patients treated with immunosuppressants, there is an increased risk of premature births and low birth weight.
Ciclosporin should not be used during pregnancy unless clearly indicated.

Lactation
Ciclosporin passes into the breast milk. Because of possible adverse effects on the infant's immune system, mothers receiving treatment with ciclosporin should not breast feed their infants.

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effects

Many side effects associated with ciclosporin therapy are dose-dependant 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 ≥ 10%, common ≥1% to < 10%.
Uncommon ≥0.1% to < 1%, rare ≥ 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, perception deafness.
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 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 precautions for use).
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Respiratory disorders:
Rare: Acute respiratory stress, dyspnoea and 'wheezing' due to capillary leak syndrome.

4.9 Overdose

Symptoms:
Little experience is available with overdosage. 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. Signs of nephrotoxicity might occur which would be expected to resolve following drug withdrawal.

Treatment measures:
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. Ciclosporin is not dialysable to any great extent, nor is it well cleared by charcoal haemoperfusion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 haemopoieisis and has no effect on the function of phagocytic cells.

5.2 Pharmacokinetic properties

Absolute bioavailability is 25 - 50% at steady and peak blood concentrations are achieved within 1 - 6 hours.

Ciclosporin is distributed largely outside the blood volume. Within blood, 33-47% is present in plasma, 4-9% in lymphocytes, 5-12% 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. The terminal elimination half-life from blood is approximately 19 hours, irrespective of the dose or route of administration.

5.3 Preclinical safety data

In carcinogenicity studies in mice, the incidence of malignant lymphoma increased. Ciclosporin was not found to be genotoxic.
In rats, decreases were observed in testicular weight, sperm count, serum testosterone levels and haploid cell population in the testis, resulting in decreased fertility.

In rats and rabbits, orally administered ciclosporin was not found to be teratogenic, but was found to be foetotoxic at doses also causing maternal toxicity. Offspring of subcutaneously treated rats showed a decreased number of nephrons, renal hypertrophy, systemic hypertension and progressive kidney insufficiency. After intravenous administration, an increased incidence of ventral septum defects was observed in foetuses.

Disturbances of the immune system were observed in offspring of rats treated during pregnancy or lactation.

The human relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Sorbitan oleate
Lecithin
Triglyceride
Polyoxyl 40 hydrogenated castor oil
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.
Leave your capsules in the foil. Only remove them when it is time to take your medicine. When a packaged blister is opened, a characteristic smell is noticeable. This is normal and does not mean that there is anything wrong with the capsule.

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 Dumex 50mg Capsules are available in 30, 50 or 60 capsules in each carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
IS-220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/028/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th January 2005

10 DATE OF REVISION OF THE TEXT

January 2008