Sigmasporin Microoral

Immunosuppressant Agent
Soft gelatin capsules and oral solution

Composition
Soft gelatin capsules
Each capsule contains:
Active ingredient: Cyclosporine USP 25mg, 50mg, and 100mg.
Excipients: Diethyleneglycol-monoethyl ether, absolute alcohol, unsaturated polyglycolysed glycerides, polyoxyl 40 hydrogenated castor oil, vitamin E, gelatin, glycerin, propylene glycol, and titanium dioxide (and iron oxide black for 25mg and 100mg).

Oral Solution
Each 1mL contains
Active ingredient: Cyclosporine USP 100mg
Excipients: Diethyleneglycol-monoethyl ether, absolute alcohol, unsaturated polyglycolysed glycerides, polyoxyl 40 hydrogenated castor oil, vitamin E, and propylene glycol.

Properties
Cyclosporine, a calcineurin inhibitor, is a potent immunosuppresant. Although the exact mechanism of its action is not clear yet but it seems that it acts specifically on lymphocytes, mainly helper T-cells, and inhibits the production and release of interleukin-2, which is a proliferative factor necessary for the induction of cytotoxic T lymphocytes in response to alloantigenic challenge, resulting in a depression of cell mediated immune response. Cyclosporine does not cause significant myelosuppression.
After oral administration, absorption of cyclosporine from the gastrointestinal tract is variable and incomplete. Ingestion of cyclosporine with food may increase its bioavailability, although the effect only appears to be significant when the meal is high in fat.
Cyclosporine is widely distributed throughout the body. Distribution in the blood is concentration- and temperature- dependent, with between 41 and 58% in erythrocytes and 10 to 20% in leucocytes; the remainder is found in plasma, about 90% protein-bound, mostly to lipoprotein. Because of distribution into blood cells whole blood concentrations are higher than, and not comparable with, plasma concentrations. Cyclosporine is reported to cross the placenta, and to be distributed into breast milk.
Cyclosporine is extensively metabolised in the liver. The terminal elimination half-life of an oral dose is reported to range from about 5 to 20 hours. It is primarily excreted in faeces via the bile. About 6% of a dose is reported to be excreted in urine, less than 0.1% unchanged. Clearance in children is reported to be more rapid.

Indications
Sigmasporin Microoral is indicated for:
- Prevention of graft rejection following bone marrow, kidney, liver, pancreas, heart, and heart-lung transplantation.
- Treatment of chronic transplant rejection in patients previously treated with other immunosuppressants.
- Prophylaxis and treatment of graft-versus-host disease after bone marrow transplantation.
- Short-term treatment of severe atopic dermatitis where conventional therapy is ineffective or inappropriate.
- Treatment of severe, recalcitrant, plaque-type psoriasis failing to respond to at least one systemic therapy or in patients unable to tolerate other systemic therapy.
- Treatment of severe, active rheumatoid arthritis when conventional second-line therapy inappropriate or ineffective.
- Treatment of nephrotic syndrome; to induce and maintain remissions of steroid-dependent and steroid-resistant nephrotic syndrome due to glomerular diseases.

Dosage
Organ transplantation
The usual *initial* dose of **Sigmasporin Microoral** when used alone is 10 - 15mg/kg 4 - 12 hours before transplantation, followed *postoperatively* by 10 - 15mg/kg daily for 1 - 2 weeks, then dosage may subsequently be reduced gradually to a daily *maintenance* dose of 2 - 6mg/kg. Dosage should be adjusted by regular monitoring of blood concentrations and renal function. Lower initial doses may be given for patients concomitantly receiving other immunosuppressant therapy (e.g. corticosteroids).
Prevention of graft rejection in bone marrow transplantation and prevention and treatment of graft-versus-host disease
An *initial* dose of 12.5 - 15mg/kg daily is usually recommended from the day before transplantation to 2 weeks postoperatively, then a *maintenance* dose of 12.5mg/kg daily for 3 - 6 months can be instituted. Then, the maintenance dose can be reduced gradually until it is *withdrawn* altogether; this may take up to a year after transplantation.
Severe atopic dermatitis
Adults over 16 years: Initially, 2.5mg/kg daily (5mg/kg daily in very severe cases) in 2 divided doses, if good initial response is not achieved within 2 weeks, increase the dose rapidly to a maximum of 5mg/kg daily. Treatment should be continued for a maximum of 8 weeks.
Children under 16 years: Use is not recommended.
Severe psoriasis
Adults over 16 years: Initially, 2.5mg/kg daily in 2 divided doses, increased gradually to a maximum of 5mg/kg daily if no improvement within 1 month; if the response is still insufficient after 6 weeks, treatment should then be discontinued.
When the condition requires rapid improvement, an *initial* dose of 5mg/kg daily is usually justified.
Children under 16 years: Use is not recommended.
Severe active rheumatoid arthritis
Adult above 18 years: Initially, 2.5mg/kg daily in 2 divided doses; if the clinical effect is insufficient dosage may then be increased gradually after 6 weeks to a maximum of 4mg/kg daily; if the response is insufficient after 3 months, treatment should then be discontinued. Maintenance dose should be adjusted according to the response and treatment should be reviewed after 6 months; continue the treatment only if the benefits outweigh the risks.
Children and patients under 18 years: Use is not recommended.
Nephrotic syndrome
The recommended dosage depends on the age and renal function. To *induce remission* in patients with normal renal function 5mg/kg daily may be given to adults and 6mg/kg daily to children, in 2 divided doses by month. In patients with *renal impairment* the *initial* dose should not exceed 2.5mg/kg daily; *maintenance* treatment should be gradually reduced to the lowest effective dose according to proteinuria and serum creatinine measurements.
Treatment may be discontinued after 3 months if there is no improvement in glomerulonephritis or glomerulosclerosis (or 6 months in membranous glomerulonephritis).
If you miss a dose
- Take the missed dose as soon as possible if remembered within 12 hours.
- Do not take the missed dose if it is almost the time for your next regular dose.
- Do not take two doses at the same time.

Contraindications
- Sensitivity to cyclosporine
- Uncontrolled hypertension
- Uncontrolled infections
- Abnormal renal function
- Malignancy
- Lactation

Precautions
Due to the fact that oversuppression of the immune system may increase the susceptibility to infection and lymphoma, it is preferable to avoid the use of other immunosuppressant agents (with the exception of corticosteroids) in combination with cyclosporine in transplant patients unless it is under supervision of a physician experienced in immunosuppressive therapy.
Regular monitoring of renal function is usually required in patient receiving cyclosporine. Dose-dependent increase in serum creatinine and urea has been reported during the first few weeks of treatment with cyclosporine; this may necessitate dose reduction in transplant patients or discontinuation of treatment in non-transplant patients. In renal graft recipients, this effect may be difficult to distinguish from graft rejection.
Hepatic function monitoring is also recommended; dosage adjustment based on bilirubin and liver enzymes may be needed.
Regular blood pressure monitoring is also required; discontinue the treatment if hypertension develops that cannot be controlled by dose reduction or antihypertensive therapy.
High dietary intake of potassium should be avoided in patients receiving cyclosporine. Serum potassium monitoring is especially recommended in patients with marked renal dysfunction.
Blood lipids measurement before initiation of therapy and thereafter is usually recommended.
Care is required in patients having hyperuricaemia or porphyria.
In patients with *atopic dermatitis* and *psoriasis*, dermatological and physical examination, including blood pressure and renal function measurements are required at least twice before starting the treatment with cyclosporine.

Excessive exposure to sunlight and the use of UVB or PUVA should be avoided during the treatment with cyclosporine.
In patients with *atopic dermatitis*, allow herpes simplex infections to clear before starting the treatment; treatment should be withdrawn if severe infection occurs.
Staphylococcus aureus skin infection (providing controlled) is not considered an absolute contraindication for the treatment with cyclosporine, but erythromycin should be avoided unless there is no other suitable alternative.
Serum creatinine should be monitored every 2 weeks throughout the period of therapy.
In patients with *psoriasis*, malignancies (including those of skin and cervix) should be excluded before the start of the treatment; biopsy should be taken from any lesion that is not typical of psoriasis. Patients with malignant or pre-malignant conditions of the skin should be treated with cyclosporine only when appropriate treatment has failed and there is no other option.
Serum creatinine should be monitored every 2 weeks for the first 3 months then every 2 months (or monthly if the dose is more than 2.5mg/kg daily); the dose should be reduced by 25 - 50% if it increases more than 30% above baseline (even if it is within the normal range); discontinue the treatment if reduction in serum creatinine is not successful within 1 month, and also if lymphoproliferative disorder develops.
In patients with *rheumatoid arthritis*, measure serum creatinine at least twice before treatment and monitor every 2 weeks for first 3 months, then every 4 weeks (or more frequently if dose increased or concomitant NSAIDs introduced or increased).
Reduce cyclosporine dose if serum creatinine increases more than 30% above baseline in more than 1 measurement; if above 50%, reduce dose by 50% (even if within normal range) and discontinue the treatment if reduction is not successful within 1 month.
In patients with *nephrotic syndrome*, reduction of the dose by 25 - 50% should be exercised if serum creatinine is more than 30% above baseline on more than one measurement. In patients with renal impairment the initial daily dose of cyclosporine should be reduced to half the usual dose. For long-term management, renal biopsies at yearly intervals should be performed.
Pregnancy: Cyclosporine crosses the placenta. Adequate and well-controlled studies in human have not been done but cyclosporine does not appear to be any more harmful than other immunosuppressant agents.

Side Effects

Dose-dependent increase in serum creatinine and urea is the major adverse effect of cyclosporine during the first few weeks of treatment (See, Precautions). Less commonly, on long-term administration of cyclosporine renal structural changes have been reported.
Other adverse effects include hypertrichosis, tremor, hypertension (especially in heart transplant patients), hepatic dysfunction, fatigue, gingival hypertrophy, and gastrointestinal disturbances.
Some other adverse reactions have occasionally been reported with the administration of cyclosporine including headache, rash (possibly allergic), mild anaemia, electrolyte disturbances (notably hyperkalaemia and hypomagnesaemia), hyperuricaemia, gout, hypercholesterolaemia, weight gain, oedema, pancreatitis, neuropathy, burning sensation in hands and feet (usually during first week), paraesthesia, confusion, convulsions, and dymenorrhoea or amenorrhoea.
Muscle weakness, cramps, myopathy, gynaecomastia (in patients concomitantly receiving spironolactone), colitis, and thrombocytopenia (sometimes with haemolytic uraemic syndrome) have rarely been reported.
As with other conventional immunosuppressive therapy, there is an increased incidence of development of malignancies and lymphoproliferative disorders in patients receiving cyclosporine therapy.

Overdosage

Medical treatment may be required in the event of an overdose. Therefore, patient should inform his doctor if a suspicion of an overdose is present.
The clinical picture of an acute overdose may include headache, flushing of the face, soreness and bleeding from the gum, hyperesthesia, hepatotoxicity, and asymptomatic nephrotoxicity.
Treatment of overdose is usually symptomatic and supportive. Forced emesis may be useful in reducing the absorption of cyclosporine for up to 2 hours after oral ingestion of the overdose. Cyclosporine is not removable by haemodialysis or charcoal haemoperfusion. Transient hepatotoxicity and nephrotoxicity usually respond to withdrawal of treatment.

Drug Interactions

Grapefruit or grapefruit juice should be avoided during the treatment with cyclosporine, as it may increase plasma concentration of cyclosporine, resulting therapy in an increased risk of toxicity.
Plasma concentration of cyclosporine may be increased upon concurrent administration with certain agents, resulting in an increased risk of toxicity. These agents include doxycycline; erythromycin, clarithromycin, and possibly other macrolides; quinupristin/dalfopristin; itraconazole, ketoconazole, and possibly fluconazole and miconazole (by inhibiting cyclosporine metabolism); chloroquine, ritonavir; diltiazem, nicardipine, and verapamil; amiodarone and propafenone; high-dose methylprednisolone (increases the risk of convulsions); danazol (by inhibiting cyclosporine metabolism); progestogens (by inhibiting cyclosporine metabolism); cimetidine; allopurinol; colchicine.
One the other hand, plasma concentration of cyclopsporin may be reduced upon concurrent administration with some other agents. These include rifampicin, intravenous trimethoprim (and possibly sulfadiazine); carbamazepine, phenobarbital, phenytoin, and primidone (by accelerating cyclosporine metabolism); griseofulvin; ticlopidine; lanreotide and octreotide (by reducing cyclosporine absorption).
The risk of hyperkalaemia may be increased upon concurrent administration of cyclosporine with ACE inhibitors and angiotensin-II antagonists; potassium-sparing diuretics; potassium salts.
Care should be taken when cyclosporine is given concomitantly with other nephrotoxic drugs as the risk of nephrotoxicity may be increased. These drugs include NSAID; aminoglycosides, co-trimoxazole (and trimethoprim alone), and quinolones; amphotericin; colchicine (increased risk of myotoxicity as well); melphalan (cytotoxic agent).
Cyclosporine may increase the plasma concentration of certain medications upon concurrent administration. These include diclofanac (halve diclofenac dose); prednisolone; nifedipine (increased risk of side effects such as gingival hyperplasia).
The absorption of cyclosporine may be increased upon concurrent administration with ursodeoxycholic acid (bile acid), and plasma-cyclosporine half-life may be prolonged upon concurrent administration with tacrolimus resulting in an increased risk of toxicity.
Care should be taken when cyclosporine is concomitantly administered with reboxetine (antidepressant agent).
Concurrent administration of cyclosporine with cytotoxic drugs may result in:

- increased risk of neurotoxicity with doxorubicin.
- increased risk of nephrotoxicity with melphalan.
- increased risk of toxicity with methotrexate.
- *In vitro* studies suggest possible interaction with docetaxel.

Concurrent administration of cyclosporine with statin (lipid-regulating agents) may increase the risk of myopathy.
As the efficacy of immunoprophylaxis is expected to be diminished during immunosupressant therapy. The administration of live vaccines should be postponed until at least 6 months after stopping the treatment with cyclosporine.

Presentations

Sigmasporin Microoral Soft gelatin capsules: Pack of 50 capsules.
Sigmasporin Microoral oral solution: Bottle of 50mL.

* *Store at a temperature of 15 - 25°C. Solution, once opened, use within 2 months. Do not refrigerate. Protect from freezing.*

THIS IS A MEDICAMENT

- Medicament is a product, which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of the children

Council of Arab Health Ministers,
Union of Arab Pharmacists

***Any information? Call Our Toll Free No.* (971) 800-4994**

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19/03/2001