For the use only of a Registered Medical Practitioner or Hospital or Laboratory

Biocon

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Cyclosporine Oral Solution IP 100 mg

PSORID® Oral Solution

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COMPOSITION
Each mL contains:
Cyclosporine IP 100 mg
Palatable base

ATC CODE :L04AD01

PROPERTIES
Cyclosporine is a highly effective and rapidly acting systemic agent for the treatment of psoriasis. Discovered in 1970 and originally used as an immunosuppressive agent in organ transplantation, it was first shown to be effective for psoriasis in 1979. Cyclosporine micro emulsion has been approved for the treatment of psoriasis since 1997 in the United States. Cyclosporine is approved by the FDA for the treatment of adult, non immunocompromised patients with severe, recalcitrant, plaque psoriasis who have failed to respond to at least one systemic therapy or in patients for whom other systemic therapies are contraindicated, or cannot be tolerated. Composition of Cyclosporine (also known as Cyclosporine A) consists of 11 amino acids. It is a lipophillic cyclic polypeptide. Its potential immunosuppressor properties have been demonstrated in animals, where it prolongs the survival of transplants such as skin, heart, kidneys, pancreas, bone marrow, small intestine and lungs.

MECHANISM OF ACTION
Cyclosporine forms a complex with the cytosolic immunophilin (cyclophilin), which binds to and inhibits the activity of the intracellular enzyme calcineurin phosphatase. This complex reduces the effect of the transcription factor in T cells (nuclear factor of activated T cells) in regulating transcription of a number of cytokine genes, the most significant being interleukin (IL) 2. IL 2 serves as the major activation factor for T cells in numerous immunological processes, including psoriasis. Cyclosporine also inhibits histamine release from mast cells and down regulates various cellular adhesion molecules adding to the prominent anti-inflammatory activity of this compound.

PHARMACOKINETICS
Peak plasma blood concentration is reached between the first and third hour after oral administration (oral solution and capsules). Absolute bio-availability is 20-50% with an average of 34% of oral preparation in stationary state.

The Cmax, Tmax and AUC 0-24 hrs (mean± SEM) of Cyclosporine solution was 858.06 ± 54.22 ng/ml, 1.42 ± 0.11 hrs and 2995.78 ± 139.32 ng hr ml-1 respectively, after a single dose of 1.8 ml solution equivalent to 180 mg Cyclosporine. The Cmax, Tmax and AUC 0-12 hrs (mean± SEM) of Cyclosporine Capsule was 792.94 ± 54.07 ng/ml, 2.09 ± 0.08 hrs and 3266.71 ± 197.12ng hr ml-1 respectively ,after single oral dose of 175 mg capsule. Assay employed was Radio Immuno Assay. The mean elimination half-life (t1/2) of single oral dose of solution and capsule was 4.87 ± 1.73 hrs and 4.80± 1.58 hrs respectively.

Distribution of Cyclosporine in large quantity is outside the blood volume, while in blood, distribution of Cyclosporine is saturation dependent. The distribution of Cyclosporine is approximately 33-47% in the plasma, 41-58% in erythrocytes, 5-12% in granulocytes, 4-9% in lymphocytes. The plasma distribution of Cyclosporine is approximately 90% bound to proteins, mainly lipoproteins. Disposition of Cyclosporine from blood is biphasic. Primary elimination is biliary, while only 6% of dose is excreted through urine. Barely 0.1% of the drug is excreted unchanged through urine. Cyclosporine is extensively metabolised with no major metabolic pathway.

THERAPEUTIC INDICATIONS
- Psoriasis: Cyclosporine is indicated for serious psoriasis when the conventional therapy is futile or unsuitable.
- Organ transplantation
- Bone-marrow transplantation
- Rheumatoid arthritis
- Nephrotic syndrome

CONTRAINDICATIONS
Cyclosporine is contraindicated in patients who are hypersensitive to the drug. It is also contraindicated in patients who have abnormal renal function; uncontrolled hypertension; malignancy (except non melanoma skin cancer); uncontrolled infection; primary or secondary immunodeficiency excluding autoimmune disease while being treated for psoriasis and rheumatoid arthritis.

WARNING AND PRECAUTIONS
General
Medical specialists who prescribe immunosuppressive therapy and manage transplant patients and who can provide adequate follow up, including regular full physical examination, measurement of blood pressure and control of laboratory safety parameters can prescribe Cyclosporine. Patients receiving Cyclosporine must be managed in centers equipped with appropriate laboratory facilities and adequate support of medical personnel.

Psoriasis
Cyclosporine should be prescribed by physicians experienced with its use in psoriasis.

Hypertension
A known common side effect of Cyclosporine is mild to moderate hypertension. Antihypertensives like calcium antagonists are generally given and can be effective agents for treating such hypertension. Due to alterations in metabolism of Cyclosporine by some calcium antagonists, dosage adjustments of Cyclosporine may be required.

Hyperkalemia/Hyperuricemia/Hypomagnesemia.
Since Cyclosporine enhances the risk of hyperkalaemia, it should be administered with caution in patients with renal dysfunction and when co-administered with 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. Cyclosporine should be used cautiously in the treatment of patients with hyperuricemia. Cyclosporine increases the clearance of magnesium.

Lipoprotein Abnormalities
Lipid profile before and after the first month of treatment must be carried out as Cyclosporine has tendency to alter lipid profile. Caution is advised in the co administration of Cyclosporine and HMG-CoA reductase inhibitor, lovastatin due to risk of myocyte necrosis.

Rheumatoid Arthritis
In due course of Cyclosporine therapy for Rheumatoid Arthritis, if hypertension develops which cannot be controlled with appropriate antihypertensive therapy, then discontinuation of the drug is recommended.

Nephrotic Syndrome
Cyclosporine should be prescribed by physicians experienced with its use. Pretreatment physical examination for patients to be treated for Nephrotic syndrome is a must.

For all patients
There should be appropriate monitoring of Cyclosporine with respect to whole blood concentrations as well as effectiveness and adverse events to guarantee maximum safety and optimal clinical outcome, in all patients, particularly in denovo patients undergoing any change in their treatment regimen.

Carcinogenesis and Mutagenesis
After proper treatment of malignant or premalignant alterations of the skin, patients should be treated with Cyclosporine and if no other option for successful therapy exists. Cyclosporine should be discontinued if malignancy occurs.

Hepatic/Renal
Hepatic and renal functioning must be monitored with repeated laboratory tests to know the status of kidney and liver.

Immune
Along the course of treatment with Cyclosporine, vaccination may be less effective. Avoid using live attenuated vaccine.

SPECIAL POPULATION
Pregnant Women:
In animals Cyclosporine is not teratogenic. As per data of women exposed to organ transplantation shows that, in contrast with traditional immunosuppressive therapy, Cyclosporine does not incite any additional risk on the course and outcome of pregnancy. In case the potential benefits outweigh the risk to fetus only then Cyclosporine should be used during pregnancy as there are no adequate well controlled studies in pregnancy.

Nursing Women
Cyclosporine passes into breast milk, hence nursing mothers receiving Cyclosporine should not breast feed.

Pediatrics
Restricted experience with Cyclosporine in children. However children of the age one year and above have received Cyclosporine in standard dose with no particular problems.

Geriatrics
Recommended doses have not reported any particular problems in the elderly. However, care should be taken in impaired renal function sometimes associated with aging which requires careful administration and may require dosage adjustment.

Monitoring
There should be monitoring of BP at 2 weeks, 4 weeks, and 6 weeks. After this there should be monthly measurement of blood pressure.

Renal functioning should be checked with measurement of serum creatinine at 2 weekly intervals for the first 2 months, then monthly thereafter. For patient who are on treatment for more than 1 year assess annual renal function using creatinine clearance to measure glomerular filtration rates. Serum lipids and magnesium should be measured twice a week.

INTERACTIONS
Cyclosporine is metabolized totally in the liver by cytochrome P 450 system and levels of Cyclosporine may vary with administration of drugs that inhibit or stimulate this system. Care should be taken while administering Cyclosporine along with medicines with noted nephrotoxic effects, like aminoglycosides, ciprofloxacin, digoxin, clotrimazole, and fibrates. Nonsteroidal antiinflammatory drugs (NSAIDs) may potentiate renal toxicity associated with Cyclosporine.

Drugs like digoxin, simvastatin, prednisolone, diclofenac and methotrexate concentration may be increased due to delayed metabolism by Cyclosporine. This may lead to toxicity of these drugs.

Grapefruit juice inhibits the metabolism of Cyclosporine by inhibiting cytochrome P 450 enzymes in the intestinal walls and should be avoided during Cyclosporine treatment, especially when using oral suspension in pediatric population.

Heavy alcohol intake may also increase Cyclosporine levels.

SIDE EFFECTS
Dose dependent side effects are seen which regress with dose reduction.

Major Adverse Effect of Cyclosporine:
Nephrotoxicity, is usually reversible on reduction of the dose.

Other common adverse effects include:
Hypertension: A known common side effect of Cyclosporine is mild to moderate hypertension which decreases gradually over the time on continuous administration. Antihypertensives are generally recommended, however Cyclosporine may cause hyperkalaemla. Therefore potassium sparing diuretics are not recommended for treating hypertension. Instead, calcium antagonists can be effective agents for treating such hypertension.

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Hyperkalaemia: It should be administered with caution in patients with renal dysfunction. If serum creatinine is increased to ≥30% of baseline, repeat the test after 2 weeks. If it is still increased to ≥30% of baseline then reduce the dose of Cyclosporine by ≥1mg/kg/day. Incase creatinine concentration reduces, continue the Cyclosporine dose. However if it is still ≥30%of baseline, then stop treatment and resume it only when creatinine returns to <10% of the baseline.

Headaches, Hyperlipidaemias, Gastrointestinal disturbances, Hepatoxicity, Hypertrichosis, Gum hyperplasia, Tremor. Hypomagnesaemia, Hyperuricaemia, Paraesthesia, and muscle cramps and myalgia.

Less frequent adverse events are:
Anemia, Thrombocytopenia, Rashes, Weight increase, Oedema, Pancreatitis, Myopathy, Neuropathy, and Hyperglycemia have been reported. The manifestations of encephalopathy are covulsions, confusion, visual disturbances including blindness, movement disorders or psychiatric disturbances.

Uncommon adverse effects are:
Optic disc oedema, including papilloedema with possible visual impairment secondary to benign intracranial hypertension.

Post marketing studies have reported cases of myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis on concomitant administration of Cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin and rarely, fluvastatin.

DOSAGE AND METHOD OF ADMINISTRATION
According to the indications and references the dosing intervals specified successively must be understood. Regular monitoring of the Cyclosporine blood levels along with kidney functions and renal functions is advised.
Psoriasis
Short Term: 12- 16 weeks of Cyclosporine therapy.
Combination Therapy: Combine with topical emollients, corticosteroids, anthralin or vitamin D3 analogues. Systemic combination may be with methotrexate, fumaric acid, mycophenolate mofetil which allows dose reduction of Cyclosporine.

Rotational Therapy: Systemic therapy mentioned above may be rotated with Cyclosporine treatment to minimize duration of Cyclosporine treatment and toxicity.

Long term Therapy: Can be given for up to 1 year at a maintenance dose of 3 to 3.5mg/kg/day up to 1 year.
Over dosage is rare but if occurs can be controlled by emesis and gastric lavage for up to 2 hours after administration with Cyclosporine. The transient hepatotoxicity and nephrotoxicity which occurs may resolve following drug withdrawal.

Psoriasis Patients Monitoring:
Blood Pressure: There should be monitoring of BP at 2 weeks, 4 weeks, and 6 weeks. After this there should be monthly measurement of blood pressure.

Renal functioning: Should be checked with measurement of serum creatinine at 2 weekly intervals for the first 2 months, then monthly thereafter. For patient who are on treatment for more than 1 year assess annual renal function using creatinine clearance to measure glomerular filtration rates. Serum lipids and magnesium should be measured twice a week.

METHOD OF ADMINISTRATION
Preparation of Oral Solution
Syringe enclosed in the wrapping must be used for making solution of the medicine. PSORID®should be diluted in a glass container (not plastic) with preferably apple or orange juice (avoid grape juice). Soft drinks can be added according to individual taste. Prepare the solution just prior to taking the solution. After having poured the medicine, mix well and drink immediately.

After drinking the dose, rinse the glass with a small quantity of the same drink and drink it for ensuring that the full dose has been taken. The same drink should be continued for the entire duration of the treatment. The syringe for measuring the medicine must not get in contact with the drink.

OVERDOSAGE
Evidence of acute overdosage of Cyclosporine capsules and oral solution is not available. However high blood levels of Cyclosporine result in acute toxic symptoms which may include: nausea, headache, hyperaesthesia in the hands and feet, flushing of face, gum soreness and bleeding and sensation of increased abdominal girth. Though the high levels may cause transient hepatotoxicity and nephrotoxicity, no permanent residual or long term squeal have been retorted. Since Cyclosporine is not dialyzable to large extent neither is it cleared by charcoal hemoperfusion, so elimination of Cyclosporine can be achieved only by non specific measures including gastric lavage.

SHELF LIFE: Please refer to carton / label.

STORAGE:
Preserve in tight containers. Store at a temperature between 25°C & 35°C, protect from light and moisture.
DO NOT REFRIGERATE
Keep out of reach of children.

PRESENTATION
Supplied in 50ml amber glass bottle containing 100 mg/mL.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No.: **1800 102 9465** or e mail us at **drugsafety@biocon.com**

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