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

Biocon

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Cyclosporine Capsules IP 25mg / 50mg / 100mg

PSORID® 25/50/100 सोरिड २५/५०/१००

Composition:
PSORID® 25
Each soft gelatin capsule contains:
Cyclosporine IP 25mg
Approved colours used in gelatin shell

PSORID® 50
Each soft gelatin capsule contains:
Cyclosporine IP 50mg
Approved colours used in gelatin shell

PSORID® 100
Each soft gelatin capsule contains:
Cyclosporine IP 100mg
Approved colours used in gelatin shell

Pharmaceutical Form: Soft gelatin capsule
ATC Code: L04AD01

DESCRIPTION:
PSORID® is an oral formulation of cyclosporine that immediately forms a microemulsion in an aqueous environment. Cyclosporine, the active principle in PSORID®, is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species Beauveria nivea. Chemically, cyclosporine is designated as [R-[R*,R*-(E)]]-cyclic-(L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L-α-amino-butyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl). 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 (e.g., PUVA, retinoids, or methotrexate) or in patients for whom other systemic therapies are contraindicated, or cannot be tolerated.

CLINICAL PHARMACOLOGY
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. Cyclopsorine 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:
The immunosuppressive activity of cyclosporine is primarily due to parent drug. Following oral administration, absorption of cyclosporine is incomplete. The extent of absorption of cyclosporine is dependent on the individual patient, the patient population, and the formulation. Elimination of cyclosporine is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in urine. The disposition of cyclosporine from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range 5 to 18 hours). The relationship between administered dose and exposure (area under the concentration versus time curve, AUC) is linear within the therapeutic dose range.

Absorption
Peak plasma blood concentration is reached between the first and third hour after oral administration. Absolute bio-availability is 20-50% with an average of 34% of oral preparation in stationary state. Following oral administration of cyclosporine, the time to peak blood cyclosporine concentrations (T_{max}) ranged from 1.5 to 2.0 hours. The administration of food with cyclosporine decreases the cyclosporine AUC and C_{max}. A high fat meal (669 kcal, 45 grams fat) consumed within one-half hour before cyclosporine administration decreased the AUC by 13% and C_{max} by 33%. The effects of a low fat meal (667 kcal, 15 grams fat) were similar.

Distribution
Cyclosporine is distributed largely outside the blood volume. The steady state volume of distribution during intravenous dosing has been reported as 3 to 5 L/kg in solid organ transplant recipients. In blood, the distribution is concentration dependent. Approximately 33% to 47% is in plasma, 4% to 9% in lymphocytes, 5% to 12% in granulocytes, and 41% to 58% in erythrocytes. At high concentrations, the binding capacity of leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins. Cyclosporine is excreted in human milk.

Metabolism
Cyclosporine is extensively metabolized by the cytochrome P-450 3A enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the co-administration of a variety of agents. At least 25 metabolites have been identified from human bile, feces, blood, and urine. The biological activity of the metabolites and their contributions to toxicity are considerably less than those of the parent compound. The major metabolites (M1, M9, and M4N) result from oxidation at the 1-beta, 9-gamma, and 4-N-demethylated positions, respectively. At steady state following the oral administration of cyclosporine, the mean AUCs for blood concentrations of M1, M9, and M4N are about 70%, 21%, and 7.5% of the AUC for blood cyclosporine concentrations, respectively.

Excretion
Only 0.1% of a cyclosporine dose is excreted unchanged in the urine. Elimination is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in the urine. Neither dialysis nor renal failure alters cyclosporine clearance significantly.

THERAPEUTIC INDICATIONS
Psoriasis
Cyclosporine is indicated for the treatment of adult, nonimmunocompromised patients with severe (i.e., extensive and/or disabling), recalcitrant, plaque psoriasis who have failed to respond to at least one systemic therapy (e.g., PUVA, retinoids, or methotrexate) or in patients for whom other systemic therapies are contraindicated, or cannot be tolerated.
While rebound rarely occurs, most patients will experience relapse with cyclosporine as with other therapies upon cessation of treatment

Kidney, Liver, and Heart Transplantation
Cyclosporine is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Cyclosporine has been used in combination with azathioprine and corticosteroids.

Rheumatoid Arthritis
Cyclosporine is indicated for the treatment of patients with severe active, rheumatoid arthritis where the disease has not adequately responded to methotrexate. Cyclosporine can be used in combination with methotrexate in rheumatoid arthritis patients who do not respond adequately to methotrexate alone.

DOSAGE AND ADMINISTRATION
The daily dose of Cyclosporine should always be given in two divided doses (BID). It is recommended that Cyclosporine be administered on a consistent schedule with regard to time of day and relation to meals. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.

Psoriasis
The initial dose of Cyclosporine should be 2.5 mg/kg/day. Cyclosporine should be taken twice daily, as a divided (1.25 mg/kg BID) oral dose. Patients should be kept at that dose for at least 4 weeks, barring adverse events. If significant clinical improvement has not occurred in patients by that time, the patient's dosage should be increased at 2-week intervals. Based on patient response, dose increases of approximately 0.5 mg/kg/day should be made to a maximum of 4.0 mg/kg/day.
Dose decreases by 25% to 50% should be made at any time to control adverse events, e.g., hypertension, elevations in serum creatinine (≥25% above the patient's pretreatment level), or clinically significant laboratory abnormalities. If dose reduction is not effective in controlling abnormalities, or if the adverse event or abnormality is severe, Cyclosporine should be discontinued. (see Monitoring)
Patients generally show some improvement in the clinical manifestations of psoriasis in 2 weeks. Satisfactory control and stabilization of the disease may take 12 to 16 weeks to achieve. Results of a dose-titration clinical trial with Cyclosporine indicate that an improvement of psoriasis by 75% or more (based on PASI) was achieved in 51% of the patients after 8 weeks and in 79% of the patients after 16 weeks. Treatment should be discontinued if satisfactory response cannot be achieved after 6 weeks at 4 mg/kg/day or the patient's maximum tolerated dose. Once a patient is adequately controlled and appears stable the dose of Cyclosporine should be lowered, and the patient treated with the lowest dose that maintains an adequate response (this should not necessarily be total clearing of the patient). In clinical trials, cyclosporine doses at the lower end of the recommended dosage range were effective in maintaining a satisfactory response in 60% of the patients. Doses below 2.5 mg/kg/day may also be equally effective.
Upon stopping treatment with cyclosporine, relapse will occur in approximately 6 weeks (50% of the patients) to 16 weeks (75% of the patients). In the majority of patients rebound does not occur after cessation of treatment with cyclosporine. Thirteen cases of transformation of chronic plaque psoriasis to more severe forms of psoriasis have been reported. There were 9 cases of pustular and 4 cases of erythrodermic psoriasis. Long term experience with Cyclosporine in psoriasis patients is limited and continuous treatment for extended periods greater than one year is not recommended. Alternation with other forms of treatment should be considered in the long term management of patients with this lifelong disease.

CONTRAINDICATIONS
Psoriasis
Psoriasis patients who are treated with cyclosporine should not receive concomitant PUVA or UVB therapy, methotrexate or other immunosuppressive agents, coal tar or radiation therapy. Psoriasis patients with abnormal renal function, uncontrolled hypertension, or malignancies should not receive cyclosporine.

General
Cyclosporine is contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

Rheumatoid Arthritis
Rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, or malignancies should not receive Cyclosporine.

WARNING AND PRECAUTIONS:
All Patients
Cyclosporine, the active ingredient of cyclosporine, can cause nephrotoxicity and hepatotoxicity. The risk increases with increasing doses of cyclosporine. Renal dysfunction including structural kidney damage is a potential consequence of cyclosporine and therefore renal function must be monitored during therapy. **Care should be taken in using cyclosporine with nephrotoxic drugs.** Patients receiving cyclosporine require frequent monitoring of serum creatinine. Elderly patients should be monitored with particular care, since decreases in renal function also occur with age. If patients are not properly monitored and doses are not properly adjusted, cyclosporine therapy can be associated with the occurrence of structural kidney damage and persistent renal dysfunction.
An increase in serum creatinine and BUN may occur during cyclosporine therapy and reflect a reduction in the glomerular filtration rate. Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated. The frequency and severity of serum creatinine elevations increase with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced without dose reduction or discontinuation.

PSORIASIS
Since cyclosporine is a potent immunosuppressive agent with a number of potentially serious side effects, the risks and benefits of using Cyclosporine should be considered before treatment of patients with psoriasis. Cyclosporine, the active ingredient in Cyclosporine, can cause nephrotoxicity and hypertension and the risk increases with increasing dose and duration of therapy. Patients who may be at increased risk such as those with abnormal renal function, uncontrolled hypertension or malignancies, should not receive Cyclosporine.
Renal dysfunction is a potential consequence of Cyclosporine therefore renal function must be monitored during therapy. Patients receiving Cyclosporine require frequent monitoring of serum creatinine. Elderly patients should be monitored with particular care, since decreases in renal function also occur with age. If patients are not properly monitored and doses are not properly adjusted, cyclosporine therapy can cause structural kidney damage and persistent renal dysfunction. An increase in serum creatinine and BUN may occur during Cyclosporine therapy and reflects a reduction in the glomerular filtration rate.
Kidney biopsies from 86 psoriasis patients treated for a mean duration of 23 months with 1.2 to 7.6 mg/kg/day of cyclosporine showed evidence of cyclosporine nephropathy in 18/86 (21%) of the patients.
The pathology consisted of renal tubular atrophy and interstitial fibrosis. On repeat biopsy of 13 of these patients maintained on various dosages of cyclosporine for a mean of 2 additional years, the number with cyclosporine induced nephropathy rose to 26/86 (30%). The majority of patients (19/26) were on a dose of ≥5.0 mg/kg/day (the highest recommended dose is 4 mg/kg/day). The patients were also on cyclosporine for greater than 15 months (18/26) and/or had a clinically significant increase in serum creatinine for greater than 1 month (21/26). Creatinine levels returned to normal range in 7 of 11 patients in whom cyclosporine therapy was discontinued.
There is an increased risk for the development of skin and lymphoproliferative malignancies in cyclosporine-treated psoriasis patients. The relative risk of malignancies is comparable to that observed in psoriasis patients treated with other immunosuppressive agents.
Tumors were reported in 32 (2.2%) of 1439 psoriasis patients treated with cyclosporine worldwide from clinical trials. Additional tumors have been reported in 7 patients in cyclosporine post marketing experience. Skin malignancies were reported in 16 (1.1%) of these patients; all but 2 of them had previously received PUVA therapy. Methotrexate was received by 7 patients. UVB and coal tar had been used by 2 and 3 patients, respectively. Seven patients had either a history of previous skin cancer or a potentially predisposing lesion was present prior to cyclosporine exposure. Of the 16 patients with skin cancer, 11 patients had 18 squamous cell carcinomas and 7 patients had 10 basal cell carcinomas.
There were two lymphoproliferative malignancies; one case of non-Hodgkin's lymphoma which required chemotherapy, and one case of mycosis fungoides which regressed spontaneously upon discontinuation of cyclosporine. There were four cases of benign lymphocytic infiltration: 3 regressed spontaneously upon discontinuation of cyclosporine, while the fourth regressed despite continuation of the drug. The remainder of the malignancies, 13 cases (0.9%), involved various organs.

Patients should not be treated concurrently with cyclosporine and PUVA or UVB, other radiation therapy, or other immunosuppressive agents, because of the possibility of excessive immunosuppression and the subsequent risk of malignancies. Patients should also be warned to protect themselves appropriately when in the sun, and to avoid excessive sun exposure. Patients should be thoroughly evaluated before and during treatment for the presence of malignancies remembering that malignant lesions may be hidden by psoriatic plaques. Skin lesions not typical of psoriasis should be biopsied before starting treatment. Patients should be treated with Cyclosporine only after complete resolution of suspicious lesions, and only if there are no other treatment options.

INTERACTIONS
Particular attention must be paid in administering cyclosporine in association with medicines with noted nephrotoxic effects, for example aminoglycosides, amphotericin B, ciprofloxacin, digoxin, melfalan, colchicine and trimethoprim. Since nonsteroidal anti-inflammatory drugs (NSAIDs) may alter the renal function, association of these with cyclosporine or an increase of their dosage, must be accompanied in the initial phase by an attentive monitoring of the renal function. Cyclosporine can increase the risk of muscular toxicity, including pain and weakness of muscles which

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may be noticed in the course of treatment with lovastatin. Hence, use of such medicines along with cyclosporine must be attentively and carefully considered. It is known that various medicines are capable of increasing or decreasing serum concentration of cyclosporine acting through competitive inhibition or induction of hepatic enzymes (in particular cytochrome P450) involved in the metabolism and excretion of cyclosporine. The following medicines can increase the serum levels of cyclosporine, e.g. ketoconazole, some macrolide antibiotics including erythromycin and josamycine, methyl prednisolone, metoclopramide, ranitidine, amiodarone, itraconazole, danazol, metronidazole, norfloxacin, and some calcium channel antagonists such as diltiazem, nicardipine and verapamil. Avoid taking nifedipine for patients who have developed gingival hypertrophy. Among the medicines that decrease the concentration of cyclosporine in plasma or in the whole blood, following have been indicated; barbiturates, carbamazepine, phenytoin and rifampicin. Hence, it is recommended that administration of cyclosporine along with these medicines must be avoided. If the concomitant administration of cyclosporine and one of these medicines is inevitable, blood concentration of cyclosporine must be monitored and appropriate modifications of dosage of cyclosporine must be brought about.

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 (>65 years of age)
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:
Before initiating treatment, a careful dermatological and physical examination, including blood pressure measurements (on at least two occasions) should be performed. Since Cyclosporine is an immunosuppressive agent, patients should be evaluated for the presence of occult infection on their first physical examination and for the presence of tumours initially, and throughout treatment with Cyclosporine. Skin lesions not typical for psoriasis should be biopsied before starting Cyclosporine. Patients with malignant or premalignant changes of the skin should be treated with Cyclosporine only after appropriate treatment of such lesions and if no other treatment option exists.
Baseline laboratories should include serum creatinine (on two occasions), BUN, CBC, serum magnesium, potassium, uric acid, and lipids.
The risk of cyclosporine nephropathy is reduced when the starting dose is low (2.5 mg/kg/day), the maximum dose does not exceed 4.0 mg/kg/day, serum creatinine is monitored regularly while cyclosporine is administered, and the dose of Cyclosporine is decreased when the rise in creatinine is greater than or equal to 25% above the patient's pre-treatment level. The increase in creatinine is generally reversible upon timely decrease of the dose of Cyclosporine or its discontinuation.
Serum creatinine and BUN should be evaluated every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable. If the serum creatinine is greater than or equal to 25% above the patient's pre-treatment level, serum creatinine should be repeated within two weeks. If the change in serum creatinine remains greater than or equal to 25% above baseline, Cyclosporine should be reduced by 25% to 50%. If at any time the serum creatinine increases by greater than or equal to 50% above pre-treatment level, Cyclosporine should be reduced by 25% to 50%. Cyclosporine should be discontinued if reversibility (within 25% of baseline) of serum creatinine is not achievable after two dosage modifications. It is advisable to monitor serum creatinine after an increase of the dose of nonsteroidal anti-inflammatory drug and after initiation of new nonsteroidal anti-inflammatory therapy during Cyclosporine treatment.
Blood pressure should be evaluated every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable, or more frequently when dosage adjustments are made. Patients without a history of previous hypertension before initiation of treatment with Cyclosporine, should have the drug reduced by 25%-50% if found to have sustained hypertension. If the patient continues to be hypertensive despite multiple reductions of Cyclosporine, then Cyclosporine should be discontinued. For patients with treated hypertension, before the initiation of Cyclosporine therapy, their medication should be adjusted to control hypertension while on Cyclosporine. Cyclosporine should be discontinued if a change in hypertension management is not effective or tolerable.
CBC, uric acid, potassium, lipids, and magnesium should also be monitored every 2 weeks for the first 3 months of therapy, and then monthly if the patient is stable or more frequently when dosage adjustments are made. Cyclosporine dosage should be reduced by 25%–50% for any abnormality of clinical concern.
In controlled trials of cyclosporine in psoriasis patients, cyclosporine blood concentrations did not correlate well with either improvement or with side effects such as renal dysfunction.
Information for Patients: Patients should be advised that any change of cyclosporine formulation should be made cautiously and only under physician supervision because it may result in the need for a change in dosage.
Patients should be informed of the necessity of repeated laboratory tests while they are receiving cyclosporine. Patients should be advised of the potential risks during pregnancy and informed of the increased risk of neoplasia. Patients should also be informed of the risk of hypertension and renal dysfunction.
Patients should be advised that during treatment with cyclosporine, vaccination may be less effective and the use of live attenuated vaccines should be avoided.
Patients should be given careful dosage instructions. Patients should be advised to take Cyclosporine on a consistent schedule with regard to time of day and relation to meals. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.
Laboratory Tests
In all patients treated with cyclosporine, renal and liver functions should be assessed repeatedly by measurement of serum creatinine, BUN, serum bilirubin, and liver enzymes. Serum lipids, magnesium, and potassium should also be monitored. Cyclosporine blood concentrations should be routinely monitored in transplant patients, and periodically monitored in rheumatoid arthritis patients.

ADVERSE EFFECTS
The principal adverse reactions associated with the use of cyclosporine in patients with psoriasis are renal dysfunction, headache, hypertension, hypertriglyceridemia, hirsutism/hypertrichosis, paraesthesia or hyperesthesia, influenza-like symptoms, nausea/vomiting, diarrhoea, abdominal discomfort, lethargy, and musculoskeletal or joint pain.

Nephrotoxicity:
In psoriasis patients treated in US controlled clinical studies within the recommended dose range, cyclosporine therapy was discontinued in 1.0% of the patients because of hypertension and in 5.4% of the patients because of increased creatinine. In the majority of cases, these changes were reversible after dose reduction or discontinuation of cyclosporine.
Frequency and severity of serum creatinine increases with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced and may result in irreversible renal damage without dose reduction or discontinuation.

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. Antihypertensive are generally recommended, however cyclosporine may cause hyperkaliemia. Therefore potassium sparing diuretics are not recommended for treating hypertension. Instead, calcium antagonists can be effective agents for treating such hypertension.
- Hyperkalemia,
- Headaches, Hyperlipidemias,
- Gastrointestinal disturbances, Hepatoxicity, Hypertrichosis, Gum hyperplasia, Tremor.
- Hypomagnesaemia, Hyperuricemia, Paranesthesia, 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 manifestation of encephalopathy is as convulsions, 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.

OVERDOSAGE
There is a minimal experience with cyclosporine overdosage. Forced emesis and gastric lavage can be of value up to 2 hours after administration of Cyclosporine. Transient hepatotoxicity and nephrotoxicity may occur which should resolve following drug withdrawal. Oral doses of cyclosporine up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, and tachycardia and, in a few patients, moderately severe, reversible impairment of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with cyclosporine in premature neonates. General supportive measures and symptomatic treatment should be followed in all cases of overdosage. Cyclosporine is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion. The oral dosage at which half of experimental animals are estimated to die is 31 times, 39 times, and >54 times the human maintenance dose for transplant patients (6mg/kg; corrections based on body surface area) in mice, rats, and rabbits.

STORAGE:
Store protected from moisture, at a temperature not exceeding 30°C. Do not refrigerate.
Keep out of reach of children.

PRESENTATION:
PSORID®25/50/100 mg Capsules
Each Blister Pack contains 6 x 5 soft gelatin capsules

Special Precaution for disposal and other handling:
Any unused medicinal product should be disposed off in accordance with the local requirements.

Shelf Life: Please refer carton/blister.

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Electronics City, Phase - II,
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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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