8291

For the use of Registered Medical Practitioner, hospital or laboratory only.

Biocon

℞

Cyclosporine Capsules IP 25mg/50mg/100mg

CYCLOPHIL ME®- 25/50/100
साइक्लोफिल एमई-२५/५०/१००

Composition:
CYCLOPHIL ME®- 25
Each soft gelatin capsule contains
Cyclosporine IP.....25 mg
Approved colours used in gelatin shell
CYCLOPHIL ME®- 50
Each soft gelatin capsule contains
Cyclosporine IP.....50 mg
Approved colours used in gelatin shell
CYCLOPHIL ME®- 100
Each soft gelatin capsule contains
Cyclosporine IP.....100 mg
Approved colours used in gelatin shell

WARNING
Only physicians experienced in management of systemic immunosuppressive therapy for the indicated disease should prescribe Cyclophil ME. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Cyclophil ME, a systemic immunosuppressant, may increase the susceptibility to infection and the development of neoplasia. In kidney, liver, and heart transplant patients Cyclophil ME may be administered with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the increase in the degree of immunosuppression in transplant patients.

Pharmaceutical Form: Soft gelatin capsule
ATC Code: L04AD01

Description
Cyclophil ME®is an oral formulation of cyclosporine that immediately forms a microemulsion in an aqueous environment. Cyclosporine, the active principle in Cyclophil ME, 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-(alpha)-amino-butyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl).

Clinical Pharmacology
Mechanism of Action:
Cyclosporine induces immunosuppression by inhibiting the first phase of T-cell activation. The first phase of T-cell activation causes transcriptional activation of immediate and early gene products (e.g., interleukins - IL-2, IL-3, and IL-4, tumor necrosis factor alpha, and interferon gamma) that allow T-cells to progress from the G_0 to G, phases. Cyclosporine binds to an immunophilin termed cyclophilin. Immunophilins (e.g., cyclophilin and FK binding proteins) are immunosuppressant-binding proteins that are distributed in all cellular compartments and play an important role in protein regulation.

The cyclosporine-cyclophilin complex then binds to and inhibits the calcium-cal modulin activated phosphatase calcineurin. The calcineurin enzyme catalyzes critical dephosphorylation reactions necessary for early lymphokine gene transcription, and subsequent early activation of T-cells. Calcineurin inhibition results in blockade of signal transduction of the nuclear factor of activated T-cells (NF-AT). The blockade of signal transduction results in failure to activate NF-AT regulated genes. NF-AT activated genes include those required for B-cell activation including interleukin (IL)-4 and CD40 ligand and those required for T-cell activation including IL-2 and interferon gamma. Cyclosporine does not affect suppressor T-cells or T-cell independent, antibody-mediated immunity

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 5-18 hours). Following intravenous administration, the blood clearance of cyclosporine (assay: HPLC) is approximately 5-7 mL/min/kg in adult recipients of renal or liver allografts.

The relationship between administered dose and exposure (area under the concentration versus time curve, AUC) is linear within the therapeutic dose range. The intersubject variability (total, %CV) of cyclosporine exposure (AUC) when Cyclosporine is administered ranges from approximately 20% to 50% in renal transplant patients. This intersubject variability contributes to the need for individualization of the dosing regimen for optimal therapy .

Absorption
The absolute bioavailability of Cyclosporine has not been determined in adults. In studies of renal transplant, rheumatoid arthritis and psoriasis patients, the mean cyclosporine AUC was approximately 20% to 50% greater and the peak blood cyclosporine concentration (C_{max}) was approximately 40% to 106% greater following administration of Cyclosporine . Following oral administration of Cyclosporine the time to peak blood cyclosporine concentrations (T_{max}) ranged from 1.5-2.0 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 ME administration decreased the AUC by 13% and C_{max} by 33%.

Distribution
Cyclosporine is distributed widely throughout the body, crosses the placenta, and is found in breast milk. Preferential uptake of cyclosporine occurs in the liver, pancreas, and adipose tissue, while it penetrates the CNS poorly. In blood, the distribution of cyclosporine is concentration dependent; as the hematocrit rises, the cyclosporine concentration in plasma decreases. Approximately 22%-47% of cyclosporine is found in plasma, 4%-9% in lymphocytes, 5%-12% in granulocytes, and 41%-58% in erythrocytes. At high drug concentrations the binding to lymphocytes and erythrocytes becomes saturated. In plasma, cyclosporine is approximately 90% bound to lipoproteins. In addition, binding to erythrocytes and lipoproteins is temperature dependent. As the temperature increases, binding to lipoproteins increases; however, binding to erythrocytes increases as the temperature decreases. Other medications that may affect the binding of cyclosporine to lipoproteins may modify the clinical response to cyclosporine.

Metabolism
Cyclosporine is metabolized extensively by the CYP3A enzyme system in the liver and to a lesser extent in the gastrointestinal tract and kidney. Agents that affect the CYP3A system (see Drug Interactions) may significantly alter the metabolism of cyclosporine. At least 25 metabolites of cyclosporine have been identified, some of which are biologically active. Although most cyclosporine metabolites show only 10%-20% of the immunosuppressive activity of the parent drug, they do contribute to toxicity. The major metabolites of cyclosporine are M1, M9, and M4N, resulting from oxidation at the 1-beta, 9-gamma, and 4-N-desmethylated positions. The percentage of dose present as M1, M9, or M4N is similar when either cyclosporine (Microemulsion) or cyclosporine (Non-Microemulsion) is administered. At steady state, concentrations and AUCs of cyclosporine metabolites may exceed that of cyclosporine. Mean AUCs for blood concentrations of these metabolites are 70%, 21%, and 7.5% respectively, of blood cyclosporine concentrations. The elimination half-life of cyclosporine is highly variable. In patients with normal hepatic function the average half-life ranges from 16-27 hours, but can vary from 10-40 hours.

Elimination
Elimination of cyclosporine and its metabolites is principally through the bile and feces. Cyclosporine undergoes enterohepatic recycling. Only 6% of the cyclosporine dose is excreted renally, of which 0.1% is excreted as unchanged cyclosporine. Although cyclosporine blood levels are widely used to assist dosing, accurate interpretation is hampered by variation in absorption, variation in protein binding, sampling error, type of assay, cross-reactivity of metabolites, enterohepatic recycling of drug, and drug interactions

Special Populations
Pediatric Population
Pharmacokinetic data from pediatric patients administered cyclosporine are very limited. In a study of 7 renal transplant patients aged 2-16, the cyclosporine clearance ranged from 9.8-15.5 mL/min/kg. In 9 liver transplant patients aged 0.6-5.6 years, clearance was 9.3±5.4 mL/min/kg . In the pediatric population, cyclophil demonstrates an increased bioavailability as compared to oil based Cyclosporine.

Geriatric Population
Comparison of single dose data from both normal elderly volunteers (N=18, mean age 69 years) and elderly rheumatoid arthritis patients (N=16, mean age 68 years) to single dose data in young adult volunteers (N=16, mean age 26 years) showed no significant difference in the pharmacokinetic parameters.

Indications
Solid Organ Transplantation
Cyclophil ME is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Cyclosporine has been used in combination with other immunosuppressants.

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

Warnings
All Patients
Cyclosporine, the active ingredient of Cyclophil ME, 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. Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated. In the event of severe and unremitting rejection, when rescue therapy with pulse steroids and monoclonal antibodies fail to reverse the rejection episode, it may be preferable to switch to alternative immunosuppressive therapy rather than increase the cyclosporine dose to excessive levels.

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of cyclosporine and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans.Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients. Hepatotoxicity associated with cyclosporine use had been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of cyclosporine were used and consisted of elevations of hepatic enzymes and bilirubin. The chemistry elevations usually decreased with a reduction in dosage.

As in patients receiving other immunosuppressants, those patients receiving cyclosporine are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents. Because of the danger of oversuppression of the immune system resulting in increased risk of infection or malignancy, a treatment regimen containing multiple immunosuppressants should be used with caution. There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone.

Encephalopathy has been described both in post-marketing reports and in the literature. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances. In many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. Predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high cyclosporine blood concentrations, and graft-versus-host disease have been noted in many but not all of the reported cases. The changes in most cases have been reversible upon discontinuation of cyclosporine, and in some cases improvement was noted after reduction of dose. It appears that patients receiving liver transplant are more susceptible to encephalopathy than those receiving kidney transplant. Another rare manifestation of cyclosporine-induced neurotoxicity, occurring in transplant patients more frequently than in other indications, is optic disc edema including papilloedema, with possible visual impairment, secondary to benign intracranial hypertension.

Precaution
General: Hypertension
Hypertension is a common side effect of cyclosporine therapy which may persist. Mild or moderate hypertension is encountered more frequently than severe hypertension and the incidence decreases over time. In recipients of kidney, liver, and heart allografts treated with cyclosporine, antihypertensive therapy may be required. However, since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used. While calcium antagonists can be effective agents in treating cyclosporine-associated hypertension, they can interfere with cyclosporine metabolism. (See DRUG INTERACTIONS)
Vaccination: During treatment with cyclosporine, vaccination may be less effective; and the use of live attenuated vaccines 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
Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. Cyclosporine was not mutagenic in appropriate test systems. Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice
An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants and patients with rheumatoid arthritis and psoriasis. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies in cyclosporine recipients is higher than in the normal, healthy population but similar to that in patients receiving other immunosuppressive therapies. Reduction or discontinuance of immunosuppression may cause the lesions to regress. No impairment in fertility was demonstrated in studies in male and female rats.

Pregnancy: Category C
Animal studies have shown reproductive toxicity in rats and rabbits. There are no adequate and well-controlled studies in pregnant women. and, therefore, cyclosporine should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers
Cyclosporine passes into breast milk. Mothers receiving treatment with cyclosporine should not breast feed.
Pediatric Use
Although no adequate and well-controlled studies have been completed in children, transplant recipients as young as one year of age have received cyclosporine with no unusual adverse effects. The safety and efficacy of cyclosporine treatment in children with juvenile rheumatoid arthritis or psoriasis below the age of 18 have not been established.

Geriatric Use
Clinical studies of cyclosporine in transplant and psoriasis patients did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experiences have not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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Drug Interactions
All of the individual drugs cited below are well substantiated to interact with cyclosporine. In addition, concomitant non-steroidal anti-inflammatory drugs, particularly in the setting of dehydration, may potentiate renal dysfunction.

Drugs That May Potentiate Renal Dysfunction

Antibiotics	*Antineoplastics*	*Anti-inflammatory Drugs*	*Gastrointestinal Agents*
ciprofloxacin gentamicin tobramycin vancomycin trimethoprim with sulfamethoxazole	melphalan ***Antifungals*** amphotericin B ketoconazole	azapropazon colchicine diclofenac naproxen sulindac	cimetidine ranitidine ***Immunosuppressives*** tacrolimus ***Other Drugs*** fibric acid derivatives (e.g. bezafibrate, fenofibrate)

Drugs That Alter Cyclosporine Concentrations
Compounds that decrease cyclosporine absorption such as orlistat should be avoided. Cyclosporine is extensively metabolized by cytochrome P-450 3A. Substances that inhibit this enzyme could decrease metabolism and increase cyclosporine concentrations. Substances that are inducers of cytochrome P-450 activity could increase metabolism and decrease cyclosporine concentrations. Monitoring of circulating cyclosporine concentrations and appropriate cyclosporine dosage adjustment are essential when these drugs are used concomitantly.

Drugs that increase Cyclosporine concentrations

Antibiotics	Anticonvulsants	Other Drugs/Dietary Supplements	
nafcillin rifampin	carbamazepine phenobarbital phenytoin	octreotide orlistat sulfinpyrazone terbinafine ticlopidine	St. John's Wort

The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 3A and thus could potentially increase the concentrations of cyclosporine, however no formal studies of the interaction are available. Care should be exercised when these drugs are administered concomitantly.
Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine, thus should be avoided.

Drugs that decrease Cyclosporine concentrations

Calcium Channel Blockers	*Antifungals*	*Antibiotics*	*Glucocorticoids*	*Other Drugs*	
diltiazem nicardipine verapamil contraceptives	fluconazole itraconazole ketoconazole	azithromycin clarithromycin erythromycin quinupristin/dalfopristin	methylprednisolone	allopurinol amiodarone bromocriptine colchicine	danazol imatinib metoclopramide

There have been reports of a serious drug interaction between cyclosporine and the herbal dietary supplement, St. John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss. Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these two drugs are administered concomitantly.

Nonsteroidal Anti-inflammatory Drug (NSAID) Interactions
Clinical status and serum creatinine should be closely monitored when cyclosporine is used with nonsteroidal anti-inflammatory agents in rheumatoid arthritis patients.Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function.,

Methotrexate Interaction
Preliminary data indicate that when methotrexate and cyclosporine were co-administered to rheumatoid arthritis patients (N=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine concentrations do not appear to have been altered (N=6).

Other Drug Interactions
Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone and HMG-CoA reductase inhibitors (statins). Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin. There are also reports on the potential of cyclosporine to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. If digoxin or colchicine are used concurrently with cyclosporine, close clinical observation is required in order to enable early detection of toxic manifestations of digoxin or colchicine, followed by reduction of dosage or its withdrawal.
Literature and postmarketing cases of myotoxicity, including pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely fluvastatin. When concurrently administered with cyclosporine, the dosage of these statins should be reduced according to label recommendations. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis. Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur. Caution is also required when cyclosporine is co-administered with potassium sparing drugs (e.g. angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists), potassium containing drugs as well as in patients on a potassium rich diet. Control of potassium levels in these situations is advisable.
Elevations in serum creatinine were observed in studies using sirolimus in combination with full-dose cyclosporine. This effect is often reversible with cyclosporine dose reduction. Simultaneous co-administration of cyclosporine significantly increases blood levels of sirolimus. To minimize increases in sirolimus blood concentrations, it is recommended that sirolimus be given 4 hours after cyclosporine administration. During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided. Frequent gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone have been reported. Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive concurrent cyclosporine because of the possibility of excessive immunosuppression

Adverse reactions
Nephrotoxicity is the most common adverse effect of systemic cyclosporine therapy and has been documented in all types of patients receiving cyclosporine. Cyclosporine-induced nephrotoxicity is most likely due to intense renal vasoconstriction, which leads to increases in serum creatinine, arterial blood pressure, and serum potassium. The frequency and severity of serum creatinine elevations increase with dose and duration of cyclosporine therapy. Nephrotoxicity has been reported in 20%-38% of transplant patients, although rates as high as 80% have been observed. In patients with cyclosporine nephrotoxicity, reducing the dose of cyclosporine often leads to improvement in renal-function indices.
Differentiating cyclosporine nephrotoxicity from graft rejection or hypertensive-induced nephrosclerosis (which may also be related to cyclosporine administration) in renal transplant patients is difficult. Clinical parameters associated with cyclosporine-induced nephrotoxicity include onset > 6 weeks post-transplant, prolonged initial non-function of kidney (acute renal tubular necrosis), cyclosporine trough blood level > 200 ng/ml, gradual rise in serum creatinine (< 0.15 mg/dL/day), serum creatinine plateau < 25% above baseline, and BUN/creatinine ratio >=20 (azotemia). Serial deterioration in renal function and morphologic changes in the kidneys characterize a form of cyclosporine-associated nephropathy.
Renal biopsies from these patients will demonstrate one or more of the following alterations: tubular vacuolization, tubular microcalcifications, peritubular capillary congestion, arteriolopathy, and a striped form of interstitial fibrosis with tubular atrophy. Though none of these morphologic changes is entirely specific, a diagnosis of cyclosporine-associated structural nephrotoxicity requires evidence of these findings. Consequences of cyclosporine nephrotoxicity include renal insufficiency with accumulation of type A (BUN, serum creatinine) and type B (potassium, uric acid) solutes. Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been observed in patients receiving systemic cyclosporine. Hyperkalemia may indicate nephrotoxicity. Occasionally patients treated with systemic cyclosporine, especially following bone marrow transplantation, have developed a syndrome similar to idiopathic thrombotic thrombocytopenic purpura (TTP) or hemolytic-uremic syndrome (HUS), which may lead to graft failure.
During systemic cyclosporine therapy, mild to moderate hypertension is encountered more frequently than severe hypertension and the incidence decreases over time. Hypertension occurs in 50% of renal transplant patients and in most cardiac transplant patients. In recipients of kidney, liver, or heart allografts treated with cyclosporine, antihypertensive therapy may be required. Hepatotoxicity in the form of elevated hepatic enzymes or hyperbilirubinemia occurs in 47% of transplant patients receiving systemic cyclosporine. Hepatic toxicity is more common during the first month of therapy when higher doses of cyclosporine are used. Elevated hepatic enzymes and serum bilirubin levels appear to be associated with trough serum levels greater than 500 ng/ml and oral doses greater than 17 mg/kg/day. Effects usually will resolve with a reduction in cyclosporine dose. Systemic cyclosporine use in transplant recipients as well as in other patients has been associated with hypercholesterolemia, including hyperlipidemia with elevations in LDL-C levels and hypertriglyceridemia. Although the significance of cyclosporine-induced hypercholesterolemia is not clear, administration of lipid-lowering therapy may affect the lipoprotein binding of cyclosporine and/or cyclosporine metabolism (see Drug Interactions).

Hypomagnesemia has been reported in some, but not all, patients experiencing seizures while receiving systemic cyclosporine therapy. Generalized tonic-clonic seizures often occur with high cyclosporine levels. In mild cases, symptoms tend to resolve spontaneously; however, dosage reduction or discontinuation of therapy may be required in more severe cases. Manifestations of encephalopathy include impaired cognition, seizures, visual impairment/disturbances (including blindness), loss of motor function, movement disorders, and psychiatric disturbances. A rare manifestation of cyclosporine-induced neurotoxicity is optic disc edema including papilledema with possible visual impairment secondary to benign intracranial hypertension. Other neurologic side effects include confusion, delirium, depression, dizziness, hallucinations, headache, hyperesthesia, insomnia, memory deficits, migraines, paresthesias, and peripheral neuropathy . Somnolence and coma have also been reported.

Some degree of hirsutism or hypertrichosis occurs in most patients receiving systemic cyclosporine. Pronounced darkening and thickening of eyebrows, side burns, and other secondary hair growth occurs in both men and women. Other dermatologic effects reported in more than 3% of patients include acneiform rash, alopecia, rash (unspecified), and skin ulcer. Coarsening of facial features has been reported in children receiving cyclosporine. Gingival hyperplasia can occur in 416% of transplant patients receiving systemic cyclosporine. It is reversible 12 months following discontinuance of cyclosporine therapy. Other adverse GI effects that occur in more than 3% of patients receiving cyclosporine include abdominal pain, anorexia, diarrhea, dyspepsia, flatulence, gingivitis, nausea/vomiting, and stomatitis.

Various types of Infection are common in patients receiving systemic cyclosporine after organ transplantation or in the treatment of other autoimmune disorders due to the immunosuppressive effects of the drug. Local and systemic infections including fungal and viral infections (e.g., herpes simplex, herpes zoster) as well as sepsis, have been reported during cyclosporine therapy. Infections reported in 13% of patients receiving cyclosporine include abscess, cellulitis, folliculitis, renal abscess, moniliasis, and tonsillitis. Respiratory tract infections including bronchitis, pharyngitis, pneumonia, rhinitis, sinusitis or other upper respiratory tract infections may occur. Other respiratory adverse reactions reported in > 3% of patients receiving cyclosporine include bronchospasm, cough, and dyspnea.

Other adverse reactions reported in at least 2% of patients receiving systemic cyclosporine include arthralgia, dysarthria (slurred speech), fatigue, fever, flu-like symptoms, flushing, gynecomastia, hyperglycemia, leg cramps, leukopenia, myalgia, and rigors. Cyclosporine may increase serum prolactin levels (i.e., hyperprolactinemia) but decreases serum testosterone levels. These changes may lead to menstrual irregularity or spermatogenesis inhibition and associated infertility. Following immunosuppressive therapy, patients may develop a secondary malignancy. Lymphomas, lymphoproliferative disorders, skin cancers, and other malignancies have been reported in patients following treatment with cyclosporine. The risk for development of these conditions appears to be related to the intensity and duration of immunosuppression rather than the use of specific agents.

Overdosage
There is a minimal experience with cyclosporine overdosage. Forced emesis can be of value up to 2 hours after administration of Cyclosporine. Transient hepatotoxicity and nephrotoxicity may occur which should resolve following drug withdrawal. 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.

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.

Newly Transplanted Patients
The initial oral dose of Cyclophil ME can be given 4-12 hours prior to transplantation or be given postoperatively. The initial dose of Cyclophil ME varies depending on the transplanted organ and the other immunosuppressive agents included in the immunosuppressive protocol.
The mean ± SD initial doses were 9±3 mg/kg/day for renal transplant patients , 8±4mg/kg/day for liver transplant patients and 7±3 mg/kg/day for heart transplant patients . Total daily doses were divided into two equal daily doses. The Cyclophil ME dose is subsequently adjusted to achieve a pre-defined cyclosporine blood concentration. Dosing should be titrated based on clinical assessments of rejection and tolerability.
In pediatric usage, the same dose and dosing regimen may be used as in adults although in several studies children have required and tolerated higher doses than those used in adults.

Storage: Store at a temperature not exceeding 30°C. Protect from moisture, heat and direct sunlight.
Keep out of reach of children.

Presentation:
CYCLOPHIL ME®- 25 : Each blister of 5 soft gelatin capsules
CYCLOPHIL ME®- 50 : Each blister of 5 soft gelatin capsules
CYCLOPHIL ME®- 100 : Each blister of 5 soft gelatin capsules

Special Precautions 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.

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

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Leaflet revised on August 2019.

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