

# CONCORD BIOTECH

Biotech for Mankind...

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

## Mycophenolate Mofetil For Oral Suspension IP 1gm / 5ml

**Mofecon™ OS mini** (pediatric Pack)

मोफेकोन ओएस मिनी

### 1. Composition

Each 5ml of reconstituted suspension contains:  
Mycophenolate Mofetil IP..... 1 gm

### 2. Dosage Form

Mycophenolate mofetil is supplied as powder for oral suspension.

### 3. Therapeutic Indication

Mofecon OS mini 1 g/5 ml powder for oral suspension is indicated in combination with cyclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

### 4. Dosage and Administration

Standard dosage for prophylaxis in renal transplant

Mycophenolate mofetil oral suspension should be initiated within 72 hours following transplantation.

Children (aged 3-months to 18 years): the recommended dose of Mycophenolate mofetil powder for oral suspension is 600 mg/m<sup>2</sup> administered twice daily (up to a maximum of 2 g daily).

Standard dosage for prophylaxis in cardiac transplant

Mycophenolate Mofetil oral suspension should be initiated within 5 days following transplantation.

Children: no data are available for paediatric cardiac transplant patients.

Standard dosage for prophylaxis in hepatic transplant

Mycophenolate Mofetil IP should be administered for the first 4 days following hepatic transplant, with oral suspension initiated as soon after this as it can be tolerated.

Children: no data are available for paediatric hepatic transplant patients.

### 5. Contraindications

Allergic reactions to Mycophenolate mofetil have been observed. Therefore, Mycophenolate mofetil is contraindicated in patients with hypersensitivity to Mycophenolate mofetil or Mycophenolic acid (MPA). Mycophenolate mofetil is contraindicated during pregnancy due to its mutagenic and teratogenic potential. Mycophenolate mofetil is contraindicated in women of childbearing potential not using highly effective contraceptive methods. It should not be given to women who are breastfeeding.

### 6. Warnings and Precautions

#### 6.1 Neoplasms

As in all patients receiving immunosuppressive regimens involving combinations of drugs, patients receiving Mycophenolate mofetil as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As with all patients at an increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

#### 6.2 Infections

Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections and sepsis. Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation, or infections caused by polyomaviruses. Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants.

Cases of Progressive Multifocal Leukoencephalopathy (PML) associated with the JC virus, sometimes fatal, have been reported in Mycophenolate mofetil treated patients. The reported cases generally had risk factors for PML, including immunosuppression and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

BK virus-associated nephropathy has been observed during the use of Mycophenolate mofetil in patients post renal transplant. This infection can be associated with serious outcomes, sometimes leading to renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

#### Blood and immune system

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with Mycophenolate mofetil in combination with other immunosuppressive agents. The mechanism for Mycophenolate mofetil induced PRCA is unknown; the relative contribution of other immunosuppressants and their combination in an immunosuppression regimen are also unknown. In some cases PRCA was found to be reversible with dose reduction or cessation of Mycophenolate mofetil therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

Patients receiving Mycophenolate mofetil should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Patients on Mycophenolate mofetil should have complete blood counts weekly during the first month of treatment, twice monthly for the second and third months, then monthly through the first year. In particular, patients receiving Mycophenolate mofetil should be monitored for neutropenia. The development of neutropenia may be related to Mycophenolate mofetil, concomitant medications, viral infection or some combination of these causes.

### 7. Drug Interactions

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation e.g. Cyclosporin to others devoid of this effect e.g. Tacrolimus, Sirolimus, Belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, antibiotics) should be used with caution due to their potential to reduce the plasma levels and efficacy of Mycophenolate mofetil. It is recommended that Mycophenolate mofetil should not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied.

Mycophenolate mofetil oral suspension contains aspartame, a source of phenylalanine (equivalent to 2.78 mg per 5mL of oral suspension). Therefore, care should be taken if Mycophenolate mofetil oral suspension is administered to patients with phenylketonuria.

#### 7.1 Interactions with other Medicinal Products and other Forms of Interaction

Acyclovir: Higher MPAG (the phenolic glucuronide of MPA) and acyclovir plasma concentrations were observed when Mycophenolate mofetil was administered with acyclovir than when the drugs were administered alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for Mycophenolate and acyclovir or its prodrugs, e.g. valacyclovir, to compete for tubular secretion, further increasing the concentrations of both drugs.

Antacids and proton pump inhibitors (PPIs): Decreased mycophenolic acid (MPA) exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with Mycophenolate mofetil. When comparing rates of transplant rejection or rates of graft loss between Mycophenolate mofetil patients taking PPIs vs. Mycophenolate mofetil patients not taking PPIs, no significant differences were seen. These data support extrapolation of this finding to all antacids because the reduction in exposure when Mycophenolate mofetil was co-administered with magnesium and aluminium hydroxides is considerably less than when Mycophenolate mofetil was co-administered with PPIs.

Cholestyramine: Following single-dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pretreated with 4 g t.i.d. of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA. Caution should be used during concomitant administration or with drugs that interfere with enterohepatic circulation.

Cyclosporin A: Cyclosporin A (CsA) pharmacokinetics were unaffected by mycophenolate mofetil. However, CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50% in renal transplant patients treated with Mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of Mycophenolate mofetil. Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which do not interfere with MPA's enterohepatic cycle.

Telmisartan: Concomitant administration of Telmisartan and Mycophenolate mofetil resulted in an approximately 30% decrease of mycophenolic acid (MPA) concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression which in turn results in an enhanced UGT1A9 expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between Mycophenolate mofetil patients with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic DDI were seen.

Ganciclovir: Based on the results of a single-dose administration study of recommended doses of oral Mycophenolate and i.v. ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF and ganciclovir, it is anticipated that coadministration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and MMF dose adjustment is not required. In patients with renal impairment in which MMF and ganciclovir or its prodrugs, e.g. valganciclovir, are coadministered, patients should be monitored carefully.

Oral contraceptives: A study of coadministration of Mycophenolate mofetil (1 g b.i.d.) and combined oral contraceptives containing ethinylestradiol (0.02-0.04 mg) and levonorgestrel (0.05-0.20 mg), desogestrel (0.15 mg) or gestodene (0.05-0.10 mg) conducted in 18 women with polystasis over 3 menstrual cycles showed no clinically relevant influence of Mycophenolate mofetil on serum levels of progesterone, LH and FSH, thus indicating no influence of Mycophenolate mofetil on the ovulation suppressing action of the oral contraceptives. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by coadministration of Mycophenolate mofetil.

Rifampicin: After correction for dose a 70% decrease in MPA exposure (AUC<sub>0-12</sub>) has been observed with concomitant rifampicin administration in a single heart-lung transplant patient. It is therefore recommended to monitor MPA exposure levels and to adjust Mycophenolate mofetil doses accordingly to maintain clinical efficacy when the drugs are administered concomitantly.

Tacrolimus: Exposure to tacrolimus concomitantly administered with Mycophenolate mofetil had no effect on the AUC or C<sub>0-12</sub> of MPAG in liver transplant recipients. A similar finding was observed in a recent study in kidney transplant recipients.

In renal transplant patients it was shown that the tacrolimus concentration did not appear to be altered by Mycophenolate mofetil. However, in hepatic transplant patients, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of Mycophenolate mofetil (1.5 g b.i.d.) were administered to patients taking tacrolimus.

Antibiotics eliminating 13-glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin classes of antibiotics) may interfere with MPAG/MPA enterohepatic recirculation thus leading to reduced systemic MPA exposure.

Information concerning the following antibiotics is available: Ciprofloxacin or amoxicillin plus clavulanic acid in pre-dose (trough) MPA concentrations of 54% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. Effects tend to diminish with continued antibiotic use and cease after discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure therefore clinical relevance of these observations is unclear.

Norfloxacin and metronidazole: Norfloxacin in combination with metronidazole reduced the MPA AUC<sub>0-12</sub> by 30% following a single dose of Mycophenolate mofetil. No such effect on the systemic exposure of MPA with either of these antibiotics occurred when they were administered separately.

Trimethoprim/sulphamethoxazole: No effect on the systemic exposure of MPA (AUC, C<sub>0-12</sub>) was seen with the combination trimethoprim/sulfamethoxazole.

Other interactions: Coadministration of probenecid with mycophenolate mofetil in monkeys raises the plasma AUC of MPAG 3-fold. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

Concomitant administration of sevelamer and Mycophenolate mofetil in adults and pediatric patients decreased the MPA C<sub>0-12</sub> and AUC<sub>0-12</sub> by 30% and 25%, respectively. This data suggest that sevelamer and other calcium-free phosphate binders preferentially should be given 2 hours after Mycophenolate mofetil intake to minimize the impact on the absorption of MPA.

Live vaccines: Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished.

### 8. Use in Special Populations

#### 8.1 Renal Impairment

Patients with severe renal impairment

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate <25 mL/min/1.73m<sup>2</sup>) outside of the immediate post-transplant period or after treatment of acute or refractory rejection, doses greater than 1 g administered twice a day should be avoided.

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Patients with delayed renal graft function post-transplant No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively.

#### 8.2 Hepatic Impairment

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

### 9. Undesirable Effects

The adverse event profile associated with the use of immunosuppressive drugs is often difficult to establish owing to the presence of underlying diseases and the concurrent use of many other medications.

#### 9.1 Clinical Trials

The principal adverse reactions associated with the administration of Mycophenolate mofetil in the prevention of renal, cardiac and hepatic transplant rejection in combination with Cyclosporin and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infection, e.g. opportunistic infections. Diarrhoea and leucopenia, followed by anaemia, nausea, abdominal pain, sepsis, nausea and vomiting, and dyspnoea were the predominant adverse events reported more frequently in patients receiving Mycophenolate mofetil in comparison to patients receiving i.v. corticosteroids.

#### Malignancies

As in patients receiving immunosuppressive regimens involving combinations of drugs, patients receiving Mycophenolate mofetil as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.

#### Opportunistic Infections

All transplant patients are at increased risk of opportunistic infections. The risk increased with total immunosuppressive load. The most common opportunistic infections in patients receiving Mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%.

#### Children (aged 3-months to 18 years)

The type and frequency of adverse drug reactions in a clinical study of 100 paediatric patients aged 3-months to 18 years given 600 (mg/m<sup>2</sup>) mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g Mycophenolate mofetil twice daily. However, the following treatment-related adverse events occurred with a frequency of > 10% in children and were more frequent in the paediatric population, particularly in children under 6 years of age, when the frequency of treatment-related adverse events were compared to adults: diarrhoea, leucopenia, sepsis, infection, anaemia.

#### 9.2 Post Marketing

##### Infections

Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of infections such as tuberculosis and atypical mycobacterial infection. Cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, have been reported in Mycophenolate mofetil treated patients. The reported cases generally had risk factors for PML, including immunosuppression and impairment of immune function.

BK virus associated nephropathy has been observed in patients treated with Mycophenolate mofetil. This infection can be associated with serious outcomes, sometimes leading to renal graft loss.

Blood and Immune System: Cases of pure red cell aplasia (PRCA) and hypogammaglobulinemia have been reported in patients treated with Mycophenolate mofetil in combination with other immunosuppressive agents.

Congenital disorders: Congenital malformations have been reported post marketing in children of patients exposed to Mycophenolate mofetil in combination with other immunosuppressants during pregnancy.

Gastro-intestinal: Colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy Other

adverse reactions during post-marketing experience with Mycophenolate mofetil are similar to those seen in the controlled renal, cardiac and hepatic transplant studies.

10. OVERDOSE

It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression. If neutropenia develops, dosing with Mycophenolate mofetil should be interrupted or the dose reduced.

MPA cannot be removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, can remove MPA by increasing excretion of the drug.

11. Pharmacological properties and Effects

11.1 Pharmacodynamic Properties

11.1.1 Mechanism of Action

Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) and therefore inhibits the de novo pathway of guanosine nucleotide synthesis. The mechanism by which MPA inhibits the enzymatic activity of IMPDH appears to be related to the ability of MPA to structurally mimic both nicotinamide adenine dinucleotide cofactor and a catalytic water molecule. This prevents the oxidation of IMP to xanthose-5'-monophosphate which is the committed step in de novo guanosine nucleotide biosynthesis. MPA has more potent cytostatic effects on lymphocytes than on other cells because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines whereas other cell types can utilize salvage pathways.

11.1.2 Clinical Efficacy Studies

Mycophenolate mofetil has been administered in combination with the following agents in clinical trials for the prevention of renal, cardiac and hepatic rejection episodes: antithymocyte globulin, OKT3, ciclosporin and corticosteroids. Mycophenolate mofetil has also been administered in combination with ciclosporin and corticosteroids for the treatment of refractory renal rejection episodes. Prior to treatment with Mycophenolate mofetil, patients may have also received antilymphocyte antithymocyte globulin and OKT3. Mycophenolate mofetil has further been used in clinical trials together with daclizumab and tacrolimus.

Prevention of organ rejection

Children

The safety, pharmacokinetics and efficacy of Mycophenolate mofetil in combination with corticosteroids and ciclosporin for the prevention of organ rejection in paediatric renal transplant patients were assessed in an open-label, multicentre study in 100 patients (aged 3-months to 18 years).

11.2 Pharmacokinetic Properties

The pharmacokinetics of MMF have been studied in renal, cardiac and hepatic transplant patients.

In general, the pharmacokinetic profile of MPA is similar in renal and in cardiac transplant patients. In the early transplant period, hepatic transplant patients receiving a 1.5 g oral MMF dose have similar MPA levels compared to renal transplant patients receiving 1 g oral

11.2.1 Absorption

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete, presystemic metabolism to the active metabolite, MPA. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 84% relative to i.v. mycophenolate mofetil. Mycophenolate mofetil can be measured systemically during intravenous infusion, however, after oral administration it is below the limit of quantitation (0.4 µg/mL).

Immediately post-transplant (<40 days) renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and  $C_{max}$  approximately 40% lower compared to the late transplant period (3-6 months post-transplant). MPA AUC values obtained following administration of 1 g b.i.d. intravenous Mycophenolate mofetil at the recommended infusion rate to renal patients in the immediate post-transplant phase are comparable to those observed following oral dosing. In hepatic transplant patients, the administration of 1 g b.i.d. intravenous Mycophenolate mofetil followed by 1.5 g b.i.d. oral Mycophenolate mofetil resulted in MPA AUC values similar to those found in renal transplant patients administered 1 g Mycophenolate mofetil b.i.d.

Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil administered at doses of 1.5 g b.i.d. to renal transplant patients. However, MPA  $C_{max}$  was decreased by 40% in the presence of food.

Equivalence of oral dosage forms

1g/5mL of Mycophenolate mofetil constituted powder for oral suspension has been shown to be bioequivalent to four 250mg capsules.

11.2.2 Distribution

Secondary increases in plasma MPA concentrations are usually observed at approximately 6-12 hours post-dose, consistent with enterohepatic recirculation. A reduction of approximately 40% in the AUC of MPA is associated with coadministration of cholestyramine (4 g t.i.d.), consistent with interruption of enterohepatic recirculation.

At clinically relevant concentrations, MPA is 97% bound to plasma albumin.

11.2.3 Metabolism

MPA is conjugated primarily by glucuronyl transferase (isoform UGT1A9) to form the inactive phenolic glucuronide of MPA (MPAG). In vivo, MPAG is converted back to free MPA via enterohepatic recirculation. A minor acylglucuronide (AcMPAG) is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some of MMF's side effects (diarrhoea, leucopenia).

11.2.4 Elimination

Oral administration of radiolabelled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the dose recovered in the urine and 6% recovered in the faeces. Most (about 87%) of a dose is excreted in the urine as MPAG. A negligible amount of drug (<1% of dose) is excreted as MPA in the urine.

At clinically encountered concentrations, MPA and MPAG are not removed by hemodialysis. However, at high MPAG concentrations (>100 µg/mL), small amounts of MPAG are removed. By interfering with enterohepatic circulation of the drug, bile acid sequestrants, such as cholestyramine, reduce MPA AUC.

MPA's disposition depends on several transporters. Organic anion-transporting polypeptides (OATPs) and multidrug resistance-associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion. Multidrug resistance protein1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney MPA and its metabolites potentially interact with renal organic anion transporters.

11.2.5 Pharmacokinetics in Special Populations

Patients with severe renal impairment

In a single-dose study (6 subjects per group), mean plasma MPA AUCs observed after oral dosing in subjects with severe chronic renal impairment (glomerular filtration rate <25 mL/min/1.73 m<sup>2</sup>) were 28-75% higher than those observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single-dose MPAG AUC was 3- to 6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment and normal healthy subjects, consistent with the known renal elimination of MPAG.

Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied.

Patients with delayed renal graft function post-transplant

In patients with delayed renal graft function post-transplant, mean MPA AUC<sub>0-12h</sub> was comparable to that seen in post-transplant patients without delayed renal graft function. There may be a transient increase in the free-fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of mycophenolate mofetil does not appear to be necessary. Mean plasma MPAG AUC<sub>0-12h</sub> was 2- to 3-fold higher than in post-transplant patients without delayed renal graft function.

In patients with primary non-functioning graft following renal transplantation, plasma concentrations of MPAG accumulated; accumulation of MPA, if any, was much smaller.

Patients with hepatic impairment

Overall, the pharmacokinetics of MPA and MPAG were relatively unaffected by hepatic parenchymal disease in volunteers with alcoholic cirrhosis dosed with oral MMF. Effects of hepatic disease on these processes probably depend on the particular disease. Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Children (aged < 18 years)

Pharmacokinetic parameters were evaluated in 55 paediatric renal transplant patients (ranging from 1 year to 18 years of age) given 600 mg/m<sup>2</sup> mycophenolate mofetil orally twice daily (up to a maximum of 1 g twice daily). This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g twice daily in the early and late posttransplant period. MPA AUC values across age groups were similar in the early and late post transplant period.

11.3 Preclinical Safety

The hematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended doses. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The non-clinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population.

11.3.1 Impairment of Fertility

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 to 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 — 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

11.3.2 Teratogenicity

In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients.

11.3.3 Other

In experimental models, mycophenolate mofetil was not tumorigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 - 3 times the systemic exposure (AUC or  $C_{max}$ ) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 — 2 times the systemic exposure (AUC or  $C_{max}$ ) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day. Two genotoxicity assays (the mouse lymphoma/thymidine kinase assay and the mouse micronucleus aberration assay) indicated a potential of mycophenolate mofetil to cause chromosomal instability at severely cytotoxic dose levels. Other genotoxicity tests (the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay) did not demonstrate mutagenic activity.

12. Storage

Storage: Store powder below 30°C.

Store reconstituted suspension at 2°C to 8°C.

Shake closed bottle well before use.

Discard any unused portion 60 days after reconstitution.

13. Special Instructions for Use, Handling and Disposal

Because mycophenolate mofetil has demonstrated teratogenic effects avoid inhalation or direct contact with skin or mucous membranes of the powder contained in Mycophenolate mofetil oral suspension (before and after constitution). If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

Mycophenolate mofetil for oral suspension each bottle of Mycophenolate mofetil for oral suspension (Mofecon OS mini) contains

17.5 g Mycophenolate mofetil in 55 gm for oral suspension yielding 1g/5mL after constitution.

Mycophenolate mofetil for oral suspension should not be mixed with any other medication.

Preparation of suspension:

1. Tap the closed bottle several times to loosen the powder.

2. Remove CR cap and peel off aluminum seal.

3. Measure 47mL of Purified Water in the measuring cup (up to the mark). Add approximately half of the total amount of purified water to

the bottle and shake the closed bottle well for about 1 minute.

4. Add the remainder of purified water to the bottle and shake the closed bottle well for about 1 minute.

5. Remove CR cap and push adapter into the neck of bottle.

6. Close the bottle with CR cap tightly. This will assure the proper fitting of adapter into the bottle.

7. Write the date of reconstitution and date of expiration in the bottle label before use.

(The shelf-life of the reconstituted suspension is 60 days).

14. Packs

225 mL bottle with 55gm powder for Oral Suspension, 1 bottle adapter, 1 measuring cup and 2 oral dispensers.

15. Shelf life

24 months when stored at recommended storage conditions

Use the reconstituted suspension within 60 days

Keep out of reach of children

16. Manufactured in India by:

CONCORD BIOTECH LIMITED

297, 298/2P, Valtherra, Ta.: Dholka

Dist.: Ahmedabad - 382225, Gujarat

Mfg. Lic.No.: G/25/2148

VP00346-00