MYHIBBIN- mycophenolate mofetil suspension
Praxis, LLC

MYHIBBIN ™(mycophenolate mofetil oral suspension)

10 OVERDOSAGE

Possible signs and symptoms of acute overdose include hematological abnormalities such as leukopenia and neutropenia, and gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, vomiting, and dyspepsia.

The experience with overdose of mycophenolate mofetil in humans is limited. The reported effects associated with overdose fall within the known safety profile of the drug. The highest dose administered to kidney transplant patients in clinical trials has been 4 g/day. In limited experience with heart and liver transplant patients in clinical trials, the highest doses used were 4 g/day or 5 g/day. At doses of 4 g/day or 5 g/day, there appears to be a higher rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea, vomiting, and/or diarrhea), and occasional hematologic abnormalities, particularly neutropenia *[see Warnings and Precautions (5.4)]* .

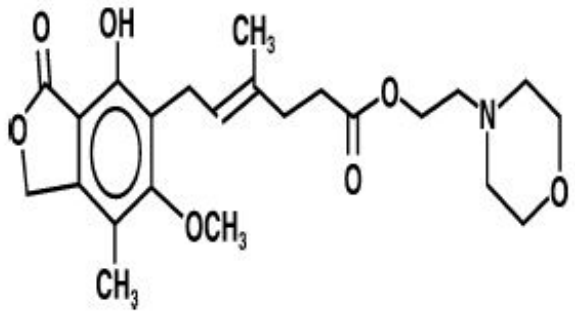
Treatment and Management

MPA and the phenolic glucuronide metabolite of MPA (MPAG) are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine *[see Clinical Pharmacology (12.3)].*

11 DESCRIPTION

MYHIBBIN (mycophenolate mofetil) is an antimetabolite immunosuppressant. It is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor.

The chemical name for mycophenolate mofetil (MMF) is 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-,2-(4-morpholinyl) ethyl ester, (E)-. It has an empirical formula of C23H31NO7, a molecular weight of 433.49, and the following structural formula:



MMF is a white or almost white, crystalline powder. It is slightly soluble in water (43

µg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6).

The drug product is an oral suspension that contains 200 mg of mycophenolate mofetil/mL. The pH of suspension is between 6 and 8.

Inactive ingredients in MYHIBBIN include dibasic sodium phosphate, glycerin, methylparaben, monobasic sodium phosphate, polysorbate 80, propylparaben, purified water, raspberry flavor, simethicone emulsion, sorbitol solution, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mycophenolate mofetil (MMF) is absorbed following oral administration and hydrolyzed to mycophenolic acid (MPA), the active metabolite. MPA is a selective uncompetitive inhibitor of the two isoforms (type I and type II) of inosine monophosphate dehydrogenase (IMPDH) leading to inhibition of the *de novo*pathway of guanosine nucleotide synthesis and blocks DNA synthesis. The mechanism of action of MPA is multifaceted and includes effects on cellular checkpoints responsible for metabolic programming of lymphocytes. MPA shifts transcriptional activities in lymphocytes from a proliferative state to catabolic processes. In vitro studies suggest that MPA modulates transcriptional activities in human CD4+ T-lymphocytes by suppressing the Akt/mTOR and STAT5 pathways that are relevant to metabolism and survival, leading to an anergic state of T-cells whereby the cells become less responsive to antigenic stimulation. Additionally, MPA enhanced the expression of negative co-stimulators such as CD70, PD-1, CTLA-4, and transcription factor FoxP3 as well as decreased the expression of positive co-stimulators CD27 and CD28.

MPA decreases proliferative responses of T- and B-lymphocytes to both mitogenic and allo-antigenic stimulation, antibody responses, as well as the production of cytokines from lymphocytes and monocytes such as GM-CSF, IFN-ɣ, IL-17, and TNF-α. Additionally, MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection.

Overall, the effect of MPA is cytostatic and reversible.

12.2 Pharmacodynamics

There is a lack of information regarding the pharmacodynamic effects of MMF.

12.3 Pharmacokinetics

Absorption

Following oral administration, MMF undergoes complete conversion to MPA, the active metabolite. In 12 healthy volunteers, the mean absolute bioavailability of oral MMF relative to intravenous MMF was 94%.

The mean (±SD) pharmacokinetic parameters estimates for MPA following the administration of MMF given as single doses to healthy volunteers, and multiple doses to kidney, heart, and liver transplant patients, are shown in **Table 6**. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-

proportional fashion in kidney transplant patients receiving multiple oral doses of MMF up to a daily dose of 3 g (1.5g twice daily) (see **Table 6**).

Table 6 Pharmacokinetic Parameters for MPA [mean (±SD)] Following Administration of MMF to Healthy Volunteers (Single Dose), and Kidney, Heart, and Liver Transplant Patients (Multiple Doses)

Healthy Volunteers	**Dose/Route**	**T_{max} (h)**	**C_{max} (mcg/mL)**	**Total AUC (mcg·h/mL)**
Single dose	1 g/oral	0.80 (±0.36) (n=129)	24.5 (±9.5) (n=129)	63.9 (±16.2) (n=117)
Kidney Transplant Patients (twice daily dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (mcg/mL)**	**Interdosing Interval AUC(0-12h) (mcg·h/mL)**
5 days	1 g	1.58 (±0.46) (n=31)	12.0 (±3.82) (n=31)	40.8 (±11.4) (n=31)
6 days	1 g/oral	1.33 (±1.05) (n=31)	10.7 (±4.83) (n=31)	32.9 (±15.0) (n=31)
Early (Less than 40 days)	1 g/oral	1.31 (±0.76) (n=25)	8.16 (±4.50) (n=25)	27.3 (±10.9) (n=25)
Early (Less than 40 days)	1.5 g/oral	1.21 (±0.81) (n=27)	13.5 (±8.18) (n=27)	38.4 (±15.4) (n=27)
Late (Greater than 3 months)	1.5 g/oral	0.90 (±0.24) (n=23)	24.1 (±12.1) (n=23)	65.3 (±35.4) (n=23)
Heart Transplant Patients (twice daily dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (mcg/mL)**	**Interdosing Interval AUC(0-12h) (mcg·h/mL)**
Early (Day before discharge)	1.5 g/oral	1.8 (±1.3) (n=11)	11.5 (±6.8) (n=11)	43.3 (±20.8) (n=9)
Late (Greater than 6 months)	1.5 g/oral	1.1 (±0.7) (n=52)	20.0 (±9.4) (n=52)	54.1 [a] (±20.4) (n=49)
Liver Transplant Patients (twice	**Dose/Route**	**T_{max}**	**C_{max}**	**Interdosing Interval**

daily dosing) Time After Transplantation	Dose/Route	(h)	(mcg/mL)	AUC(0-12h) (mcg·h/mL)
4 to 9 days	1 g	1.50 (±0.517) (n=22)	17.0 (±12.7) (n=22)	34.0 (±17.4) (n=22)
Early (5 to 8 days)	1.5 g/oral	1.15 (±0.432) (n=20)	13.1 (±6.76) (n=20)	29.2 (±11.9) (n=20)
Late (Greater than 6 months)	1.5 g/oral	1.54 (±0.51) (n=6)	19.3 (±11.7) (n=6)	49.3 (±14.8) (n=6)

[a]AUC(0-12h) values quoted are extrapolated from data from samples collected over 4 hours.

In the early post-transplant period (less than 40 days post-transplant), kidney, heart, and liver transplant patients had mean MPA AUCs approximately 20% to 41% lower and mean C_{max}approximately 32% to 44% lower compared to the late transplant period (i.e., 3 to 6 months post-transplant) (non-stationarity in MPA pharmacokinetics).

In liver transplant patients, administration of 1.5 g twice daily oral MMF resulted in mean MPA AUC estimates similar to those found in kidney transplant patients administered 1 g MMF twice daily.

Effect of Food

Food (27 g fat, 650 calories) had no effect on the extent of absorption (MPA AUC) of MMF when administered at doses of 1.5 g twice daily to kidney transplant patients. However, MPA $C_{max}$was decreased by 40% in the presence of food *[see Dosage and Administration (2.1)].*

Distribution

The mean (±SD) apparent volume of distribution of MPA in 12 healthy volunteers was approximately 3.6 (±1.5) L/kg. At clinically relevant concentrations, MPA is 97% bound to plasma albumin. The phenolic glucuronide metabolite of MPA (MPAG) is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable kidney transplant patients; however, at higher MPAG concentrations (observed in patients with kidney impairment or delayed kidney graft function), the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

*In vitro*studies to evaluate the effect of other agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 25 mg/dL with human serum albumin) and MPAG (at ≥ 460 mcg/mL with plasma proteins) increased the free fraction of MPA. MPA at concentrations as high as 100 mcg/mL had little effect on the binding of warfarin, digoxin or propranolol, but decreased the binding of theophylline from 53% to 45% and phenytoin from 90% to 87%.

Elimination

Mean (±SD) apparent half-life and plasma clearance of MPA are 17.9 (±6.5) hours and

193 (±48) mL/min following oral administration.

Metabolism

MPA is metabolized principally by glucuronyl transferase to form MPAG, which is not pharmacologically active. *In vivo*, MPAG is converted to MPA during enterohepatic recirculation. The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered in the urine following oral administration of MMF to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)- morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Due to the enterohepatic recirculation of MPAG/MPA, secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours post-dose. Bile sequestrants, such as cholestyramine, reduce MPA AUC by interfering with this enterohepatic recirculation of the drug *[see Overdosage (10)and Drug Interaction Studiesbelow*].

Excretion

Negligible amount of drug is excreted as MPA (less than 1% of dose) in the urine. Orally administered radiolabeled MMF resulted in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG. At clinically encountered concentrations, MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (> 100 mcg/mL), small amounts of MPAG are removed.

Increased plasma concentrations of MMF metabolites (MPA 50% increase and MPAG about a 3-fold to 6-fold increase) are observed in patients with renal insufficiency *[see Specific Populations].*

Specific Populations

Patients with Renal Impairment

The mean (±SD) pharmacokinetic parameters for MPA following the administration of oral MMF given as single doses to non-transplant subjects with renal impairment are presented in **Table 7**.

Plasma MPA AUC observed after oral dosing to volunteers with severe chronic renal impairment (GFR < 25 mL/min/1.73 m^2) was about 75% higher relative to that observed in healthy volunteers (GFR > 80 mL/min/1.73 m^2). In addition, the single-dose plasma MPAG AUC was 3-fold to 6-fold higher in volunteers with severe renal impairment than in volunteers with mild renal impairment or healthy volunteers, consistent with the known renal elimination of MPAG. No data are available on the safety of long-term exposure to this level of MPAG. Multiple dosing of MMF in patients with severe chronic renal impairment has not been studied.

Patients with Delayed Graft Function or Nonfunction

In patients with delayed renal graft function post-transplant, mean MPA AUC(0-12h) was comparable to that seen in post-transplant patients without delayed renal graft function. There is a potential for a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. However, dose adjustment does not appear to be necessary in patients with delayed renal graft function. Mean plasma MPAG AUC(0-12h) was 2-fold to 3-fold higher than in post-transplant patients

without delayed renal graft function *[see Dosage and Administration (2.5)].*

In eight patients with primary graft non-function following kidney transplantation, plasma concentrations of MPAG accumulated about 6-fold to 8-fold after multiple dosing for 28 days. Accumulation of MPA was about 1-fold to 2-fold.

The pharmacokinetics of MMF are not altered by hemodialysis. Hemodialysis usually does not remove MPA or MPAG. At high concentrations of MPAG (> 100 mcg/mL), hemodialysis removes only small amounts of MPAG.

Patients with Hepatic Impairment

The mean (± SD) pharmacokinetic parameters for MPA following the administration of oral MMF given as single doses to non-transplant subjects with hepatic impairment is presented in **Table 7**.

In a single-dose (1 g oral) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC as compared to healthy volunteers in other studies, thus making comparisons between volunteers with alcoholic cirrhosis and healthy volunteers difficult.

Table 7 Pharmacokinetic Parameters for MPA [mean (±SD)] Following Single Doses of MMF Capsules in Chronic Renal and Hepatic Impairment

Pharmacokinetic Parameters for Renal Impairment				
	Dose	**T_{max} (h)**	**C_{max} (mcg/mL)**	**AUC(0-96h) (mcg·h/mL)**
Healthy Volunteers GFR greater than 80 mL/min/1.73 m^2 (n=6)	1 g	0.75 (±0.27)	25.3 (±7.99)	45.0 (±22.6)
Mild Renal Impairment GFR 50 to 80 mL/min/1.73 m^2 (n=6)	1 g	0.75 (±0.27)	26.0 (±3.82)	59.9 (±12.9)
Moderate Renal Impairment GFR 25 to 49 mL/min/1.73 m^2 (n=6)	1 g	0.75 (±0.27)	19.0 (±13.2)	52.9 (±25.5)
Severe Renal Impairment GFR less than 25 mL/min/1.73 m^2 (n=7)	1 g	1.00 (±0.41)	16.3 (±10.8)	78.6 (±46.4)
Pharmacokinetic Parameters for Hepatic Impairment				

	Dose	T_{max} (h)	C_{max} (mcg/mL)	AUC(0-48h) (mcg·h/mL)
Healthy Volunteers (n=6)	1 g	0.63 (±0.14)	24.3 (±5.73)	29.0 (±5.78)
Alcoholic Cirrhosis (n=18)	1 g	0.85 (±0.58)	22.4 (±10.1)	29.8 (±10.7)

Pediatric Patients

The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging from 1 year to 18 years of age) receiving MMF oral suspension at a dose of 600 mg/m ^{2}twice daily (up to a maximum of 1 g twice daily) after allogeneic kidney transplantation. The pharmacokinetic data for MPA is provided in **Table 8**.

Table 8 Mean (±SD) Computed Pharmacokinetic Parameters for MPA by Age and Time After Allogeneic Kidney Transplantation

Age Group	(n)	Time	T_{max} (h)		Dose Adjusted [a] C_{max} (mcg/mL)		Dose Adjusted [a] AUC_{0-12} (mcg·h/mL)	
1 to less than 2 yr	(6) [d]	Early (Day 7)	3.03	(4.70)	10.3	(5.80)	22.5	(6.66)
1 to less than 6 yr	(17)		1.63	(2.85)	13.2	(7.16)	27.4	(9.54)
6 to less than 12 yr	(16)		0.940	(0.546)	13.1	(6.30)	33.2	(12.1)
12 to 18 yr	(21)		1.16	(0.830)	11.7	(10.7)	26.3	(9.14) [b]
1 to less than 2 yr	(4) [d]	Late (Month 3)	0.725	(0.276)	23.8	(13.4)	47.4	(14.7)
1 to less than 6 yr	(15)		0.989	(0.511)	22.7	(10.1)	49.7	(18.2)
6 to less than 12 yr	(14)		1.21	(0.532)	27.8	(14.3)	61.9	(19.6)
12 to 18 yr	(17)		0.978	(0.484)	17.9	(9.57)	53.6	(20.3) [c]
1 to less than 2 yr	(4) [d]	Late (Month 9)	0.604	(0.208)	25.6	(4.25)	55.8	(11.6)
1 to less than 6 yr	(12)		0.869	(0.479)	30.4	(9.16)	61.0	(10.7)
6 to less than 12 yr	(11)		1.12	(0.462)	29.2	(12.6)	66.8	(21.2)
12 to 18 yr	(14)		1.09	(0.518)	18.1	(7.29)	56.7	(14.0)

[a]adjusted to a dose of 600 mg/m ^{2}
[b]n=20
[c]n=16
[d]a subset of 1 to < 6 yr

The MMF oral suspension dose of 600 mg/m ^{2}twice daily (up to a maximum of 1 g twice daily) achieved mean MPA AUC values in pediatric patients similar to those seen in adult kidney transplant patients receiving oral doses of 1 g twice daily in the early post-transplant period. There was wide variability in the data. As observed in adults, early post-transplant MPA AUC values were approximately 45% to 53% lower than those observed in the later post-transplant period (>3 months). MPA AUC values were similar in the early and late post-transplant period across the 1 to 18-year age range.

A comparison of dose-normalized (to 600 mg/m ^{2}) MPA AUC values in 12 pediatric kidney transplant patients less than 6 years of age at 9 months post-transplant with those values in 7 pediatric liver transplant patients [median age 17 months (range: 10 – 60 months)] and at 6 months and beyond post-transplant revealed that, at the same dose, there were on average 23% lower AUC values in the pediatric liver compared to pediatric kidney patients. This is consistent with the need for higher dosing in adult liver transplant patients compared to kidney transplant patients to achieve the same exposure.

In adult transplant patients administered the same dosage of MMF, there is similar MPA exposure among kidney transplant and heart transplant patients. Based on the established similarity in MPA exposure between pediatric kidney transplant and adult kidney transplant patients at their respective approved doses, it is expected that MPA exposure at the recommended dosage will be similar in pediatric heart transplant and adult heart transplant patients.

Male and Female Patients

Data obtained from several studies were pooled to look at any gender-related differences in the pharmacokinetics of MPA (data were adjusted to 1 g oral dose). Mean (±SD) MPA AUC (0-12h) for males (n=79) was 32.0 (±14.5) and for females (n=41) was 36.5 (±18.8) mcg•h/mL while mean (±SD) MPA $C_{max}$was 9.96 (±6.19) in the males and 10.6 (±5.64) mcg/mL in the females. These differences are not of clinical significance.

Geriatric Patients

The pharmacokinetics of MMF and its metabolites have not been found to be altered in geriatric transplant patients when compared to younger transplant patients.

Drug Interaction Studies

Acyclovir

Coadministration of MMF (1 g) and acyclovir (800 mg) to 12 healthy volunteers resulted in no significant change in MPA AUC and C_{max}. However, MPAG and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively.

Antacids with Magnesium and Aluminum Hydroxides

Absorption of a single dose of MMF (2 g) was decreased when administered to 10 rheumatoid arthritis patients also taking Maalox ®TC (10 mL qid). The $C_{max}$and AUC(0-24h) for MPA were 33% and 17% lower, respectively, than when MMF was administered

alone under fasting conditions.

Proton Pump Inhibitors (PPIs)

Coadministration of PPIs (e.g., lansoprazole, pantoprazole) in single doses to healthy volunteers and multiple doses to transplant patients receiving MMF has been reported to reduce the exposure to MPA. An approximate reduction of 30 to 70% in the C_{max} and 25% to 35% in the AUC of MPA has been observed, possibly due to a decrease in MPA solubility at an increased gastric pH.

Cholestyramine

Following single-dose administration of 1.5 g MMF to 12 healthy volunteers pretreated with 4 g three times a day of cholestyramine for 4 days, MPA AUC decreased approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine.

Cyclosporine

Cyclosporine (Sandimmune ®) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.5 g twice daily of MMF in 10 stable kidney transplant patients. The mean (±SD) AUC(0-12h) and C_{max} of cyclosporine after 14 days of multiple doses of MMF were 3290 (±822) ng•h/mL and 753 (±161) ng/mL, respectively, compared to 3245 (±1088) ng•h/mL and 700 (±246) ng/mL, respectively, 1 week before administration of MMF.

Cyclosporine A interferes with MPA enterohepatic recirculation. In kidney transplant patients, mean MPA exposure (AUC(0-12h)) was approximately 30-50% greater when MMF was administered without cyclosporine compared with when MMF was coadministered with cyclosporine. This interaction is due to cyclosporine inhibition of multidrug-resistance-associated protein 2 (MRP-2) transporter in the biliary tract, thereby preventing the excretion of MPAG into the bile that would lead to enterohepatic recirculation of MPA. This information should be taken into consideration when MMF is used without cyclosporine.

Drugs Affecting Glucuronidation

Concomitant administration of drugs inhibiting glucuronidation of MPA may increase MPA exposure (e.g., increase of MPA AUC (0-∞) by 35% was observed with concomitant administration of isavuconazole).

Concomitant administration of telmisartan and MMF resulted in an approximately 30% decrease in 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 glucuronidation activity.

Ganciclovir

Following single-dose administration to 12 stable kidney transplant patients, no pharmacokinetic interaction was observed between MMF (1.5 g) and intravenous ganciclovir (5 mg/kg). Mean (±SD) ganciclovir AUC and C_{max} (n=10) were 54.3 (±19.0) mcg•h/mL and 11.5 (±1.8) mcg/mL, respectively, after coadministration of the two drugs, compared to 51.0 (±17.0) mcg•h/mL and 10.6 (±2.0) mcg/mL, respectively, after administration of intravenous ganciclovir alone. The mean (±SD) AUC and C_{max} of MPA (n=12) after coadministration were 80.9 (±21.6) mcg•h/mL and 27.8 (±13.9)

mcg/mL, respectively, compared to values of 80.3 (±16.4) µg•h/mL and 30.9 (±11.2) mcg/mL, respectively, after administration of MMF alone.

Oral Contraceptives

A study of coadministration of MMF (1 g twice daily) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) was conducted in 18 women with psoriasis over 3 consecutive menstrual cycles. Mean serum levels of LH, FSH and progesterone were not significantly affected. Mean AUC(0-24h) was similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel AUC(0-24h) significantly decreased by about 15%. There was large inter-patient variability (%CV in the range of 60% to 70%) in the data, especially for ethinylestradiol.

Sevelamer

Concomitant administration of sevelamer and MMF in adult and pediatric patients decreased the mean MPA C_{max} and AUC (0-12h) by 36% and 26% respectively.

Antimicrobials

Antimicrobials eliminating beta-glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin classes of antimicrobials) may interfere with the MPAG/MPA enterohepatic recirculation thus leading to reduced systemic MPA exposure. Information concerning antibiotics is as follows:

- Trimethoprim/Sulfamethoxazole: Following single-dose administration of MMF (1.5 g) to 12 healthy male volunteers on day 8 of a 10-day course of trimethoprim 160 mg/sulfamethoxazole 800 mg administered twice daily, no effect on the bioavailability of MPA was observed. The mean (±SD) AUC and C_{max} of MPA after concomitant administration were 75.2 (±19.8) mcg•h/mL and 34.0 (±6.6) µg/mL, respectively, compared to 79.2 (±27.9) mcg•h/mL and 34.2 (±10.7) mcg/mL, respectively, after administration of MMF alone.
- Norfloxacin and Metronidazole: Following single-dose administration of MMF (1 g) to 11 healthy volunteers on day 4 of a 5-day course of a combination of norfloxacin and metronidazole, the mean MPA AUC(0-48h) was significantly reduced by 33% compared to the administration of MMF alone ($p<0.05$). The mean (±SD) MPA AUC(0-48h) after coadministration of MMF with norfloxacin or metronidazole separately was 48.3 (±24) mcg•h/mL and 42.7 (±23) mcg•h/mL, respectively, compared with 56.2 (±24) mcg•h/mL after administration of MMF alone.
- Ciprofloxacin and Amoxicillin Plus Clavulanic Acid *:*A total of 64 MMF -treated kidney transplant recipients received either oral ciprofloxacin 500 mg twice daily or amoxicillin plus clavulanic acid 375 mg three times daily for 7 or at least 14 days, respectively. Approximately 50% reductions in median trough MPA concentrations (pre-dose) from baseline (MMF alone) were observed in 3 days following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. These reductions in trough MPA concentrations tended to diminish within 14 days of antimicrobial therapy and ceased within 3 days of discontinuation of antibiotics.
- Rifampin: In a single heart-lung transplant patient, after correction for dose, a 67% decrease in MPA exposure (AUC(0-12h)) has been observed with concomitant administration of MMF and rifampin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week oral carcinogenicity study in mice, MMF in daily doses up to 180 mg/kg was not tumorigenic. The highest dose tested was 0.2 times the recommended clinical dose (2 g/day) in renal transplant patients and 0.15 times the recommended clinical dose (3 g/day) in cardiac transplant patients when corrected for differences in body surface area (BSA). In a 104-week oral carcinogenicity study in rats, MMF in daily doses up to 15 mg/kg was not tumorigenic. The highest dose was 0.035 times the recommended clinical dose in kidney transplant patients and 0.025 times the recommended clinical dose in heart transplant patients when corrected for BSA. While these animal doses were lower than those given to patients, they were maximal in those species and were considered adequate to evaluate the potential for human risk *[see Warnings and Precautions (5.2)].*

The genotoxic potential of MMF was determined in five assays. MMF was genotoxic in the mouse lymphoma/thymidine kinase assay and the *in vivo*mouse micronucleus assay. MMF was not genotoxic in the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay.

MMF had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. This dose represents 0.05 times the recommended clinical dose in renal transplant patients and 0.03 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.01 times the recommended clinical dose in renal transplant patients and 0.005 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

14 CLINICAL STUDIES

14.1 Kidney Transplantation

Adults

The three *de novo*kidney transplantation studies compared two dose levels of oral mycophenolate mofetil (1 g twice daily and 1.5 g twice daily) with azathioprine (2 studies) or placebo (1 study) to prevent acute rejection episodes. One of the two studies with azathioprine (AZA) control arm also included anti-thymocyte globulin (ATGAM ®) induction therapy. The geographic location of the investigational sites of these studies are included in **Table 9**.

In all three *de novo*kidney transplantation studies, the primary efficacy endpoint was the proportion of patients in each treatment group who experienced treatment failure within the first 6 months after transplantation. Treatment failure was defined as biopsy-proven acute rejection on treatment or the occurrence of death, graft loss or early termination from the study for any reason without prior biopsy-proven rejection.

Mycophenolate mofetil, in combination with corticosteroids and cyclosporine, reduced (statistically significant at 0.05 level) the incidence of treatment failure within the first 6 months following transplantation (**Table 9).** Patients who prematurely discontinued treatment were followed for the occurrence of death or graft loss, and the cumulative

incidence of graft loss and patient death combined are summarized in **Table 10**. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination.

Table 9 Treatment Failure in De Novo Kidney Transplantation Studies

USA Study **(N=499 patients)**	**MYCOPHENOLATE MOFETIL 2 g/day** **(n=167 patients)**	**MYCOPHENOLATE MOFETIL 3 g/day** **(n=166 patients)**	**AZA 1 to 2 mg/kg/day (n=166 patients)**
	All 3 groups received anti-thymocyte globulin induction, cyclosporine and corticosteroids		
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection	9.6%	12.7%	6.0%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38.0%
Europe/Canada/Australia Study (N=503 patients)	**MYCOPHENOLATE MOFETIL 2 g/day (n=173 patients)**	**MYCOPHENOLATE MOFETIL 3 g/day (n=164 patients)**	**AZA 100 to 150 mg/day (n=166 patients)**
	No induction treatment administered; all 3 groups received cyclosporine and corticosteroids.		
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%
Europe Study **(N=491 patients)**	**MYCOPHENOLATE MOFETIL 2 g/day** **(n=165 patients)**	**MYCOPHENOLATE MOFETIL 3 g/day** **(n=160 patients)**	**Placebo** **(n=166 patients)**
	No induction treatment administered; all 3 groups received cyclosporine and corticosteroids.		
All treatment failures	30.3%	38.8%	56.0%
Early termination without prior acute rejection	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17.0%	13.8%	46.4%

*Does not include death and graft loss as reason for early termination.

No advantage of mycophenolate mofetil at 12 months with respect to graft loss or patient death (combined) was established (**Table 10**). Numerically, patients receiving mycophenolate mofetil 2 g/day and 3 g/day experienced a better outcome than controls

in all three studies; patients receiving mycophenolate mofetil 2 g/day experienced a better outcome than mycophenolate mofetil 3 g/day in two of the three studies. Patients in all treatment groups who terminated treatment early were found to have a poor outcome with respect to graft loss or patient death at 1 year.

Table 10 De Novo Kidney Transplantation Studies Cumulative Incidence of Combined Graft Loss or Patient Death at 12 Months

Study	MYCOPHENOLATE MOFETIL 2 g/day	MYCOPHENOLATE MOFETIL 3 g/day	Control (AZA or Placebo)
USA	8.5%	11.5%	12.2%
Europe/Canada/Australia	11.7%	11.0%	13.6%
Europe	8.5%	10.0%	11.5%

Pediatrics- De Novo Kidney transplantation PK Study with Long Term Follow-Up One open-label, safety and pharmacokinetic study of mycophenolate mofetil oral suspension 600 mg/m ^{2}twice daily (up to 1 g twice daily) in combination with cyclosporine and corticosteroids was performed at centers in the United States (9), Europe (5) and Australia (1) in 100 pediatric patients (3 months to 18 years of age) for the prevention of renal allograft rejection. Mycophenolate mofetil was well tolerated in pediatric patients [see Adverse Reactions (6.1)]. The rate of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6 years to <12 years, 12 years to 18 years). The overall biopsy-proven rejection rate at 6 months was comparable to adults. The combined incidence of graft loss (5%) and patient death (2%) at 12 months post-transplant was similar to that observed in adult kidney transplant patients.

14.2 Heart Transplantation

A double-blind, randomized, comparative, parallel-group, multicenter study in primary *de novo*heart transplant recipients was performed at centers in the United States (20), in Canada (1), in Europe (5) and in Australia (2). The total number of patients enrolled (ITT population) was 650; 72 never received study drug and 578 received study drug (Safety Population). Patients received mycophenolate mofetil 1.5 g twice daily (n=289) or AZA 1.5 to 3 mg/kg/day (n=289), in combination with cyclosporine (Sandimmune ®or Neoral ®) and corticosteroids as maintenance immunosuppressive therapy. The two primary efficacy endpoints were: (1) the proportion of patients who, after transplantation, had at least one endomyocardial biopsy-proven rejection with hemodynamic compromise, or were re-transplanted or died, within the first 6 months, and (2) the proportion of patients who died or were re-transplanted during the first 12 months following transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection for up to 6 months and for the occurrence of death for 1 year.

The analyses of the endpoints showed:

- Rejection: No difference was established between mycophenolate mofetil and AZA with respect to biopsy-proven rejection with hemodynamic compromise.
- Survival: Mycophenolate mofetil was shown to be at least as effective as AZA in preventing death or re-transplantation at 1 year (see **Table 11**).

Table 11 De Novo Heart Transplantation Study Rejection at 6 Months/Death or Re-transplantation at 1 Year

	All Patients (ITT)		Treated Patients	
	AZA N = 323	**MYCOPHENOLATE MOFETIL N = 327**	**AZA N = 289**	**MYCOPHENOLATE MOFETIL N = 289**
Biopsy-proven rejection with hemodynamic compromise at 6 months [a]	121 (38%)	120 (37%)	100 (35%)	92 (32%)
Death or re-transplantation at 1 year	49 (15.2%)	42 (12.8%)	33 (11.4%)	18 (6.2%)

[a]Hemodynamic compromise occurred if any of the following criteria were met: pulmonary capillary wedge pressure ≥20 mm or a 25% increase; cardiac index <2.0 L/min/m ^{2}or a 25% decrease; ejection fraction ≤30%; pulmonary artery oxygen saturation ≤60% or a 25% decrease; presence of new S $_3$gallop; fractional shortening was ≤20% or a 25% decrease; inotropic support required to manage the clinical condition.

14.3 Liver Transplantation

A double-blind, randomized, comparative, parallel-group, multicenter study in primary hepatic transplant recipients was performed at centers in the United States (16), in Canada (2), in Europe (4) and in Australia (1). The total number of patients enrolled was 565. Per protocol, patients received mycophenolate mofetil 1.5 g twice daily orally or AZA 1 to 2 mg/kg/day orally, in combination with cyclosporine (Neoral ®) and corticosteroids as maintenance immunosuppressive therapy. The actual median oral dose of AZA on study was 1.5 mg/kg/day (range of 0.3 to 3.8 mg/kg/day) initially and 1.26 mg/kg/day (range of 0.3 to 3.8 mg/kg/day) at 12 months. The two primary endpoints were: (1) the proportion of patients who experienced, in the first 6 months post-transplantation, one or more episodes of biopsy-proven and treated rejection or death or re-transplantation, and (2) the proportion of patients who experienced graft loss (death or re-transplantation) during the first 12 months post-transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection and for the occurrence of graft loss (death or re-transplantation) for 1 year.

In combination with corticosteroids and cyclosporine, mycophenolate mofetil demonstrated a lower rate of acute rejection at 6 months and a similar rate of death or re-transplantation at 1 year compared to AZA (**Table 12**).

Table 12 De Novo Liver Transplantation Study Rejection at 6 Months/Death or Retransplantation at 1 Year

	AZA N = 287	**MYCOPHENOLATE MOFETIL N = 278**

Biopsy-proven, treated rejection at 6 months (includes death or re-transplantation)	137 (47.7%)	107 (38.5%)
Death or re-transplantation at 1 year	42 (14.6%)	41 (14.7%)

15 REFERENCES

1. “OSHA Hazardous Drugs.” OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*

16 HOW SUPPLIED/STORAGE AND HANDLING

Handling and Disposal

Mycophenolate mofetil has demonstrated teratogenic effects in humans *[see Warnings and Precautions (5.1)and Use in Specific Populations (8.1)]* . Wearing disposable gloves is recommended when wiping the outer surface of the bottle and or bottle cap. Avoid direct contact of MYHIBBIN with skin or mucous membranes *[see Dosage and Administration (2.6)].* Follow applicable special handling and disposal procedures [1]. Do not use after 60 days of first opening the bottle.

MYHIBBIN is supplied as a white to off-white oral suspension of mycophenolate mofetil 200 mg/mL and it is supplied with a child resistant cap:

- 175 mL of suspension in 225 mL bottle..... NDC 24338-018-01

Storage and Stability

- Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].
- Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

17.1 Embryofetal Toxicity

Pregnancy loss and malformation

- Inform females of reproductive potential and pregnant women that use of MYHIBBIN during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations. Advise that they must use an acceptable form of contraception *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3)].*
- Encourage pregnant women to enroll in the Pregnancy Exposure Registry. This registry monitors pregnancy outcomes in women exposed to mycophenolate *[see Use in Specific Populations (8.1)].*

Contraception

- Discuss pregnancy testing, pregnancy prevention and planning with females of reproductive potential *[see Use in Specific Populations (8.3)].*
- Females of reproductive potential must use an acceptable form of birth control during the entire MYHIBBIN therapy and for 6 weeks after stopping MYHIBBIN, unless the patient chooses abstinence .MYHIBBIN may reduce effectiveness of oral contraceptives. Use of additional barrier contraceptive methods is recommended *[see Use in Specific Populations (8.3)].*
- For patients who are considering pregnancy, discuss appropriate alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of MYHIBBIN should be discussed with the patient.
- Advise sexually active male patients and/or their partners to use effective contraception during the treatment of the male patient and for at least 90 days after cessation of treatment. This recommendation is based on findings of animal studies *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)].*

17.2 Development of Lymphoma and Other Malignancies

- Inform patients that they are at increased risk of developing lymphomas and other malignancies, particularly of the skin, due to immunosuppression [*see Warnings and Precautions (5.2)*].
- Advise patients to limit exposure to sunlight and ultraviolet (UV) light by wearing protective clothing and use of broad-spectrum sunscreen with high protection factor.

17.3 Increased Risk of Serious Infections

Inform patients that they are at increased risk of developing a variety of infections due to immunosuppression. Instruct them to contact their physician if they develop any of the signs and symptoms of infection explained in the Medication Guide [*see Warnings and Precautions (5.3)*].

17.4 Blood Dyscrasias

Inform patients that they are at increased risk for developing blood adverse effects such as anemia or low white blood cells. Advise patients to immediately contact their healthcare provider if they experience any evidence of infection, unexpected bruising, or bleeding, or any other manifestation of bone marrow suppression [*see Warnings and Precautions (5.4)*].

17.5 Gastrointestinal Tract Complications

Inform patients that MYHIBBIN can cause gastrointestinal tract complications including bleeding, intestinal perforations, and gastric or duodenal ulcers. Advise the patient to contact their healthcare provider if they have symptoms of gastrointestinal bleeding, or sudden onset or persistent abdominal pain *[see Warnings and Precautions (5.5)]* .

17.6 Acute Inflammatory Syndrome

Inform patients that acute inflammatory reactions have been reported in some patients who received mycophenolate mofetil. Some reactions were severe, requiring hospitalization. Advise patients to contact their physician if they develop fever, joint stiffness, joint pain or muscle pains *[see Warnings and Precautions (5.7)]* .

17.7 Immunizations

Inform patients that MYHIBBIN can interfere with the usual response to immunizations. Before seeking vaccines on their own, advise patients to discuss first with their physician *[see Warnings and Precautions (5.8)*].

17.8 Administration Instructions

- Advise patients to avoid contact of the skin or mucous membranes with MYHIBBIN. If such contact occurs, they must wash the area of contact thoroughly with soap and water. In case of ocular contact, rinse eyes with plain water.
- Advise patients to take a missed dose as soon as they remember, except if it is closer than 2 hours to the next scheduled dose; in this case they should continue to take MYHIBBIN at the usual times.

17.9 Blood Donation

Advise patients not to donate blood during therapy and for at least 6 weeks following discontinuation of MYHIBBIN [*see Warnings and Precautions (5.9)*].

17.10 Semen Donation

Advise males of childbearing potential not to donate semen during therapy and for 90 days following discontinuation of MYHIBBIN *[see Warnings and Precautions (5.10)]* .

17.11 Potential to Impair Driving and Use of Machinery

Advise patients that MYHIBBIN can affect the ability to drive or operate machines. Patients should avoid driving or operating machines if they experience somnolence, confusion, dizziness, tremor or hypotension during treatment with MYHIBBIN [*see Warnings and Precautions (5.12)*].

Distributed by:

Azurity Pharmaceuticals, Inc.
Woburn, MA 01801 USA

MYH-PI-01 Rev. 05/2024

MEDICATION GUIDE **MYHIBBIN ™(my hib in)** **(mycophenolate mofetil oral suspension)**
Read the Medication Guide that comes with MYHIBBIN before you start taking it and each time you refill your prescription. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.
What is the most important information I should know about MYHIBBIN? **MYHIBBIN can cause serious side effects, including:** **Increased risk of loss of a pregnancy (miscarriage) and higher risk of birth defects.** Females who take MYHIBBIN during pregnancy have a higher risk of miscarriage during the first 3 months (first trimester), and a higher risk that their baby will be born with birth defects.

- **If you are a female who can become pregnant**, your healthcare provider must talk with you about acceptable birth control methods (contraceptive counseling) to use while taking MYHIBBIN. You should have 1 pregnancy test immediately before starting MYHIBBIN and another pregnancy test 8 to 10 days later. Pregnancy tests should be repeated during routine follow-up visits with your healthcare provider. Talk to your healthcare provider about the results of all of your pregnancy tests.
  You must use acceptable birth control during your entire MYHIBBIN treatment and for 6 weeks after stopping MYHIBBIN, unless at any time you choose to avoid sexual intercourse (abstinence) with a man completely. MYHIBBIN decreases blood levels of the hormones in birth control pills that you take by mouth. Birth control pills may not work as well while you take MYHIBBIN, and you could become pregnant. If you take birth control pills while using MYHIBBIN you must also use another form of birth control. Talk to your healthcare provider about other birth control methods that you can use while taking MYHIBBIN.
- **If you are a sexually active male whose female partner can become pregnant while you are taking MYHIBBIN**, use effective contraception during treatment and for at least 90 days after stopping MYHIBBIN.
- **If you plan to become pregnant**, talk with your healthcare provider. Your healthcare provider will decide if other medicines to prevent rejection may be right for you.
- **If you become pregnant while taking MYHIBBIN**, **do not stop taking MYHIBBIN. Call your healthcare provider right away.** You and your healthcare provider may decide that other medicines to prevent rejection may be right for you. You and your healthcare provider should report your pregnancy to the Mycophenolate Pregnancy Registry either:
  - By phone at **1-800-617-8191 or**
  - By visiting the REMS website at: **www.mycophenolateREMS.com**

  The purpose of this registry is to gather information about the health of you and your baby.

Increased risk of getting certain cancers. People who take MYHIBBIN have a higher risk of getting lymphoma, and other cancers, especially skin cancer. Tell your healthcare provider if you have:

- unexplained fever, prolonged tiredness, weight loss or lymph node swelling
- a brown or black skin lesion with uneven borders, or one part of the lesion does not look like the other
- a change in the size and color of a mole
- a new skin lesion or bump
- any other changes to your health

Increased risk of getting serious infections. MYHIBBIN weakens the body's immune system and affects your ability to fight infections. Serious infections can happen with MYHIBBIN and can lead to hospitalizations and death. These serious infections can include:

- **Viral infections.** Certain viruses can live in your body and cause active infections when your immune system is weak. Viral infections that can happen with MYHIBBIN include:
  - Shingles, other herpes infections, and cytomegalovirus (CMV). CMV can cause serious tissue and blood infections.
  - BK virus. BK virus can affect how your kidney works and cause your transplanted

kidney to fail.
  - Hepatitis B and C viruses. Hepatitis viruses can affect how your liver works. Talk to your healthcare provider about how hepatitis viruses may affect you.
  - COVID-19
- **A brain infection called Progressive Multifocal Leukoencephalopathy (PML).**In some patients, MYHIBBIN may cause an infection of the brain that may cause death. You are at risk for this brain infection because you have a weakened immune system. Call your healthcare provider right away if you have any of the following symptoms:
  - weakness on one side of the body
  - you do not care about things you usually care about (apathy)
  - you are confused or have problems thinking
  - you cannot control your muscles
- **Fungal infections.**Yeasts and other types of fungal infections can happen with MYHIBBIN and can cause serious tissue and blood infections (See **" What are the possible side effects of MYHIBBIN?"**).

Call your healthcare provider right away if you have any of the following signs and symptoms of infection:

- temperature of 100.5°F or greater
- cold symptoms, such as a runny nose or sore throat
- flu symptoms, such as an upset stomach, stomach pain, vomiting or diarrhea
- earache or headache
- pain during urination
- white patches in the mouth or throat
- unexpected bruising or bleeding
- cuts, scrapes or incisions that are red, warm and oozing pus

See **" What are the possible side effects of MYHIBBIN?"** for information about other serious side effects.

What is MYHIBBIN?

- MYHIBBIN is a prescription medicine to prevent rejection (antirejection medicine) in people who have received a kidney, heart or liver transplant. Rejection is when the body's immune system perceives the new organ as a "foreign" threat and attacks it.
- MYHIBBIN is used with other medicines containing cyclosporine and corticosteroids.

Do not take MYHIBBIN if you:

- **are allergic to mycophenolate mofetil or any of the ingredients in MYHIBBIN.**See the end of this Medication Guide for a complete list of ingredients in MYHIBBIN.

Before taking MYHIBBIN tell your healthcare provider about all of your medical conditions, including if you:

- have any digestive problems, such as ulcers.
- have Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, or another rare inherited deficiency hypoxanthine-guanine phosphoribosyl-transferase (HGPRT). You should not take MYHIBBIN if you have one of these disorders.
- plan to receive any vaccines. People taking MYHIBBIN should not receive live

vaccines. Some vaccines may not work as well during treatment with MYHIBBIN.
- are pregnant or plan to become pregnant. See **" What is the most important information I should know about MYHIBBIN?"**
- are breastfeeding or plan to breastfeed. It is not known if MYHIBBIN passes into breast milk. You and your healthcare provider will decide if you will take MYHIBBIN or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Some medicines may affect the way MYHIBBIN works, and MYHIBBIN may affect how some medicines work.
Especially tell your healthcare provider if you take:
- birth control pills (oral contraceptives). See **" What is the most important information I should know about MYHIBBIN?"**
- sevelamer (Renagel, Renvela). These products should be taken at least 2 hours after taking MYHIBBIN.
- acyclovir (Zovirax), valacyclovir (Valtrex), ganciclovir (CYTOVENE-IV, Vitrasert), valganciclovir (VALCYTE).
- rifampin (Rifater, Rifamate, Rimactane, Rifadin).
- antacids that contain magnesium and aluminum (MYHIBBIN and the antacid should not be taken at the same time).
- proton pump inhibitors (PPIs) (Prevacid, Protonix).
- sulfamethoxazole/trimethoprim (BACTRIM, BACTRIM DS).
- norfloxacin (Noroxin ®) and metronidazole (Flagyl, Flagyl ER, Flagyl IV, Metro IV, Helidac, Pylera).
- ciprofloxacin (Cipro, Cipro XR, Ciloxan, Proquin XR) and amoxicillin plus clavulanic acid (Augmentin, Augmentin XR).
- azathioprine (Azasan, Imuran).
- cholestyramine (Questran Light, Questran, Locholest Light, Locholest, Prevalite).

Know the medicines you take. Keep a list of all your medicines. Show them to your healthcare provider or pharmacist when you get a new medicine. Do not take any new medicine without talking with your doctor.

How should I take MYHIBBIN?
- Take MYHIBBIN exactly as prescribed.
- Do not stop taking MYHIBBIN or change the dose unless your healthcare provider tells you to.
- If you miss a dose of MYHIBBIN, or you are not sure when you took your last dose, take your prescribed dose of MYHIBBIN as soon as you remember. If your next dose is less than 2 hours away, skip the missed dose and take your next dose at your normal scheduled time. Do not take 2 doses at the same time. Call your healthcare provider if you are not sure what to do.
- Take MYHIBBIN on an empty stomach, unless your healthcare provider tells you otherwise.
- **If you are not able to swallow mycophenolate mofetil tablets or capsules, your doctor may prescribe MYHIBBIN. This is a liquid form of mycophenolate mofetil.**
- Do not mix MYHIBBIN with any other medicine. MYHIBBIN should not be mixed with any type of liquids before taking the dose.

- **Do not**let MYHIBBIN come in contact with your skin or mucous membranes.
  - If you accidentally get the oral suspension on the skin, wash the area well with soap and water.
  - If you accidentally get the oral suspension in your eyes or other mucous membranes, rinse with plain water.
- If you take too much MYHIBBIN, call your healthcare provider or the poison control center right away.

What should I avoid while taking MYHIBBIN?

- Avoid becoming pregnant. (See **" What is the most important information I should know about MYHIBBIN?"**)
- Limit the amount of time you spend in sunlight. Avoid using tanning beds or sunlamps. People who take MYHIBBIN have a higher risk of getting skin cancer (See **" What is the most important information I should know about MYHIBBIN?"**). Wear protective clothing when you are in the sun and use a broad-spectrum sunscreen with a high protection factor. This is especially important if your skin is very fair or if you have a family history of skin cancer.
- You should not donate blood while taking MYHIBBIN and for at least 6 weeks after stopping MYHIBBIN.
- You should not donate sperm while taking MYHIBBIN and for 90 days after stopping MYHIBBIN.
- MYHIBBIN may influence your ability to drive and use machines (See " **What are the possible side effects of MYHIBBIN?**". If you experience drowsiness, confusion, dizziness, tremor, or low blood pressure during treatment with MYHIBBIN, you should be cautious about driving or using heavy machines.

What are the possible side effects of MYHIBBIN?
MYHIBBIN may cause serious side effects, including:

- See **" What is the most important information I should know about MYHIBBIN?"**
- **Low blood cell counts.** People taking high doses of MYHIBBIN each day may have a decrease in blood counts, including:
  - **white blood cells, especially neutrophils.**Neutrophils fight against bacterial infections. You have a higher chance of getting an infection when your white blood cell count is low. This is most common from 1 month to 6 months after your transplant.
  - **red blood cells.**Red blood cells carry oxygen to your body tissues. You have a higher chance of getting severe anemia when your red blood cell count is low.
  - **platelets**. Platelets help with blood clotting.

  Your healthcare provider will do blood tests before you start taking MYHIBBIN and during treatment with MYHIBBIN to check your blood cell counts. Tell your healthcare provider right away if you have any signs of infection (See **" What is the most important information I should know about MYHIBBIN?"**), including any unexpected bruising or bleeding. Also, tell your doctor if you have unusual tiredness, lack of energy, dizziness or fainting.
- **Stomach problems.**Stomach problems including intestinal bleeding, a tear in your intestinal wall (perforation) or stomach ulcers can happen in people who take MYHIBBIN. Bleeding can be severe and you may have to be hospitalized for treatment. Call your doctor right away if you have sudden or severe stomach-area

pain or stomach-area pain that does not go away, or if you have diarrhea.
- **Inflammatory reactions.**Some people taking MYHIBBIN may have an inflammatory reaction with fever, joint stiffness, joint pain, and muscle pain. Some of these reactions may require hospitalization. This reaction could happen within weeks to months after your treatment with MYHIBBIN starts or if your dose is increased. Call your healthcare provider right away if you experience these symptoms.

The most common side effects of MYHIBBIN include:

- diarrhea
- blood problems including low white and red blood cell counts
- infections
- blood pressure problems
- fast heart beat
- swelling of the lower legs, ankles and feet
- changes in laboratory blood levels, including high levels of blood sugar (hyperglycemia)
- stomach problems including diarrhea, constipation, nausea and vomiting
- rash
- nervous system problems such as headache, dizziness and tremor

Side effects that can happen more often in children than in adults taking MYHIBBIN include:

- stomach area pain
- fever
- infection
- pain
- blood infection (sepsis)
- diarrhea
- vomiting
- sore throat
- colds (respiratory tract infections)
- high blood pressure
- low white blood cell count
- low red blood cell count

These are not all of the possible side effects of MYHIBBIN. Tell your doctor about any side effect that bothers you or that does not go away.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **You may also report side effects to Azurity Pharmaceuticals, Inc. at 1-800-461-7449.**

How should I store MYHIBBIN?

- Store MYHIBBIN at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Do not freeze.
- Wear gloves when wiping the MYHIBBIN bottle and bottle cap.

Keep MYHIBBIN and all medicines out of the reach of children.

General information about the safe and effective use of MYHIBBIN.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use MYHIBBIN for a condition for which it was not prescribed. Do not give MYHIBBIN to other people, even if they have the same symptoms that you have. It may harm them.
This Medication Guide summarizes the most important information about MYHIBBIN. If you would like more information, talk with your doctor. You can ask your pharmacists or healthcare provider information about MYHIBBIN that is written for health professionals.

What are the ingredients in MYHIBBIN?
Active ingredient: Mycophenolate Mofetil
Inactive ingredients:
MYHIBBIN: dibasic sodium phosphate, glycerin, methylparaben, monobasic sodium

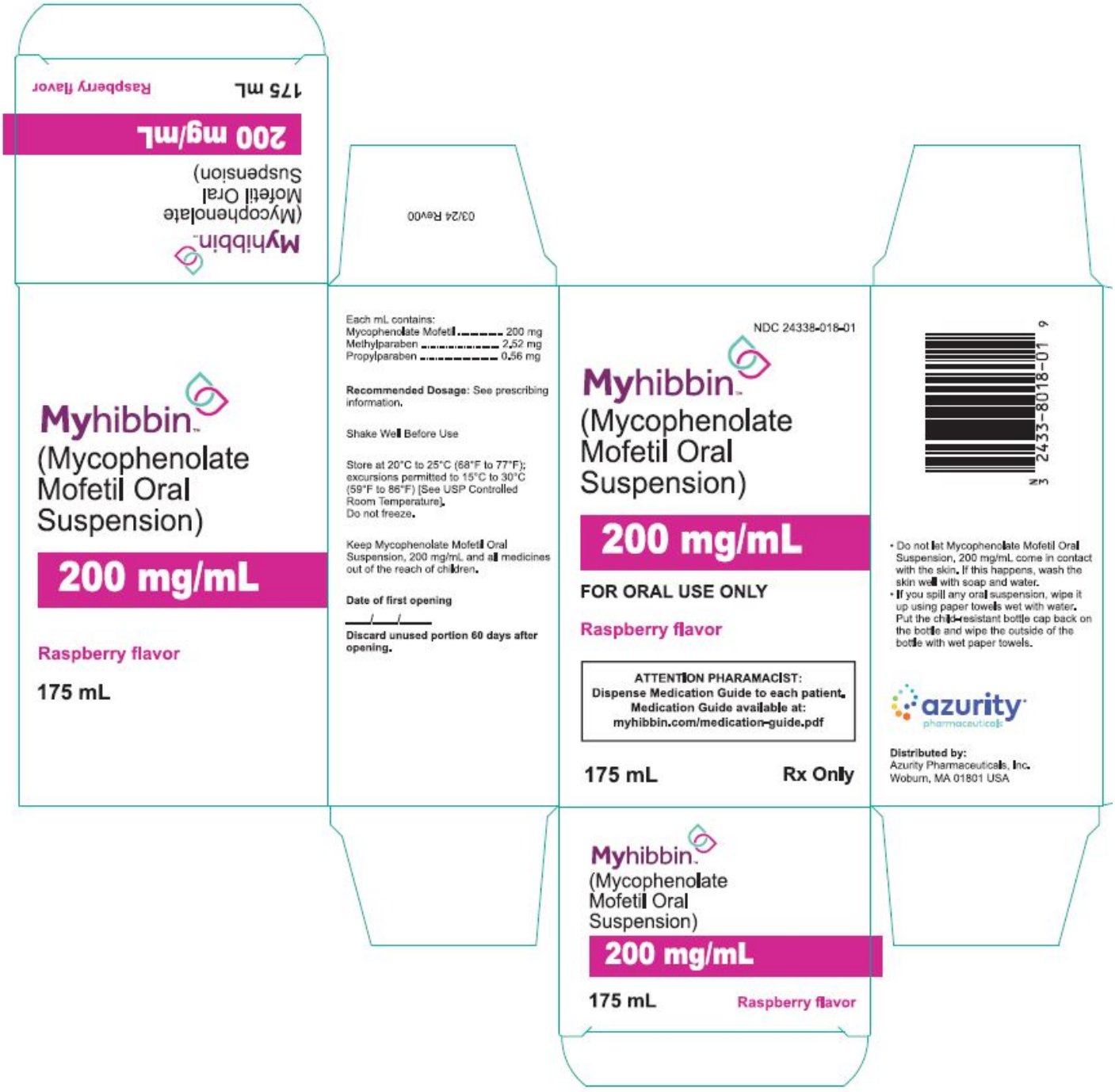
phosphate, polysorbate 80, propylparaben, purified water, raspberry flavor, simethicone emulsion, sorbitol solution, and xanthan gum.

Distributed by:
Azurity Pharmaceuticals, Inc.
Woburn, MA 01801 USA

This Medication Guide has been approved by the U.S. Food and Drug Administration
Approved: 05/2024
MYH-MG-01

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

MYHIBBIN Oral Suspension, 200 mg/mL - NDC 24338-018-01 - 175 mL Carton label



MYHIBBIN Oral Suspension, 200 mg/mL - NDC 24338-018-01 - 175 mL Bottle label

MYHIBBIN

mycophenolate mofetil suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-403
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
MYCOPHENOLATE MOFETIL (UNII: 9242ECW6R0) (MYCOPHENOLIC ACID - UNII:HU9DX48N0T)	MYCOPHENOLATE MOFETIL	200 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
GLYCERIN (UNII: PDC6A3C0OX)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	
SORBITOL SOLUTION (UNII: 8KW3E207O2)	
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM (UNII: 3980JIH2SW)	
SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM (UNII: GR686LBA74)	
WATER (UNII: 059QF0KO0R)	
XANTHAN GUM (UNII: TTV12P4NEE)	

Product Characteristics			
Color	white (White to off-white)	**Score**	
Shape		**Size**	
Flavor	RASPBERRY	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-403-01	1 in 1 CARTON	06/10/2024	
1		175 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA216482	06/10/2024	

Labeler - Praxis, LLC (016329513)

Establishment

Name	Address	ID/FEI	Business Operations
Praxis, LLC		016329513	manufacture(59368-403) , label(59368-403) , pack(59368-403)

Revised: 1/2023 Praxis, LLC