

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-110

APPROVED DRAFT LABELING

1 Rapamune®
2 (sirolimus)
3 Oral Solution and Tablets
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6 *****

- 7 * WARNING: *
- 8 * Increased susceptibility to infection and the possible *
- 9 * development of lymphoma may result from immunosuppression. *
- 10 * Only physicians experienced in immunosuppressive therapy and *
- 11 * management of renal transplant patients should use Rapamune®. *
- 12 * Patients receiving the drug should be managed in facilities *
- 13 * equipped and staffed with adequate laboratory and supportive *
- 14 * medical resources. The physician responsible for maintenance *
- 15 * therapy should have complete information requisite for the *
- 16 * follow-up of the patient. *

17 *****

18
19 **DESCRIPTION**

20 Rapamune® (sirolimus) is an immunosuppressive agent. Sirolimus is a macrocyclic lactone
21 produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus (also known as
22 rapamycin) is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34*aS*)-
23 9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34*a*-hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-
24 [(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-
25 6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-
26 1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is C₅₁H₇₉NO₁₃ and its molecular
27 weight is 914.2. The structural formula of sirolimus is shown below.
28

Title: ISIS/Draw:11943
Creator: Windows PS
CreationDate:

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31 Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in
32 benzyl alcohol, chloroform, acetone, and acetonitrile.
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35 Rapamune® is available for administration as an oral solution containing 1 mg/mL sirolimus
36 and as a white, triangular-shaped tablet containing 1 mg sirolimus.

37
38 The inactive ingredients in Rapamune® Oral Solution are Phosal 50 PG®
39 (phosphatidylcholine, propylene glycol, monodiglycerides, ethanol, soy fatty acids, and
40 ascorbyl palmitate) and polysorbate 80. Rapamune Oral Solution contains 1.5% - 2.5%
41 ethanol.

42
43 The inactive ingredients in Rapamune® Tablets include sucrose, lactose, polyethylene glycol
44 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium
45 dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000,
46 glyceryl monooleate, carnauba wax, and other ingredients.

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49 **CLINICAL PHARMACOLOGY**

50 **Mechanism of Action**

51 Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to
52 antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that
53 is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody
54 production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-
55 12), to generate an immunosuppressive complex. The sirolimus:FKBP-12 complex has no
56 effect on calcineurin activity. This complex binds to and inhibits the activation of the
57 mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition
58 suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G₁ to the
59 S phase of the cell cycle.

60
61 Studies in experimental models show that sirolimus prolongs allograft (kidney, heart, skin,
62 islet, small bowel, pancreatico-duodenal, and bone marrow) survival in mice, rats, pigs,
63 and/or primates. Sirolimus reverses acute rejection of heart and kidney allografts in rats and
64 prolonged the graft survival in presensitized rats. In some studies, the immunosuppressive
65 effect of sirolimus lasted up to 6 months after discontinuation of therapy. This tolerization
66 effect is alloantigen specific.

67
68 In rodent models of autoimmune disease, sirolimus suppresses immune-mediated events
69 associated with systemic lupus erythematosus, collagen-induced arthritis, autoimmune type I
70 diabetes, autoimmune myocarditis, experimental allergic encephalomyelitis, graft-versus-host
71 disease, and autoimmune uveoretinitis.

72

73 **Pharmacokinetics**

74 Sirolimus pharmacokinetic activity has been determined following oral administration in
75 healthy subjects, pediatric dialysis patients, hepatically-impaired patients, and renal
76 transplant patients.

77

78 **Absorption**

79 Following administration of Rapamune® Oral Solution, sirolimus is rapidly absorbed, with a
80 mean time-to-peak concentration (t_{max}) of approximately 1 hour after a single dose in healthy
81 subjects and approximately 2 hours after multiple oral doses in renal transplant recipients.
82 The systemic availability of sirolimus was estimated to be approximately 14% after the
83 administration of Rapamune Oral Solution. The mean bioavailability of sirolimus after
84 administration of the tablet is about 27% higher relative to the oral solution. Sirolimus oral
85 tablets are not bioequivalent to the oral solution; however, clinical equivalence has been
86 demonstrated at the 2-mg dose level. (See Clinical Studies and Dosage and Administration).
87 Sirolimus concentrations, following the administration of Rapamune Oral Solution to stable
88 renal transplant patients, are dose proportional between 3 and 12 mg/m².

89
90 **Food effects:** In 22 healthy volunteers receiving Rapamune Oral Solution, a high-fat meal
91 (1.88 kcal, 54.7% fat) altered the bioavailability characteristics of sirolimus. Compared to
92 fasting, a 34% decrease in the peak blood sirolimus concentration (C_{max}), a 3.5-fold increase
93 in the time-to-peak concentration (t_{max}), and a 35% increase in total exposure (AUC) was
94 observed. After administration of Rapamune Tablets and a high-fat meal in 24 healthy
95 volunteers, C_{max} , t_{max} , and AUC showed increases of 65%, 32%, and 23%, respectively. To
96 minimize variability, both Rapamune Oral Solution and Tablets should be taken consistently
97 with or without food (See DOSAGE AND ADMINISTRATION).

98 99 **Distribution**

100 The mean (\pm SD) blood-to-plasma ratio of sirolimus was 36 (\pm 17.9) in stable renal allograft
101 recipients, indicating that sirolimus is extensively partitioned into formed blood elements.
102 The mean volume of distribution (V_{ss}/F) of sirolimus is 12 \pm 7.52 L/kg. Sirolimus is
103 extensively bound (approximately 92%) to human plasma proteins. In man, the binding of
104 sirolimus was shown mainly to be associated with serum albumin (97%), α_1 -acid
105 glycoprotein, and lipoproteins.

106 107 **Metabolism**

108 Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein.
109 Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven (7)
110 major metabolites, including hydroxy, demethyl, and hydroxydemethyl, are identifiable in
111 whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine
112 samples. Glucuronide and sulfate conjugates are not present in any of the biologic matrices.
113 Sirolimus is the major component in human whole blood and contributes to more than 90%
114 of the immunosuppressive activity.

115 116 **Excretion**

117 After a single dose of [¹⁴C]sirolimus in healthy volunteers, the majority (91%) of
118 radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in
119 urine.

120

121 **Pharmacokinetics in renal transplant patients**

122 Rapamune Oral Solution: Pharmacokinetic parameters for sirolimus oral solution given
 123 daily in combination with cyclosporine and corticosteroids in renal transplant patients are
 124 summarized below based on data collected at months 1, 3, and 6 after transplantation. There
 125 were no significant differences in any of these parameters with respect to treatment group or
 126 month.

127

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN RENAL
 TRANSPLANT PATIENTS (MULTIPLE DOSE ORAL SOLUTION)^{a,b}

n	Dose	C _{max,ss} ^c (ng/mL)	t _{max,ss} (h)	AUC _{τ,ss} ^c (ng•h/mL)	CL/F/WT ^d (mL/h/kg)
19	2 mg	12.2 ± 6.2	3.01 ± 2.40	158 ± 70	182 ± 72
23	5 mg	37.4 ± 21	1.84 ± 1.30	396 ± 193	221 ± 143

a: Sirolimus administered four hours after cyclosporine oral solution (MODIFIED) (e.g., Neoral[®] Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral[®] Soft Gelatin Capsules).

b: As measured by the Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).

c: These parameters were dose normalized prior to the statistical comparison.

d: CL/F/WT = oral dose clearance.

128

129 Whole blood sirolimus trough concentrations, as measured by immunoassay, (mean ± SD)
 130 for the 2 mg/day and 5 mg/day dose groups were 8.59 ± 4.01 ng/mL (n = 226) and 17.3 ±
 131 7.4 ng/mL (n = 219), respectively. Whole blood trough sirolimus concentrations, as
 132 measured by LC/MS/MS, were significantly correlated (r² = 0.96) with AUC_{τ,ss}. Upon
 133 repeated twice daily administration without an initial loading dose in a multiple-dose study,
 134 the average trough concentration of sirolimus increases approximately 2 to 3-fold over the
 135 initial 6 days of therapy at which time steady state is reached. A loading dose of 3 times the
 136 maintenance dose will provide near steady-state concentrations within 1 day in most
 137 patients. The mean ± SD terminal elimination half life (t_{1/2}) of sirolimus after multiple
 138 dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.

139

140 Rapamune Tablets: Pharmacokinetic parameters for sirolimus tablets administered daily in
 141 combination with cyclosporine and corticosteroids in renal transplant patients are
 142 summarized below based on data collected at months 1 and 3 after transplantation.

143

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN RENAL
TRANSPLANT PATIENTS (MULTIPLE DOSE TABLETS)^{a,b}

n	Dose (2 mg/day)	C _{max,ss} ^c (ng/mL)	t _{max,ss} (h)	AUC _{τ,ss} ^c (ng•h/mL)	CL/F/WT ^d (mL/h/kg)
17	Oral solution	14.4 ± 5.3	2.12 ± 0.84	194 ± 78	173 ± 50
13	Tablets	15.0 ± 4.9	3.46 ± 2.40	230 ± 67	139 ± 63

a: Sirolimus administered four hours after cyclosporine oral solution (MODIFIED, (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules).

b: As measured by the Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).

c: These parameters were dose normalized prior to the statistical comparison.

d: CL/F/WT = weight-normalized oral dose clearance.

144

145 Whole blood sirolimus trough concentrations (mean ± SD), as measured by immunoassay,
146 for the 2 mg oral solution and 2 mg tablets over 6 months, were 8.94 ± 4.36 ng/mL (n = 172)
147 and 9.48 ± 3.85 ng/mL (n = 179), respectively. Whole blood trough sirolimus
148 concentrations, as measured by LC/MS/MS, were significantly correlated (r² = 0.85) with
149 AUC_{τ,ss}. Mean whole blood sirolimus trough concentrations in patients receiving either
150 Rapamune Oral Solution or Rapamune Tablets with a loading dose of three times the
151 maintenance dose achieved steady-state concentrations within 24 hours after the start of dose
152 administration.

153

154 **Special Populations**

155 **Hepatic impairment:** Sirolimus (15 mg) was administered as a single oral dose to 18
156 subjects with normal hepatic function and to 18 patients with Child-Pugh classification A or
157 B hepatic impairment, in which hepatic impairment was primary and not related to an
158 underlying systemic disease. Shown below are the mean ± SD pharmacokinetic parameters
159 following the administration of sirolimus oral solution.

160

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN 18
HEALTHY SUBJECTS AND 18 PATIENTS WITH HEPATIC IMPAIRMENT
(15 MG SINGLE DOSE – ORAL SOLUTION)

Population	C _{max,ss} ^a (ng/mL)	t _{max} (h)	AUC _{0-∞} (ng•h/mL)	CL/F/WT (mL/h/kg)
Healthy subjects	78.2 ± 18.3	0.82 ± 0.17	970 ± 272	215 ± 76
Hepatic impairment	77.9 ± 23.1	0.84 ± 0.17	1567 ± 616	144 ± 62

a: As measured by LC/MS/MS.

161

162 Compared with the values in the normal hepatic group, the hepatic impairment group had
163 higher mean values for sirolimus AUC (61%) and t_{1/2} (43%) and had lower mean values for
164 sirolimus CL/F/WT (33%). The mean t_{1/2} increased from 79 ± 12 hours in subjects with
165 normal hepatic function to 113 ± 41 hours in patients with impaired hepatic function. The
166 rate of absorption of sirolimus was not altered by hepatic disease, as evidenced by C_{max} and
167 t_{max} values. However, hepatic diseases with varying etiologies may show different effects
168 and the pharmacokinetics of sirolimus in patients with severe hepatic dysfunction is

169 unknown. Dosage adjustment is recommended for patients with mild to moderate hepatic
170 impairment (see **DOSAGE AND ADMINISTRATION**).

171
172 **Renal impairment:** The effect of renal impairment on the pharmacokinetics of sirolimus is
173 not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites.

174
175 **Pediatric:** Limited pharmacokinetic data are available in pediatric patients. The table below
176 summarizes pharmacokinetic data obtained in pediatric dialysis patients with chronically
177 impaired renal function.

178

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PEDIATRIC PATIENTS
WITH STABLE CHRONIC RENAL FAILURE MAINTAINED ON HEMODIALYSIS OR
PERITONEAL DIALYSIS (1, 3, 9, 15 MG/M² SINGLE DOSE)

Age Group (y)	n	t _{max} (h)	t _{1/2} (h)	CL/F/WT (mL/h/kg)
5-11	9	1.1 ± 0.5	71 ± 40	580 ± 450
12-18	11	0.79 ± 0.17	55 ± 18	450 ± 232

179

180 **Geriatric:** Clinical studies of Rapamune did not include a sufficient number of patients > 65
181 years of age to determine whether they will respond differently than younger patients. After
182 the administration of Rapamune Oral Solution, sirolimus trough concentration data in 35
183 renal transplant patients > 65 years of age were similar to those in the adult population
184 (n=822) 18 to 65 years of age. Similar results were obtained after the administration of
185 Rapamune Tablets to 12 renal transplant patients > 65 years of age compared with adults
186 (n=167) 18 to 65 years of age.

187

188 **Gender:** After the administration of Rapamune Oral Solution, sirolimus oral dose clearance
189 in males was 12% lower than that in females; male subjects had a significantly longer t_{1/2}
190 than did female subjects (72.3 hours versus 61.3 hours). A similar trend in the effect of
191 gender on sirolimus oral dose clearance and t_{1/2} was observed after the administration of
192 Rapamune Tablets. Dose adjustments based on gender are not recommended.

193

194 **Race:** In large phase III trials using Rapamune Oral Solution and cyclosporine oral solution
195 (MODIFIED) (eg, Neoral[®] Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g.,
196 Neoral[®] Soft Gelatin Capsules), there were no significant differences in mean trough
197 sirolimus concentrations over time between black (n = 139) and non-black (n = 724) patients
198 during the first 6 months after transplantation at sirolimus doses of 2 mg/day and 5 mg/day.
199 Similarly, after administration of Rapamune Tablets (2 mg/day) in a phase III trial, mean
200 sirolimus trough concentrations over 6 months were not significantly different among black
201 (n = 51) and non-black (n = 128) patients.

202

203 **CLINICAL STUDIES**

204 **Rapamune[®] Oral Solution:** The safety and efficacy of Rapamune[®] Oral Solution for the
205 prevention of organ rejection following renal transplantation were assessed in two
206 randomized, double-blind, multicenter, controlled trials. These studies compared two dose
207 levels of Rapamune Oral Solution (2 mg and 5 mg, once daily) with azathioprine (Study 1)

208 or placebo (Study 2) when administered in combination with cyclosporine and
 209 corticosteroids. Study 1 was conducted in the United States at 38 sites. Seven hundred
 210 nineteen (719) patients were enrolled in this trial and randomized following transplantation;
 211 284 were randomized to receive Rapamune Oral Solution 2 mg/day, 274 were randomized to
 212 receive Rapamune Oral Solution 5 mg/day, and 161 to receive azathioprine 2-3 mg/kg/day.
 213 Study 2 was conducted in Australia, Canada, Europe, and the United States, at a total of 34
 214 sites. Five hundred seventy-six (576) patients were enrolled in this trial and randomized
 215 before transplantation; 227 were randomized to receive Rapamune Oral Solution 2 mg/day,
 216 219 were randomized to receive Rapamune Oral Solution 5 mg/day, and 130 to receive
 217 placebo. In both studies, the use of antilymphocyte antibody induction therapy was
 218 prohibited. In both studies, the primary efficacy endpoint was the rate of efficacy failure in
 219 the first 6 months after transplantation. Efficacy failure was defined as the first occurrence
 220 of an acute rejection episode (confirmed by biopsy), graft loss, or death.

221
 222 The tables below summarize the results of the primary efficacy analyses from these trials.
 223 Rapamune Oral Solution, at doses of 2 mg/day and 5 mg/day, significantly reduced the
 224 incidence of efficacy failure (statistically significant at the <0.025 level; nominal
 225 significance level adjusted for multiple [2] dose comparisons) at 6 months following
 226 transplantation compared to both azathioprine and placebo.
 227
 228

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 6 MONTHS: STUDY 1^a

Parameter	Rapamune [®] Oral Solution 2 mg/day (n = 284)	Rapamune [®] Oral Solution 5 mg/day (n = 274)	Azathioprine 2-3 mg/kg/day (n = 161)
Efficacy failure at 6 months	18.7	16.8	32.3
<i>Components of efficacy failure</i>			
Biopsy-proven acute rejection	16.5	11.3	29.2
Graft loss	1.1	2.9	2.5
Death	0.7	1.8	0
Lost to follow-up	0.4	0.7	0.6

a: Patients received cyclosporine and corticosteroids.

229

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 6 MONTHS: STUDY 2^a

Parameter	Rapamune [®] Oral Solution 2 mg/day (n = 227)	Rapamune [®] Oral Solution 5 mg/day (n = 219)	Placebo (n = 130)
Efficacy failure at 6 months	30.0	25.6	47.7
<i>Components of efficacy failure</i>			
Biopsy-proven acute rejection	24.7	19.2	41.5
Graft loss	3.1	3.7	3.9
Death	2.2	2.7	2.3
Lost to follow-up	0	0	0

a: Patients received cyclosporine and corticosteroids.

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Patient and graft survival at 1 year were co-primary endpoints. The table below shows graft and patient survival at 1 year in Study 1 and Study 2. The graft and patient survival rates at 1 year were similar in the Rapamune- and comparator-treated patients.

1-YEAR GRAFT AND PATIENT SURVIVAL (%)^a

Parameter	Rapamune [®] Oral Solution 2 mg/day	Rapamune [®] Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
	Study 1	(n = 284)	(n = 274)	(n = 161)
Graft survival	94.7	92.7	93.8	
Patient survival	97.2	96.0	98.1	
Study 2	(n = 227)	(n = 219)		(n = 130)
Graft survival	89.9	90.9		87.7
Patient survival	96.5	95.0		94.6

a: Patients received cyclosporine and corticosteroids.

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The reduction in the incidence of first biopsy-confirmed acute rejection episodes in Rapamune-treated patients compared to the control groups included a reduction in all grades of rejection.

PERCENTAGE OF EFFICACY FAILURE BY RACE AT 6 MONTHS

Parameter	Rapamune [®] Oral Solution 2 mg/day	Rapamune [®] Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
	Study 1			
Black (n=166)	34.9 (n=63)	18.0 (n=61)	33.3 (n=42)	
Nonblack (n=553)	14.0 (n=221)	16.4 (n=213)	31.9 (n=119)	
Study 2				
Black (n=66)	30.8 (n=26)	33.7 (n=27)		38.5 (n=13)
Non-black (n=510)	29.9 (n=201)	24.5 (n=192)		48.7 (n=117)

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In Study 1, which was prospectively stratified by race within center, efficacy failure was similar for Rapamune Oral Solution 2 mg/day and lower for Rapamune Oral Solution 5 mg/day compared to azathioprine in black patients. In Study 2, which was not prospectively stratified by race, efficacy failure was similar for both Rapamune Oral Solution doses compared to placebo in black patients. The decision to use the higher dose of Rapamune Oral Solution in black patients must be weighed against the increased risk of dose-dependent adverse events that were observed with the Rapamune Oral Solution 5 mg dose (see ADVERSE REACTIONS).

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (CC/MIN) BY NANKIVELL EQUATION AT 12 MONTHS POST TRANSPLANT

Parameter	Rapamune [®]	Rapamune [®]	Azathioprine	Placebo
	Oral Solution 2 mg/day	Oral Solution 5 mg/day	2-3 mg/kg/day	
Study 1	(n=233)	(n=226)	(n=127)	
Mean (SE)	57.4 (1.28)	55.1 (1.28)	65.9 (1.69)	
Study 2	(n=190)	(n=175)		(n=101)
Mean (SE)	54.9 (1.26)	52.9 (1.46)		61.7 (1.81)

251

252 Mean glomerular filtration rates (GFR) at one year post transplant were calculated by using
253 the Nankivell equation for all subjects in Studies 1 and 2 who had serum creatinine
254 measured at 12 months. In Studies 1 and 2 mean GFR, at 12 months, were lower in patients
255 treated with cyclosporine and Rapamune Oral Solution compared to those treated with
256 cyclosporine and the respective azathioprine or placebo control.

257

258 Within each treatment group in Studies 1 and 2, mean GFR at one year post transplant was
259 lower in patients who experienced at least 1 episode of biopsy-proven acute rejection,
260 compared to those who did not.

261

262 Renal function should be monitored and appropriate adjustment of the immunosuppression
263 regimen should be considered in patients with elevated serum creatinine levels (see
264 PRECAUTIONS).

265

266 **Rapamune[®] Tablets:** The safety and efficacy of Rapamune Oral Solution and Rapamune
267 Tablets for the prevention of organ rejection following renal transplantation were compared
268 in a randomized multicenter controlled trial (Study 3). This study compared a single dose
269 level (2 mg, once daily) of Rapamune Oral Solution and Rapamune Tablets when
270 administered in combination with cyclosporine and corticosteroids. The study was
271 conducted at 30 centers in Australia, Canada, and the United States. Four hundred seventy-
272 seven (477) patients were enrolled in this study and randomized before transplantation; 238
273 patients were randomized to receive Rapamune Oral Solution 2 mg/day and 239 patients
274 were randomized to receive Rapamune Tablets 2 mg/day. In this study, the use of
275 antilymphocyte antibody induction therapy was prohibited. The primary efficacy endpoint
276 was the rate of efficacy failure in the first 3 months after transplantation. Efficacy failure
277 was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft
278 loss, or death.

279

280 The table below summarizes the result of the primary efficacy analysis at 3 months from this
281 trial. The overall rate of efficacy failure in the tablet treatment group was equivalent to the
282 rate in the oral solution treatment group.

283

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 3 MONTHS: STUDY 3^a

	Rapamune [®] Oral Solution (n = 238)	Rapamune [®] Tablets (n = 239)
Efficacy Failure at 3 months	23.5	24.7
<i>Components of efficacy failure</i>		
Biopsy-proven acute rejection	18.9	17.6
Graft loss	3.4	6.3
Death	1.3	0.8

a: Patients received cyclosporine and corticosteroids.

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285

286 The table below summarizes the results of the primary efficacy analysis at 6 months after
287 transplantation.

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 6 MONTHS: STUDY 3^a

	Rapamune [®] Oral Solution (n = 238)	Rapamune [®] Tablets (n = 239)
Efficacy Failure at 6 months	26.1	27.2
<i>Components of efficacy failure</i>		
Biopsy-proven acute rejection	21.0	19.2
Graft loss	3.4	6.3
Death	1.7	1.7

a: Patients received cyclosporine and corticosteroids.

288

289 Graft and patient survival at 12 months were co-primary efficacy endpoints. There was no
290 significant difference between the oral solution and tablet formulations for both graft and
291 patient survival. Graft survival was 92.0% and 88.7% for the oral solution and tablet
292 treatment groups, respectively. The patient survival rates in the oral solution and tablet
293 treatment groups were 95.8% and 96.2%, respectively.

294

295 The mean GFR at 12 months, calculated by the Nankivell equation, were not significantly
296 different for the oral solution group and for the tablet group.

297

298 The table below summarizes the mean GFR at one-year post-transplantation for all subjects
299 in Study 3 who had serum creatinine measured at 12 months.

300

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (CC/MIN) BY
NANKIVELL EQUATION AT 12 MONTHS POST TRANSPLANT: STUDY 3

	Rapamune [®] Oral Solution	Rapamune [®] Tablets
Mean (SE)	58.3 (1.64) n=166	58.5 (1.44) n=162

301

302 **INDICATIONS AND USAGE**

303 Rapamune is indicated for the prophylaxis of organ rejection in patients receiving renal
304 transplants. It is recommended that Rapamune be used in a regimen with cyclosporine and
305 corticosteroids.

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308 **CONTRAINDICATIONS**

309 Rapamune is contraindicated in patients with a hypersensitivity to sirolimus or its
310 derivatives or any component of the drug product.

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313 **WARNINGS**

314 Increased susceptibility to infection and the possible development of lymphoma and other
315 malignancies, particularly of the skin, may result from immunosuppression (see ADVERSE
316 REACTIONS). Oversuppression of the immune system can also increase susceptibility to
317 infection including opportunistic infections, fatal infections, and sepsis. Only physicians
318 experienced in immunosuppressive therapy and management of organ transplant patients
319 should use Rapamune. Patients receiving the drug should be managed in facilities equipped
320 and staffed with adequate laboratory and supportive medical resources. The physician
321 responsible for maintenance therapy should have complete information requisite for the
322 follow-up of the patient.

323
324 As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light
325 should be limited by wearing protective clothing and using a sunscreen with a high
326 protection factor.

327
328 Increased serum cholesterol and triglycerides, that may require treatment, occurred more
329 frequently in patients treated with Rapamune compared to azathioprine or placebo controls.
330 (see PRECAUTIONS).

331
332 In phase III studies, mean serum creatinine was increased and mean glomerular filtration rate
333 was decreased in patients treated with Rapamune and cyclosporine compared to those treated
334 with cyclosporine and placebo or azathioprine controls (see CLINICAL STUDIES). Renal
335 function should be monitored during the administration of maintenance immunosuppression
336 regimens including Rapamune in combination with cyclosporine, and appropriate
337 adjustment of the immunosuppression regimen should be considered in patients with
338 elevated serum creatinine levels. Caution should be exercised when using agents which are
339 known to impair renal function (see PRECAUTIONS).

340
341
342 In clinical trials, Rapamune has been administered concurrently with corticosteroids and
343 with the following formulations of cyclosporine:

344
345 Sandimmune[®] Injection (cyclosporine injection)

346 Sandimmune[®] Oral Solution (cyclosporine oral solution)

347 Sandimmune® Soft Gelatin Capsules (cyclosporine capsules)
348 Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED])
349 Neoral® Oral Solution (cyclosporine oral solution [MODIFIED])

350

351 The efficacy and safety of the use of Rapamune in combination with other
352 immunosuppressive agents has not been determined.

353

354

355 **PRECAUTIONS**

356 **General**

357 Rapamune is intended for oral administration only.

358

359 Lymphocele, a known surgical complication of renal transplantation, occurred significantly
360 more often in a dose-related fashion in Rapamune-treated patients. Appropriate post-
361 operative measures should be considered to minimize this complication.

362

363 **Lipids**

364 The use of Rapamune® in renal transplant patients was associated with increased serum
365 cholesterol and triglycerides that may require treatment.

366

367 In phase III clinical trials, in *de novo* renal transplant recipients who began the study with
368 normal, fasting, total serum cholesterol (fasting serum cholesterol < 200 mg/dL), there was
369 an increased incidence of hypercholesterolemia (fasting serum cholesterol > 240 mg/dL) in
370 patients receiving both Rapamune® 2 mg and Rapamune® 5 mg compared to azathioprine
371 and placebo controls.

372

373 In phase III clinical trials, in *de novo* renal transplant recipients who began the study with
374 normal, fasting, total serum triglycerides (fasting serum triglycerides < 200 mg/dL), there
375 was an increased incidence of hypertriglyceridemia (fasting serum triglycerides > 500
376 mg/dL) in patients receiving Rapamune® 2 mg and Rapamune® 5 mg compared to
377 azathioprine and placebo controls.

378

379 Treatment of new-onset hypercholesterolemia with lipid-lowering agents was required in 42
380 -52% of patients enrolled in the Rapamune arms of the study compared to 16% of patients in
381 the placebo arm and 22% of patients in the azathioprine arm.

382

383 Renal transplant patients have a higher prevalence of clinically significant hyperlipidemia.
384 Accordingly, the risk/benefit should be carefully considered in patients with established
385 hyperlipidemia before initiating an immunosuppressive regimen including Rapamune.

386

387 Any patient who is administered Rapamune should be monitored for hyperlipidemia using
388 laboratory tests and if hyperlipidemia is detected, subsequent interventions such as diet,
389 exercise, and lipid-lowering agents, as outlined by the National Cholesterol Education
390 Program guidelines, should be initiated.

391

392 In the limited number of patients studied, the concomitant administration of Rapamune and
393 HMG-CoA reductase inhibitors and/or fibrates appeared to be well tolerated. Nevertheless,
394 all patients administered Rapamune with cyclosporine, in conjunction with an HMG-CoA
395 reductase inhibitor, should be monitored for the development of rhabdomyolysis.

396

397 **Renal Function**

398 Patients treated with cyclosporine and Rapamune were noted to have higher serum creatinine
399 levels and lower glomerular filtration rates compared to patients treated with cyclosporine
400 and placebo or azathioprine controls. Renal function should be monitored during the
401 administration of maintenance immunosuppression regimens including Rapamune in
402 combination with cyclosporine, and appropriate adjustment of the immunosuppression
403 regimen should be considered in patients with elevated serum creatinine levels. Caution
404 should be exercised when using agents (eg, aminoglycosides, and amphotericin B) that are
405 known to have a deleterious effect on renal function.

406

407 **Antimicrobial Prophylaxis**

408 Cases of *Pneumocystis carinii* pneumonia have been reported in patients not receiving
409 antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for *Pneumocystis carinii*
410 pneumonia should be administered for 1 year following transplantation.

411

412 Cytomegalovirus (CMV) prophylaxis is recommended for 3 months after transplantation,
413 particularly for patients at increased risk for CMV disease.

414

415 **Information for Patients**

416 Patients should be given complete dosage instructions (see Patient Instructions). Women of
417 childbearing potential should be informed of the potential risks during pregnancy and that
418 they should use effective contraception prior to initiation of Rapamune therapy, during
419 Rapamune therapy and for 12 weeks after Rapamune therapy has been stopped (see
420 PRECAUTIONS: Pregnancy).

421

422 Patients should be told that exposure to sunlight and UV light should be limited by wearing
423 protective clothing and using a sunscreen with a high protection factor because of the
424 increased risk for skin cancer (see WARNINGS).

425

426 **Laboratory Tests**

427 It is prudent to monitor blood sirolimus levels in patients likely to have altered drug
428 metabolism, in patients ≥ 13 years who weigh less than 40 kg, in patients with hepatic
429 impairment, and during concurrent administration of potent CYP3A4 inducers and inhibitors
430 (see PRECAUTIONS: Drug Interactions).

431

432 **Drug Interactions**

433 Sirolimus is known to be a substrate for both cytochrome CYP3A4 and P-glycoprotein. The
434 pharmacokinetic interaction between sirolimus and concomitantly administered drugs is

435 discussed below. Drug interaction studies have not been conducted with drugs other than
436 those described below.

437

438 **Cyclosporine capsules MODIFIED:**

439 **Rapamune Oral Solution:** In a single dose drug-drug interaction study, 24 healthy volunteers
440 were administered 10 mg sirolimus either simultaneously or 4 hours after a 300 mg dose of
441 Neoral[®] Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous
442 administration, the mean C_{max} and AUC of sirolimus were increased by 116% and 230%,
443 respectively, relative to administration of sirolimus alone. However, when given 4 hours after
444 Neoral[®] Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) administration, sirolimus
445 C_{max} and AUC were increased by 37% and 80%, respectively, compared to administration of
446 sirolimus alone.

447

448 Mean cyclosporine C_{max} and AUC were not significantly affected when sirolimus was given
449 simultaneously or when administered 4 hours after Neoral[®] Soft Gelatin Capsules
450 (cyclosporine capsules [MODIFIED]). However, after multiple-dose administration of
451 sirolimus given 4 hours after Neoral[®] in renal post-transplant patients over 6 months,
452 cyclosporine oral-dose clearance was reduced, and lower doses of Neoral[®] Soft Gelatin
453 Capsules (cyclosporine capsules [MODIFIED]) were needed to maintain target cyclosporine
454 concentration.

455

456 **Rapamune Tablets:** In a single-dose drug-drug interaction study, 24 healthy volunteers were
457 administered 10 mg sirolimus (Rapamune Tablets) either simultaneously or 4 hours after a
458 300 mg dose of Neoral[®] Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For
459 simultaneous administration, mean C_{max} and AUC were increased by 512% and 148%,
460 respectively, relative to administration of sirolimus alone. However, when given 4 hours after
461 cyclosporine administration, sirolimus C_{max} and AUC were both increased by only 33%
462 compared with administration of sirolimus alone.

463

464 **Because of the effect of cyclosporine capsules (MODIFIED), it is recommended that**
465 **sirolimus should be taken 4 hours after administration of cyclosporine oral solution**
466 **(MODIFIED) and/or cyclosporine capsules (MODIFIED), (see DOSAGE AND**
467 **ADMINISTRATION).**

468

469 **Cyclosporine oral solution:** In a multiple-dose study in 150 psoriasis patients, sirolimus
470 0.5, 1.5, and 3 mg/m²/day was administered simultaneously with Sandimmune[®] Oral
471 Solution (cyclosporine Oral Solution) 1.25 mg/kg/day. The increase in average sirolimus
472 trough concentrations ranged between 67% to 86% relative to when sirolimus was
473 administered without cyclosporine. The intersubject variability (%CV) for sirolimus trough
474 concentrations ranged from 39.7% to 68.7%. There was no significant effect of multiple-
475 dose sirolimus on cyclosporine trough concentrations following Sandimmune[®] Oral Solution
476 (cyclosporine oral solution) administration. However, the %CV was higher (range 85.9% -
477 165%) than those from previous studies.

478

479 Sandimmune® Oral Solution (cyclosporine oral solution) is not bioequivalent to Neoral® Oral
480 Solution (cyclosporine oral solution MODIFIED), and should not be used interchangeably.
481 Although there is no published data comparing Sandimmune® Oral Solution (cyclosporine
482 oral solution) to SangCya® Oral Solution (cyclosporine oral solution [MODIFIED]), they
483 should not be used interchangeably. Likewise, Sandimmune® Soft Gelatin Capsules
484 (cyclosporine capsules) are not bioequivalent to Neoral® Soft Gelatin Capsules (cyclosporine
485 capsules [MODIFIED]) and should not be used interchangeably.

486

487 **Diltiazem:** The simultaneous oral administration of 10 mg of sirolimus oral solution and
488 120 mg of diltiazem to 18 healthy volunteers significantly affected the bioavailability of
489 sirolimus. Sirolimus C_{max} , t_{max} , and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively.
490 Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites
491 desacetyldiltiazem and desmethyl diltiazem. If diltiazem is administered, sirolimus should
492 be monitored and a dose adjustment may be necessary.

493

494 **Ketoconazole:** Multiple-dose ketoconazole administration significantly affected the rate and
495 extent of absorption and sirolimus exposure after administration of Rapamune Oral Solution,
496 as reflected by increases in sirolimus C_{max} , t_{max} , and AUC of 4.3-fold, 38%, and 10.9-fold,
497 respectively. However, the terminal $t_{1/2}$ of sirolimus was not changed. Single-dose sirolimus
498 did not affect steady-state 12-hour plasma ketoconazole concentrations. It is recommended
499 that sirolimus oral solution and oral tablets should not be administered with ketoconazole.

500

501 **Rifampin:** Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg
502 daily for 14 days, followed by a single 20 mg-dose of sirolimus, greatly increased sirolimus
503 oral-dose clearance by 5.5-fold (range = 2.8 to 10), which represents mean decreases in AUC
504 and C_{max} of about 82% and 71%, respectively. In patients where rifampin is indicated,
505 alternative therapeutic agents with less enzyme induction potential should be considered.

506

507 *Drugs which may be coadministered without dose adjustment*

508 Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of
509 drugs listed below. A synopsis of the type of study performed for each drug is provided.
510 Sirolimus and these drugs may be coadministered without dose adjustments.

511

512 **Acyclovir:** Acyclovir, 200 mg, was administered once daily for 3 days followed by a single
513 10-mg dose of sirolimus oral solution on day 3 in 20 adult healthy volunteers.

514

515 **Digoxin:** Digoxin, 0.25 mg, was administered daily for 8 days and a single 10-mg dose of
516 sirolimus oral solution was given on day 8 to 24 healthy volunteers.

517

518 **Glyburide:** A single 5-mg dose of glyburide and a single 10-mg dose of sirolimus oral
519 solution were administered to 24 healthy volunteers. Sirolimus did not affect the
520 hypoglycemic action of glyburide.

521

522 **Nifedipine:** A single 60-mg dose of nifedipine and a single 10-mg dose of sirolimus oral
523 solution were administered to 24 healthy volunteers.

524

525 **Norgestrel/ethinyl estradiol (Lo/Ovral[®]):** Sirolimus oral solution, 2 mg, was given daily
526 for 7 days to 21 healthy female volunteers on norgestrel/ethinyl estradiol.

527

528 **Prednisolone:** Pharmacokinetic information was obtained from 42 stable renal transplant
529 patients receiving daily doses of prednisone (5-20 mg/day) and either single or multiple
530 doses of sirolimus oral solution (0.5-5 mg/m² q 12h).

531

532 **Sulfamethoxazole/trimethoprim (Bactrim[®]):** A single oral dose of sulfamethoxazole
533 (400 mg)/trimethoprim, (80 mg) was given to 15 renal transplant patients receiving daily
534 oral doses of sirolimus (8 to 25 mg/m²).

535

536 **Other drug interactions**

537 Sirolimus is extensively metabolized by the CYP3A4 isoenzyme in the gut wall and liver.
538 Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus
539 may be influenced by drugs that affect this isoenzyme. Inhibitors of CYP3A4 may decrease
540 the metabolism of sirolimus and increase sirolimus levels, while inducers of CYP3A4 may
541 increase the metabolism of sirolimus and decrease sirolimus levels.

542

543 Drugs that may increase sirolimus blood concentrations include:

544 Calcium channel blockers: nifedipine, verapamil.

545 Antifungal agents: clotrimazole, fluconazole, itraconazole.

546 Macrolide antibiotics: clarithromycin, erythromycin, troleandomycin.

547 Gastrointestinal prokinetic agents: cisapride, metoclopramide.

548 Other drugs: bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g.,
549 ritonavir, indinavir).

550

551 Drugs that may decrease sirolimus levels include:

552 Anticonvulsants: carbamazepine, phenobarbital, phenytoin.

553 Antibiotics: rifabutin, rifapentine.

554

555 This list is not all inclusive.

556

557 Care should be exercised when drugs that are metabolized by CYP3A4 are administered
558 concomitantly with Rapamune. Grapefruit juice reduces CYP3A4-mediated metabolism of
559 Rapamune and must not be used for dilution (see DOSAGE AND ADMINISTRATION).

560

561 *Vaccination*

562 Immunosuppressants may affect response to vaccination. Therefore, during treatment with
563 Rapamune, vaccination may be less effective. The use of live vaccines should be avoided;
564 live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG,
565 yellow fever, varicella, and TY21a typhoid.

566

567 **Drug-Laboratory Test Interactions**

568 There are no studies on the interactions of sirolimus in commonly employed clinical
569 laboratory tests.

570

571 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

572 Sirolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, the Chinese
573 hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward
574 mutation assay, or the *in vivo* mouse micronucleus assay.

575

576 Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse
577 study at dosages of 0, 12.5, 25 and 50/6 (dosage lowered from 50 to 6 mg/kg/day at week 31
578 due to infection secondary to immunosuppression) there was a statistically significant
579 increase in malignant lymphoma at all dose levels (approximately 16 to 135 times the
580 clinical doses adjusted for body surface area) compared to controls. In a second mouse study
581 at dosages of 0, 1, 3 and 6 mg/kg (approximately 3 to 16 times the clinical dose adjusted for
582 body surface area), hepatocellular adenoma and carcinoma (males), were considered
583 Rapamune related. In the 104-week rat study at dosages of 0, 0.05, 0.1, and 0.2 mg/kg/day
584 (approximately 0.4 to 1 times the clinical dose adjusted for body surface area), there was a
585 statistically significant increased incidence of testicular adenoma in the 0.2 mg/kg/day
586 group.

587

588 There was no effect on fertility in female rats following the administration of sirolimus at
589 dosages up to 0.5 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body
590 surface area). In male rats, there was no significant difference in fertility rate compared to
591 controls at a dosage of 2 mg/kg (approximately 4 to 11 times the clinical doses adjusted for
592 body surface area). Reductions in testicular weights and/or histological lesions (e.g., tubular
593 atrophy and tubular giant cells) were observed in rats following dosages of 0.65 mg/kg
594 (approximately 1 to 3 times the clinical doses adjusted for body surface area) and above and
595 in a monkey study at 0.1 mg/kg (approximately 0.4 to 1 times the clinical doses adjusted for
596 body surface area) and above. Sperm counts were reduced in male rats following the
597 administration of sirolimus for 13 weeks at a dosage of 6 mg/kg (approximately 12 to 32
598 times the clinical doses adjusted for body surface area), but showed improvement by 3
599 months after dosing was stopped.

600

601 **Pregnancy**

602 *Pregnancy Category C:* Sirolimus was embryo/feto toxic in rats at dosages of 0.1 mg/kg and
603 above (approximately 0.2 to 0.5 the clinical doses adjusted for body surface area).

604 Embryo/feto toxicity was manifested as mortality and reduced fetal weights (with associated
605 delays in skeletal ossification). However, no teratogenesis was evident. In combination
606 with cyclosporine, rats had increased embryo/feto mortality compared to Rapamune alone.

607 There were no effects on rabbit development at the maternally toxic dosage of 0.05 mg/kg
608 (approximately 0.3 to 0.8 times the clinical doses adjusted for body surface area). There are
609 no adequate and well controlled studies in pregnant women. Effective contraception must
610 be initiated before Rapamune therapy, during Rapamune therapy, and for 12 weeks after
611 Rapamune therapy has been stopped. Rapamune should be used during pregnancy only if
612 the potential benefit outweighs the potential risk to the embryo/fetus.

613

614 **Use during lactation**

615 Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether
616 sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of sirolimus
617 in infants are not known. Because many drugs are excreted in human milk and because of
618 the potential for adverse reactions in nursing infants from sirolimus, a decision should be
619 made whether to discontinue nursing or to discontinue the drug, taking into account the
620 importance of the drug to the mother.

621

622 **Pediatric use**

623 The safety and efficacy of Rapamune in pediatric patients below the age of 13 years have not
624 been established.

625

626 **Geriatric use**

627 Clinical studies of Rapamune Oral Solution or Tablets did not include sufficient numbers of
628 patients aged 65 and over to determine whether safety and efficacy differ in this population
629 from younger patients. Data pertaining to sirolimus trough concentrations suggest that dose
630 adjustments based upon age in geriatric renal patients are not necessary.

631

632

633 **ADVERSE REACTIONS**

634 **Rapamune® Oral Solution:** The incidence of adverse reactions was determined in two
635 randomized, double-blind, multicenter controlled trials in which 499 renal transplant
636 patients received Rapamune Oral Solution 2 mg/day, 477 received Rapamune Oral Solution
637 5 mg/day, 160 received azathioprine, and 124 received placebo. All patients were treated
638 with cyclosporine and corticosteroids. Data (≥ 12 months post-transplant) presented in the
639 table below show the adverse reactions that occurred in any treatment group with an
640 incidence of $\geq 20\%$.

641

642 Specific adverse reactions associated with the administration of Rapamune Oral Solution
643 occurred at a significantly higher frequency than in the respective control group. For both
644 Rapamune Oral Solution 2 mg/day and 5 mg/day these include hypercholesterolemia,
645 hyperlipemia, hypertension, and rash; for Rapamune Oral Solution 2 mg/day acne; and for
646 Rapamune Oral Solution 5 mg/day anemia, arthralgia, diarrhea, hypokalemia, and
647 thrombocytopenia. The elevations of triglycerides and cholesterol and decreases in platelets
648 and hemoglobin occurred in a dose related manner in patients receiving Rapamune.

649

650 Patients maintained on Rapamune Oral Solution 5 mg/day, when compared to patients on
651 Rapamune Oral Solution 2 mg/day, demonstrated an increased incidence of the following
652 adverse events: anemia, leukopenia, thrombocytopenia, hypokalemia, hyperlipemia, fever,
653 and diarrhea.

ADVERSE EVENTS OCCURRING AT A FREQUENCY OF $\geq 20\%$ IN ANY TREATMENT GROUP IN
PREVENTION OF ACUTE RENAL REJECTION TRIALS (%)^a AT ≥ 12 MONTHS POST-
TRANSPLANTATION FOR STUDIES 1 AND 2

Body System	Rapamune ^a Oral Solution -----2 mg/day-----		Rapamune ^a Oral Solution -----5 mg/day-----		Azathioprine 2-3 mg/kg/day	Placebo
	Study 1 (n = 281)	Study 2 (n = 218)	Study 1 (n = 269)	Study 2 (n = 208)	Study 1 (n = 160)	Study 2 (n = 124)
	Adverse Event					
Body As A Whole						
Abdominal pain	28	29	30	36	29	30
Asthenia	38	22	40	28	37	28
Back pain	16	23	26	22	23	20
Chest pain	16	18	19	24	16	19
Fever	27	23	33	34	33	35
Headache	23	34	27	34	21	31
Pain	24	33	29	29	30	25
Cardiovascular System						
Hypertension	43	45	39	49	29	48
Digestive System						
Constipation	28	36	34	38	37	31
Diarrhea	32	25	42	35	28	27
Dyspepsia	17	23	23	25	24	34
Nausea	31	25	36	31	39	29
Vomiting	21	19	25	25	31	21
Hemic And Lymphatic System						
Anemia	27	23	37	33	29	21
Leukopenia	9	9	15	13	20	8
Thrombocytopenia	13	14	20	30	9	9
Metabolic And Nutritional						
Creatinine increased	35	39	37	40	28	38
Edema	24	20	16	18	23	15
Hypercholesteremia (See WARNINGS and PRECAUTIONS)	38	43	42	46	33	23
Hyperkalemia	15	17	12	14	24	27
Hyperlipemia (See WARNINGS and PRECAUTIONS)	38	45	44	57	28	23
Hypokalemia	17	11	21	17	11	9
Hypophosphatemia	20	15	23	19	20	19
Peripheral edema	60	54	64	58	58	48
Weight gain	21	11	15	8	19	15
Musculoskeletal System						
Arthralgia	25	25	27	31	21	18
Nervous System						
Insomnia	14	13	22	14	18	8
Tremor	31	21	30	22	28	19
Respiratory System						
Dyspnea	22	24	28	30	23	30
Pharyngitis	17	16	16	21	17	22
Upper respiratory infection	20	26	24	23	13	23

ADVERSE EVENTS OCCURRING AT A FREQUENCY OF $\geq 20\%$ IN ANY TREATMENT GROUP IN PREVENTION OF ACUTE RENAL REJECTION TRIALS (%)^a AT ≥ 12 MONTHS POST-TRANSPLANTATION FOR STUDIES 1 AND 2

Body System	Rapamune ^a Oral Solution -----2 mg/day-----		Rapamune ^a Oral Solution -----5 mg/day-----		Azathioprine 2-3 mg/kg/day	Placebo
	Study 1 (n = 281)	Study 2 (n = 218)	Study 1 (n = 269)	Study 2 (n = 208)	Study 1 (n = 160)	Study 2 (n = 124)
	Adverse Event					
Skin And Appendages						
Acne	31	22	20	22	17	19
Rash	12	10	13	20	6	6
Urogenital System						
Urinary tract infection	20	26	23	33	31	26

a: Patients received cyclosporine and corticosteroids.

655

656 At 12 months, there were no significant differences in incidence rates for clinically
657 important opportunistic or common transplant-related infections across treatment groups,
658 with the exception of mucosal infections with *Herpes simplex*, which occurred at a
659 significantly greater rate in patients treated with Rapamune 5 mg/day than in both of the
660 comparator groups.

661

662 The table below summarizes the incidence of malignancies in the two controlled trials for
663 the prevention of acute rejection. At 12 months following transplantation, there was a very
664 low incidence of malignancies and there were no significant differences among treatment
665 groups.

666

INCIDENCE (%) OF MALIGNANCIES IN PREVENTION OF ACUTE RENAL REJECTION TRIALS: AT 12 MONTHS POST-TRANSPLANT^a

Malignancy	Rapamune ^a Oral Solution 2 mg/day (n = 511)	Rapamune ^a Oral Solution 5 mg/day (n = 493)	Azathioprine 2-3 mg/kg/day (n = 161)	Placebo (n = 130)
	Lymphoma/lymphoproliferative disease	0.4	1.4	0.6
Non-melanoma skin carcinoma	0.4	1.4	1.2	3.1
Other malignancy	0.6	0.6	0	0

a: Patients received cyclosporine and corticosteroids

667

668 Among the adverse events that were reported at a rate of $\geq 3\%$ and $< 20\%$, the following were
669 more prominent in patients maintained on Rapamune 5 mg/day, when compared to patients
670 on Rapamune 2 mg/day: epistaxis, lymphocele, insomnia, thrombotic thrombocytopenic
671 purpura (hemolytic-uremic syndrome), skin ulcer, increased LDH, hypotension, facial
672 edema.

673

674 The following adverse events were reported with $\geq 3\%$ and $< 20\%$ incidence in patients in any
675 Rapamune treatment group in the two controlled clinical trials for the prevention of acute
676 rejection, BODY AS A WHOLE: abdomen enlarged, abscess, ascites, cellulitis, chills, face
677 edema, flu syndrome, generalized edema, hernia, *Herpes zoster* infection, lymphocele,
678 malaise, pelvic pain, peritonitis, sepsis; CARDIOVASCULAR SYSTEM: atrial fibrillation,

679 congestive heart failure, hemorrhage, hypervolemia, hypotension, palpitation, peripheral
680 vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis,
681 vasodilatation; DIGESTIVE SYSTEM: anorexia, dysphagia, eructation, esophagitis,
682 flatulence, gastritis, gastroenteritis, gingivitis, gum hyperplasia, ileus, liver function tests
683 abnormal, mouth ulceration, oral moniliasis, stomatitis; ENDOCRINE SYSTEM:
684 Cushing's syndrome, diabetes mellitus, glycosuria; HEMIC AND LYMPHATIC SYSTEM:
685 ecchymosis, leukocytosis, lymphadenopathy, polycythemia, thrombotic thrombocytopenic
686 purpura (hemolytic-uremic syndrome); METABOLIC AND NUTRITIONAL: acidosis,
687 alkaline phosphatase increased, BUN increased, creatine phosphokinase increased,
688 dehydration, healing abnormal, hypercalcemia, hyperglycemia, hyperphosphatemia,
689 hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, lactic dehydrogenase
690 increased, SGOT increased, SGPT increased, weight loss; MUSCULOSKELETAL
691 SYSTEM: arthrosis, bone necrosis, leg cramps, myalgia, osteoporosis, tetany; NERVOUS
692 SYSTEM: anxiety, confusion, depression, dizziness, emotional lability, hypertonia,
693 hypesthesia, hypotonia, insomnia, neuropathy, paresthesia, somnolence; RESPIRATORY
694 SYSTEM: asthma, atelectasis, bronchitis, cough increased, epistaxis, hypoxia, lung edema,
695 pleural effusion, pneumonia, rhinitis, sinusitis; SKIN AND APPENDAGES: fungal
696 dermatitis, hirsutism, pruritus, skin hypertrophy, skin ulcer, sweating; SPECIAL SENSES:
697 abnormal vision, cataract, conjunctivitis, deafness, ear pain, otitis media, tinnitus;
698 UROGENITAL SYSTEM: albuminuria, bladder pain, dysuria, hematuria, hydronephrosis,
699 impotence, kidney pain, kidney tubular necrosis, nocturia, oliguria, pyelonephritis, pyuria,
700 scrotal edema, testis disorder, toxic nephropathy, urinary frequency, urinary incontinence,
701 urinary retention.

702

703 Less frequently occurring adverse events included: mycobacterial infections, Epstein-Barr
704 virus infections, and pancreatitis.

705

706

707 **Rapamune® Tablets:** The safety profile of the tablet did not differ from that of the oral
708 solution formulation. The incidence of adverse reactions up to 12 months was determined in
709 a randomized, multicenter controlled trial (Study 3) in which 229 renal transplant patients
710 received Rapamune Oral Solution 2 mg once daily and 228 patients received Rapamune
711 Tablets 2 mg once daily. All patients were treated with cyclosporine and corticosteroids.
712 The adverse reactions that occurred in either treatment group with an incidence of $\geq 20\%$ in
713 Study 3 are similar to those reported for Studies 1 & 2. There was no notable difference in
714 the incidence of these adverse events between treatment groups (oral solution versus tablets)
715 in Study 3, with the exception of acne, which occurred more frequently in the oral solution
716 group, and tremor which occurred more frequently in the tablet group, particularly in Black
717 patients.

718

719 The adverse events that occurred in patients with an incidence of $\geq 3\%$ and $< 20\%$ in either
720 treatment group in Study 3 were similar to those reported in Studies 1 & 2. There was no
721 notable difference in the incidence of these adverse events between treatment groups (oral
722 solution versus tablets) in Study 3, with the exception of hypertonia, which occurred more

723 frequently in the oral solution group and diabetes mellitus which occurred more frequently
724 in the tablet group. Hispanic patients in the tablet group experienced hyperglycemia more
725 frequently than Hispanic patients in the oral solution group. In Study 3 alone, menorrhagia,
726 metrorrhagia, and polyuria occurred with an incidence of $\geq 3\%$ and $< 20\%$.

727

728 The clinically important opportunistic or common transplant-related infections were
729 identical in all three studies and the incidences of these infections were similar in Study 3
730 compared with Studies 1&2. The incidence rates of these infections were not significantly
731 different between the oral solution and tablet treatment groups in Study 3.

732

733 In Study 3 (at 12 months), there were two cases of lymphoma/lymphoproliferative disorder
734 in the oral solution treatment group (0.8%) and two reported cases of
735 lymphoma/lymphoproliferative disorder in the tablet treatment group (0.8%). These
736 differences were not statistically significant and were similar to the incidences observed in
737 Studies 1 & 2.

738

739 **Other clinical experience:** Cases of pneumonitis with no identified infectious etiology,
740 sometimes with an interstitial pattern, have occurred in patients receiving
741 immunosuppressive regimens including Rapamune. In some cases, the pneumonitis has
742 resolved upon discontinuation of Rapamune.

743

744

745 **OVERDOSAGE**

746 There is minimal experience with overdose. During clinical trials, there were two accidental
747 Rapamune ingestions, of 120 mg and 150 mg. One patient, receiving 150 mg, experienced
748 an episode of transient atrial fibrillation. The other patient experienced no adverse effects.
749 General supportive measures should be followed in all cases of overdose. Based on the poor
750 aqueous solubility and high erythrocyte binding of Rapamune, it is anticipated that
751 Rapamune is not dialyzable to any significant extent.

752

753 In mice and rats, the acute oral lethal dose was greater than 800 mg/kg.

754

755

756 **DOSAGE AND ADMINISTRATION**

757 It is recommended that Rapamune Oral Solution and Tablets be used in a regimen with
758 cyclosporine and corticosteroids. Two-mg Rapamune oral solution has been demonstrated to
759 be clinically equivalent to 2-mg Rapamune oral tablets; hence, are interchangeable on a mg
760 to mg basis. However, it is not known if higher doses of Rapamune oral solution are
761 clinically equivalent to higher doses of tablets on a mg to mg basis. (See Clinical
762 Pharmacology: Absorption). Rapamune is to be administered orally once daily. The initial
763 dose of Rapamune should be administered as soon as possible after transplantation. For de
764 novo transplant recipients, a loading dose of Rapamune of 3 times the maintenance dose
765 should be given. A daily maintenance dose of 2 mg is recommended for use in renal
766 transplant patients, with a loading dose of 6 mg. Although a daily maintenance dose of 5

767 mg, with a loading dose of 15, mg was used in clinical trials of the oral solution and was
768 shown to be safe and effective, no efficacy advantage over the 2 mg dose could be
769 established for renal transplant patients. Patients receiving 2 mg of Rapamune Oral Solution
770 per day demonstrated an overall better safety profile than did patients receiving 5 mg of
771 Rapamune Oral Solution per day.

772

773 To minimize the variability of exposure to Rapamune, this drug should be taken consistently
774 with or without food. Grapefruit juice reduces CYP3A4-mediated metabolism of Rapamune
775 and must not be administered with Rapamune or used for dilution.

776

777 **It is recommended that sirolimus be taken 4 hours after administration of cyclosporine**
778 **oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED).**

779

780 **Dosage Adjustments**

781 The initial dosage in patients ≥ 13 years who weigh less than 40 kg should be adjusted, based
782 on body surface area, to 1 mg/m²/day. The loading dose should be 3 mg/m².

783

784 It is recommended that the maintenance dose of Rapamune be reduced by approximately one
785 third in patients with hepatic impairment. It is not necessary to modify the Rapamune
786 loading dose. Dosage need not be adjusted because of impaired renal function.

787

788 **Blood Concentration Monitoring**

789 Routine therapeutic drug level monitoring is not required in most patients. Blood sirolimus
790 levels should be monitored in pediatric patients, in patients with hepatic impairment, during
791 concurrent administration of strong CYP3A4 inducers and inhibitors, and/or if cyclosporine
792 dosing is markedly reduced or discontinued. In controlled clinical trials with concomitant
793 cyclosporine, mean sirolimus whole blood trough levels, as measured by immunoassay,
794 were 9 ng/mL (range 4.5 – 14 ng/mL [10th to 90th percentile]) for the 2 mg/day treatment
795 group, and 17 ng/mL (range 10 - 28 ng/mL [10th to 90th percentile]) for the 5 mg/day dose.

796

797 Results from other assays may differ from those with an immunoassay. On average,
798 chromatographic methods (HPLC UV or LC/MS/MS) yield results that are approximately
799 20% lower than the immunoassay for whole blood concentration determinations.

800 Adjustments to the targeted range should be made according to the assay utilized to
801 determine sirolimus trough concentrations. Therefore, comparison between concentrations
802 in the published literature and an individual patient concentration using current assays must
803 be made with detailed knowledge of the assay methods employed. A discussion of the
804 different assay methods is contained in *Clinical Therapeutics*, Volume 22, Supplement B,
805 April 2000.

806

807 **Instructions for Dilution and Administration of Rapamune® Oral Solution**

808 **Bottles**

809

810 The amber oral dose syringe should be used to withdraw the prescribed amount of
811 Rapamune® Oral Solution from the bottle. Empty the correct amount of Rapamune from the
812 syringe into only a glass or plastic container holding at least two (2) ounces (¼ cup, 60 mL)
813 of water or orange juice. No other liquids, including grapefruit juice, should be used for
814 dilution. Stir vigorously and drink at once. Refill the container with an additional volume
815 (minimum of four [4] ounces (½ cup, 120 mL)) of water or orange juice, stir vigorously, and
816 drink at once.

817

818 **Pouches**

819 When using the pouch, squeeze the entire contents of the pouch into only a glass or plastic
820 container holding at least two (2) ounces (1/4 cup, 60 mL) of water or orange juice. No
821 other liquids, including grapefruit juice, should be used for dilution. Stir vigorously and
822 drink at once. Refill the container with an additional volume (minimum of four [4] ounces
823 (½ cup, 120 mL)) of water or orange juice, stir vigorously, and drink at once.

824

825 **Handling and Disposal**

826 Since Rapamune is not absorbed through the skin, there are no special precautions.
827 However, if direct contact with the skin or mucous membranes occurs, wash thoroughly with
828 soap and water; rinse eyes with plain water.

829

830

831 **HOW SUPPLIED**

832 Rapamune® Oral Solution is supplied at a concentration of 1 mg/mL in:

833

834 1. Cartons:

835 NDC # 0008-1030-06, containing a 2 oz (60 mL fill) amber glass bottle.

836 NDC # 0008-1030-15, containing a 5 oz (150 mL fill) amber glass bottle.

837

838 In addition to the bottles, each carton is supplied with an oral syringe adapter for fitting into
839 the neck of the bottle, sufficient disposable amber oral syringes and caps for daily dosing,
840 and a carrying case.

841

842 2. Cartons;

843 NDC # 0008-1030-03, containing 30 unit-of-use laminated aluminum pouches of 1 mL.

844 NDC # 0008-1030-07, containing 30 unit-of-use laminated aluminum pouches of 2 mL.

845 NDC # 0008-1030-08, containing 30 unit-of-use laminated aluminum pouches of 5 mL.

846

847 Rapamune® Tablets are available as follows: 1 mg, white, triangular-shaped tablets marked
848 "RAPAMUNE 1 mg" on one side.

849 NDC # 0008-1031-05, bottle of 100 tablets.

850 NDC # 0008-1031-10, Redipak® cartons of 100 tablets (10 blister cards of 10 tablets
851 each).

852

853

854 **Storage**

855 Rapamune® Oral Solution bottles and pouches should be stored protected from light and
856 refrigerated at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, the contents should be
857 used within one month. If necessary, the patient may store both the pouches and the bottles
858 at room temperatures up to 25°C (77°F) for a short period of time (e.g., several days, but
859 not longer than 30 days).

860

861 An amber syringe and cap are provided for dosing and the product may be kept in the
862 syringe for a maximum of 24 hours at room temperatures up to 25°C (77°F) or refrigerated
863 at 2°C to 8°C (36°F to 46°F). The syringe should be discarded after one use. After dilution,
864 the preparation should be used immediately.

865

866 Rapamune Oral Solution provided in bottles may develop a slight haze when refrigerated. If
867 such a haze occurs allow the product to stand at room temperature and shake gently until the
868 haze disappears. The presence of this haze does not affect the quality of the product.

869

870 Rapamune® Tablets should be stored at 20° to 25°C (USP Controlled Room Temperature)
871 (68° - 77°F). Use cartons to protect blister cards and strips from light. Dispense in a tight,
872 light-resistant container as defined in the USP.

873

874 **R_x only.**

875

876 US Pat. Nos.: 5,100,899; 5,212,155; 5, 308,847; 5,403,833; 5,536,729.

877

878

879 Wyeth Laboratories

880 Division of Wyeth-Ayerst Pharmaceuticals Inc.

881 Philadelphia, PA 19101

882

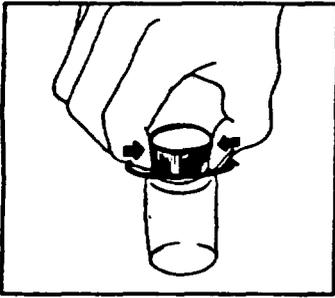
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18 August 2000

ADMINISTRATION

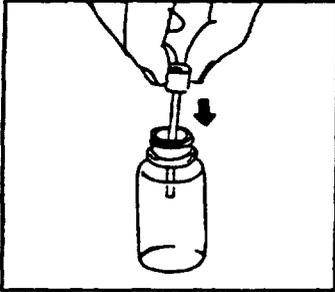
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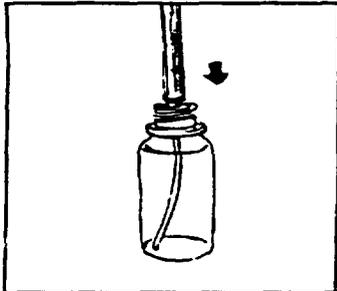


1. Open the solution bottle. Remove the safety cap by squeezing the tabs on the cap and twisting counterclockwise.

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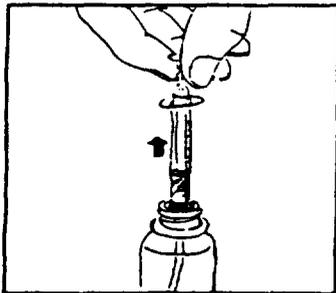


2. On first use, insert the adapter assembly (plastic tube with stopper) tightly into the bottle until it is even with the top of the bottle. Do not remove the adapter assembly from the bottle once inserted.



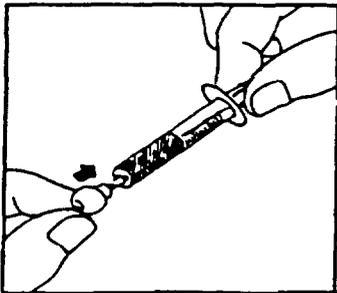
3. For each use, tightly insert one of the amber syringes with the plunger fully depressed into the opening in the adapter.

4



4. Withdraw the prescribed amount of Rapamune® Oral Solution by gently pulling out the plunger of the syringe until the bottom of the black line of the plunger is even with the appropriate mark on the syringe. Always keep the bottle in an upright position. If bubbles form in the syringe, empty the syringe into the bottle and repeat the procedure.

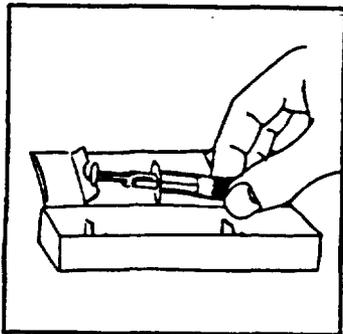
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5. You may have been instructed to carry your medication with you. If it is necessary to carry the filled syringe, place a cap securely on the syringe — the cap should snap into place.

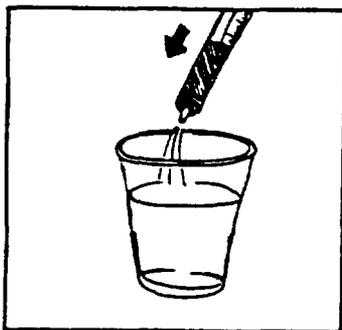
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6. Then place the capped syringe in the enclosed carrying case. Once in the syringe, the medication may be kept at room temperature or refrigerated and should be used within 24 hours. Extreme temperatures (below 36°F and above 86°F) should be avoided. Remember to keep this medication out of the reach of children.

7



7. Empty the syringe into a glass or plastic cup containing at least 2 ounces (1/4 cup; 60 mL) of water or orange juice, stir vigorously for one (1) minute and drink immediately. Refill the container with at least 4 ounces (1/2 cup; 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Apple juice, grapefruit juice or other liquids are NOT to be used. Only glass or plastic cups should be used to dilute Rapamune® Oral Solution. The syringe and cap should be used once and then discarded.

8



8. Always store the bottles of medication in the refrigerator. When refrigerated, a slight haze may develop in the solution. The presence of a haze does not affect the quality of the product. If this happens, bring the Rapamune® Oral Solution to room temperature and shake until the haze disappears. If it is necessary to wipe clean the mouth of the bottle before returning the product to the refrigerator, wipe with a dry cloth to avoid introducing water, or any other liquid, into the bottle.

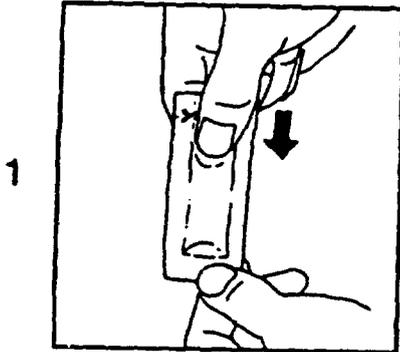
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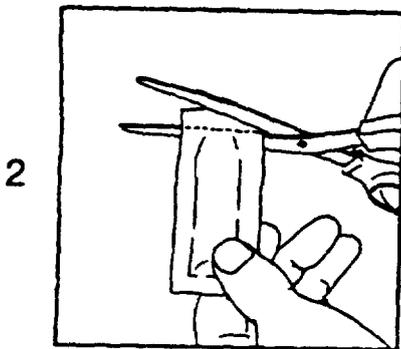
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PATIENT INSTRUCTIONS FOR RAPAMUNE® ORAL SOLUTION ADMINISTRATION

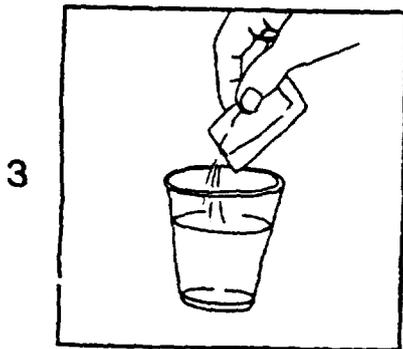
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1. Before opening the pouch, squeeze the pouch from the neck area to push the contents into the lower part of the pouch.



2. Carefully open the pouch by folding the marked area and then cutting with a scissors along the marked line near the top of the pouch.



3. Squeeze the entire contents of the pouch into a glass or plastic cup containing at least 2 ounces (1/4 cup; 60 mL) of water or orange juice, stir vigorously for one (1) minute and drink immediately. Refill the container with at least 4 ounces (1/2 cup, 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Apple juice, grapefruit juice or other liquids are NOT to be used. Only glass or plastic cups should be used to dilute Rapamune® Oral Solution.

1013

1014

1015

4. Unused pouches should be stored in the refrigerator.