

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-110**

**APPROVED DRAFT LABELING**

1 **Rapamune®**  
2 **(sirolimus)**  
3 **Oral Solution and Tablets**  
4  
5

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] oxazacyclohentracontine-  
26 1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is C<sub>51</sub>H<sub>79</sub>NO<sub>13</sub> and its molecular  
27 weight is 914.2. The structural formula of sirolimus is shown below.  
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30  
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.  
33  
34

25 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.

47

48

## 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 G<sub>1</sub> 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/m<sup>2</sup>.

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%),  $\alpha_1$ -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 [<sup>14</sup>C]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)<sup>a,b</sup>**

n	Dose	C <sub>max,ss</sub> <sup>c</sup> (ng/mL)	t <sub>max,ss</sub> (h)	AUC <sub>τ,ss</sub> <sup>c</sup> (ng•h/mL)	CL/F/WT <sup>d</sup> (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<sup>®</sup> Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral<sup>®</sup> 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 (r<sup>2</sup> = 0.96) with AUC<sub>τ,ss</sub>. 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<sub>1/2</sub>) 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

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