

**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 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:

29
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 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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.