CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-110

APPROVED DRAFT LABELING

Rapamune®
(sirolimus)
Oral Solution and Tablets

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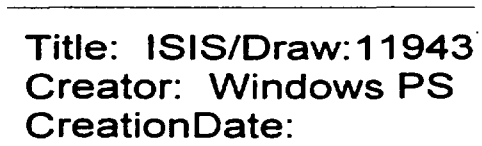
DESCRIPTION

Rapamune® (sirolimus) is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus (also known as 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*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2. The structural formula of sirolimus is shown below.



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

Rapamune® is available for administration as an oral solution containing 1 mg/mL sirolimus and as a white, triangular-shaped tablet containing 1 mg sirolimus.

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

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

CLINICAL PHARMACOLOGY

Mechanism of Action

Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus:FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G_1 to the S phase of the cell cycle.

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

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

Pharmacokinetics

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

Absorption

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

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

Distribution

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

Metabolism

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

Excretion

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

Pharmacokinetics in renal transplant patients

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

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)	$AUC_{\tau,ss}$[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.

Whole blood sirolimus trough concentrations, as measured by immunoassay, (mean ± SD) for the 2 mg/day and 5 mg/day dose groups were 8.59 ± 4.01 ng/mL (n = 226) and 17.3 ± 7.4 ng/mL (n = 219), respectively. Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated ($r^2 = 0.96$) with $AUC_{\tau,ss}$. Upon repeated twice daily administration without an initial loading dose in a multiple-dose study, the average trough concentration of sirolimus increases approximately 2 to 3-fold over the initial 6 days of therapy at which time steady state is reached. A loading dose of 3 times the maintenance dose will provide near steady-state concentrations within 1 day in most patients. The mean ± SD terminal elimination half life ($t_{½}$) of sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.

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

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