CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-110

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA: 21-110	**Submission Date:** 10/29/99, 7/26/00, 8/9/00, 8/15/00, 8/17/00
Generic Name, Strength and Formulation:	Sirolimus (Rapamycin) 1 mg tablets
Brand Name: Rapamune®	**Date Assigned:** 11/4/99
Applicant: Wyeth Ayerst	**Final Review:** 9/25/00
Submission Code: 3S	**Reviewer:** Kofi A. Kumi, Ph.D.

SYNOPSIS

The applicant submitted an original New Drug Application for Rapamune® (sirolimus, rapamycin) 1 mg oral tablets to be used for the prophylaxis of organ rejection in patients receiving renal transplants. Rapamune (1 mg/mL) oral solution is already approved for the same indication. Rapamune oral solution is approved to be administered in combination with cyclosporine and corticosteroids. Rapamune oral tablets were not bioequivalent to the oral solution. Therefore, the NDA was primarily based on a clinical study in which Rapamune oral tablets in combination with cyclosporine (Neoral) and corticosteroids were compared to Rapamune oral solution in combination with cyclosporine and corticosteroids.

The primary questions that the reviewer focused on during the review of the application were the following: 1) Is the oral tablet bioequivalent to the oral solution? 2) Did food have an effect on the bioavailability of the tablet dosage form? 3) How does the overall pharmacokinetics of sirolimus after administration of the oral tablet compare to that after administration of the oral solution 4) Is the interaction between sirolimus and cyclosporine after administration of Rapamune oral tablets and Neoral similar to that observed after administration of Rapamune oral solution with Neoral? 5) Has the applicant provided sufficient justification to waive bioequivalence studies between the oval and triangular shaped tablets?

Bioequivalence: The 90% confidence interval evaluations indicated that six 1 mg tablets were not bioequivalent to 6 mL of the 1 mg/mL oral solution per the regulatory criteria of 80 to 125% for the log-transformed Cmax and AUC. Based on the geometric least square (GLS) mean ratios, the mean bioavailability of sirolimus from the tablet was approximately 27% higher relative to the solution formulation.

Food Effect: The administration of sirolimus oral tablets [redacted] with a high fat meal (1.88 Kcal, 54.7% fat) increased the Cmax and AUC by 65% and 23%, respectively, when compared to the values obtained when administered under fasting conditions. Tmax was increased by 19 mins when administered with food relative to under fasting conditions. To avoid large variability in Cmax, it is recommended that sirolimus tablets be taken consistently with or without food.

Pharmaokinetics in Renal Transplant Patients: A subset of patients in the pivotal clinical study (study 309) had full concentration-time profiles determined. The mean ± SD trough concentrations for sirolimus for 2 mg sirolimus oral solution and tablets were 8.94 ± 4.36 (n =172) and 9.48 ± 3.85 ng/mL (n = 179), respectively. The average sirolimus pharmacokinetic

parameters at steady state in renal transplant patients for both the oral solution and tablet formulations are provided in the following table.

Sirolimus Pharmacokinetic Parameters at Steady State in Renal Transplant Patients

Parameter	Solution (Dose=2mg) (n=17)	Tablet (Dose=2mg) (n=13)
	Mean ± SD	
Cmax (ng/mL)	14.39 ± 5.31	15.00 ± 4.88
AUC (0-24) (ng*h/mL)	194 ± 78	230 ± 67
Tmax (h)	2.12 ± 0.84	3.46 ± 2.40
Cl/F/Wt (mL*h/kg)	172.5 ± 49.6	138.9 ± 62.9

No statistically significant differences between the two formulation were observed in whole blood sirolimus Cmax or AUC(0-24h). However, the statistical power for detecting a 20% difference in treatment at the α level of 0.05 was 50% for Cmax and 39% for AUC. Hence, inference of no difference in the pharmacokinetic parameters of the two formulations should be made with caution.

The mean ± SD trough cyclosporine concentration on day 30, 90, 120,180 when given with the oral solution were 348 ± 180 (n=146), 252 ± 125 (n=82), 242 ± 84 (n=44) and 206 ± 91 (n = 12) ng/mL, respectively. The mean ± SD cyclosporine trough concentration at day 30, 90, 120 and 180 when given with the tablet were 329 ± 154 (n=202), 250 ± 137 (n=166), 249 ± 154 (n=105) and 206 ± 84 (n= 52) ng/mL, respectively. There was not a significant treatment difference in the trough concentrations for the two treatment groups. Cyclosporine concentrations are therapeutically monitored and maintained within predetermined therapeutic range. The average cyclosporine concentrations in this study were generally greater than the mid-point of the therapeutic range.

Rapamune Tablet- Neoral Interaction: The simultaneous administration of sirolimus and CsA resulted in a 512% increase in Cmax, 30% decrease in tmax and 148% increase in AUC. The half-life of sirolimus was unchanged after simultaneous administration. Delaying sirolimus administration by 4 hours after CsA dose resulted in 33% increase in Cmax and AUC. Tmax was reduced by 33% and T ½ remained unchanged. It is recommended that sirolimus tablets like the oral solution be administered 4 hours after cyclosporine administration.

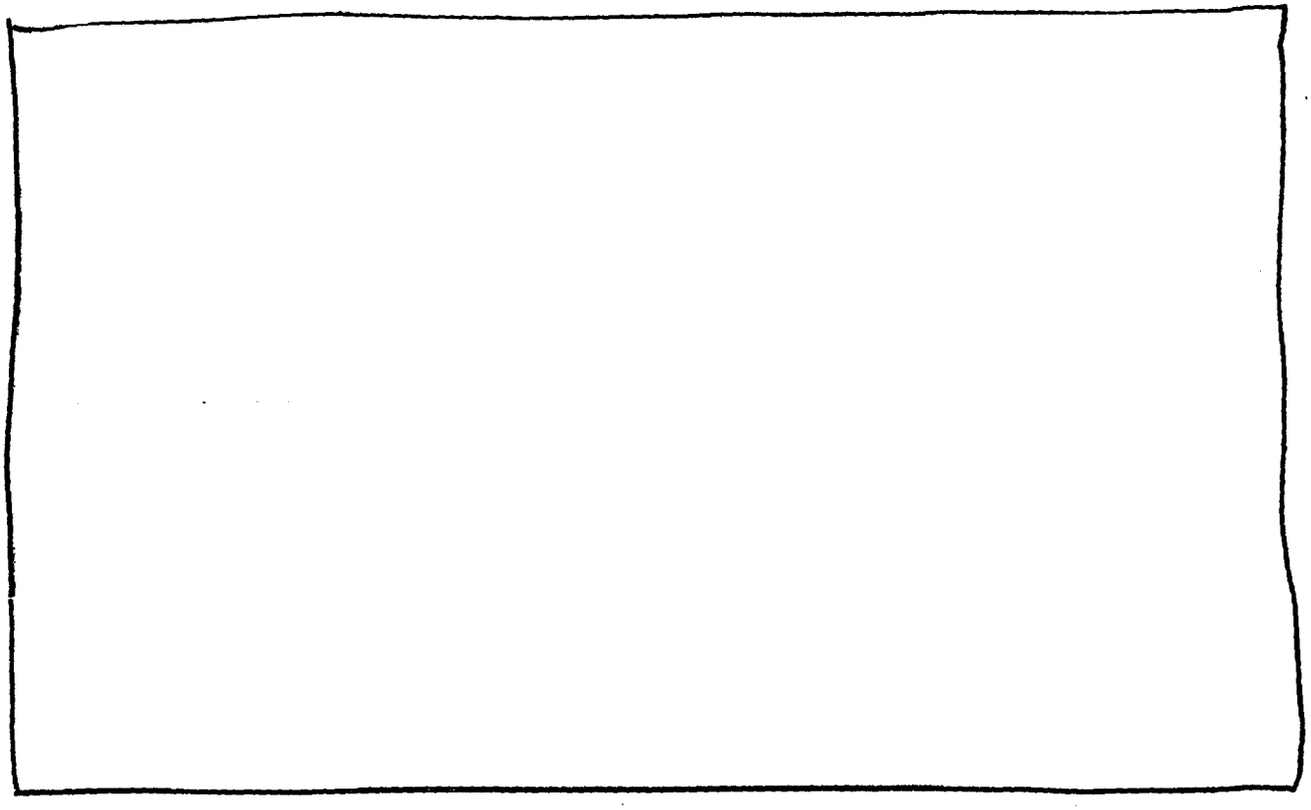
WAIVER REQUEST RECOMMENDATION

During drug product development, the applicant changed the 1 mg Rapamune® tablet from oval to triangular. New triangular shaped tablets representing the final market trade dress were manufactured using identical formulation composition as the oval shape tablets. The applicant requested a waiver of bioequivalence study between the triangular and oval shaped tablets. The waiver request was based on in vitro dissolution comparison data and tablet surface area comparisons. The applicant also provided a [redacted] in vitro/in vivo correlation (IVIVC) for Rapamune tablets.

It is recommended that the waiver of bioequivalence study between the triangular and oval shaped tablets be granted for the following reasons: The sameness of the dissolution profiles based on similarity factor (f2) calculations (f2> 50) for the triangular and oval tablets. The small difference (about 3%) in surface area between the two shapes.

The in vitro/in vivo correlation (IVIVC) submitted developed is inadequate and not acceptable. It is recommended that the IVIVC submitted should not be used as the basis of granting a waiver of bioequivalence study if changes (pre and post approval) are made in the formulation or shape of the tablet.

DISSOLUTION



GENERAL COMMENTS

Sirolimus tablet is not bioequivalent to the oral solution on a mg per mg basis. However, therapeutic equivalence has been demonstrated at the 2 mg dose level. Therefore, sirolimus oral solution can be interchanged with the oral tablets only at the 2 mg dose level. It is not known whether other doses of sirolimus oral tablets are equivalent to similar doses (on mg/mg basis) of the oral solution. It is recommended that other doses are not interchanged.

The clinical significance of the 65% increase in Cmax after administration with food is not known. However, the Cmax values observed after administration with food is within the concentration range (5- 25 ng/mL) postulated by the sponsor to be the therapeutic range. To avoid variability in therapeutic concentration, it is recommended Rapamune tablets be administered consistently with or without food.

It is recommended that as a phase IV commitment, the applicant continue to evaluate the effect of ethnicity on the pharmacokinetics of sirolimus. This will facilitate the determination of the optimum dosing regimen for various ethnic populations.

It is recommended that as a phase IV commitment, the applicant continue to explore the optimum therapeutic concentration for sirolimus in renal transplant patients.

COMMENTS TO BE FORWARDED TO SPONSOR

A) The waiver of bioequivalence study comparing Rapamune 1-mg triangular to oval shaped tablet is granted. The decision was based on the following: 1) Similarity factor (f2) determinations, which were greater than 50. 2) The small difference in surface area between the oval and triangular shaped tablets did not result in significant differences in the dissolution profiles of the oval and triangular shaped tablets.

B) The [redacted] in vitro and in vivo correlation (IVIVC) proposed is inadequate and unacceptable. Hence, the IVIVC that the sponsor submitted cannot be used as the basis of granting waivers on pre-approval and post approval changes in the tablet dosage formulation. The rationale behind this decision is that the IVIVC was developed using 3 data points one of which was obtained from the solution formulation. IVIVC cannot be developed with information from an oral solution. A minimum of 3 solid oral dosage formulations (preferably more than 3) is needed to attempt a [redacted] correlation.

C) It is suggested that in future development plans for Rapamune tablets, the applicant evaluate the dose proportionality of Rapamune tablet doses that include 2 and 5 mg.

D) It is recommended that as a phase IV commitment, the applicant continue to evaluate the effect of ethnicity on the pharmacokinetics of sirolimus. This will facilitate the determination of the optimum dosing regimen for various ethnic populations.

E) It is recommended that as a phase IV commitment, the applicant continue to explore the optimum therapeutic concentration for sirolimus in renal transplant patients.

RECOMMENDATION

The studies submitted to the Human Pharmacokinetics and Bioavailability Section of NDA 21-110 to fulfil sections 320 and 201.5 of 21 CFR are acceptable and support a recommendation for approval.

APPEARS THIS WAY
ON ORIGINAL

CPB Briefing Attendees: OCPB: Drs. J. Lazor, A. Selen, D. Bashaw, K. Reynolds, J. Kim, J. Digiacinto, K. Kumi. ONDC: Dr. M. Seggel (Chemist), DSPIDP: Dr. R. Tiernan (Medical Officer)

/S/ 9/27/00

Kofi A. Kumi, Ph.D.
Reviewer
Clinical Pharm. & Biopharm.
HFD-590 Section
DPEIII, OCPB

RD/FT /S/ 9/27/2000

Arzu Selen, Ph.D. (2° Reviewer)
Deputy Director
DPE III, OCPB

Concurrence /S/ 9/27/2000

Funmi Ajayi, Ph.D.
Team Leader,
Clinical Pharm. & Biopharm.
HFD-590 Section
DPEIII, OCPB

NDA 21-110 (Original)

CC:	HFD-590	Division Files /MO/R Tiernan /PM/M Bacho
	HFD-340	/Viswanathan
	HFD-880	/TLDPEIII/F Ajayi /DPEIII/K Kumi /DPEIII Drug Files