OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
BPCA Summary Review

NDA:	**21-083 (SE5-019)**
	21-110 (SE5-024)
Submission Date:	**13 September 2004**
Drug Product:	**Sirolimus Oral Solution, Tablets**
Trade Name:	**Rapammune®**
Sponsor:	**Wyeth**
Submission Type:	**Pediatric Supplemental NDA**

I. Executive Summary

A. Recommendations

Two studies (Studies 217-US and 315-WW) were conducted to fulfill the requirements of a Pediatric Written request for the evaluation of efficacy, safety, and pharmacokinetics (PK) of sirolimus (SRL). Study #217 was an efficacy/safety (with optional PK sub-) study involving renal transplant patients (2 to 20 years old) who were considered of high-immunologic risk for developing chronic allograft nephropathy (defined as having a history of at least 1 acute allograft rejection episode). Study #315 was a study that investigated sirolimus pharmacokinetics of pediatric renal transplant patients (3 to 18 years old); only those who received a kidney transplant for the first time were enrolled. The majority of the PK information was obtained from pediatric patients from Study 315 (n =44/47); full PK profiles were obtained from 3 patients enrolled in Study 217 (n=3/47). The actual (mean ± SD) sirolimus doses given at the time of PK profiling were: 2.22 ± 1.0 mg/m^2 (3-5 years), 1.65 ± 0.4 mg/m^2 (6-11 years), and 1.86 ± 0.6 mg/m^2 (12-18 years).

The clinical pharmacology findings of the combined Studies 217 & 315 indicate that younger pediatric renal transplant patients (3 to 5 years old) given sirolimus with cyclosporine (SRL + CsA) have a 57% lower dose-normalized sirolimus exposure (AUC_{ss}) and a 3-fold higher sirolimus CL/F/WT compared to adolescents (12-18 years). Older pediatric patients (6 to 11 years old) have 13% lower dose-normalized sirolimus AUC_{ss} and a 1.6-fold higher CL/F/WT than adolescents. The adolescents in the studies achieved a dose-normalized sirolimus AUC_{ss} that was comparable to that attained in adult PK studies. In general, body weight (kg) and body surface area (m^2) appeared to have greater influence on sirolimus oral clearance rather than age. However, the sirolimus dosing and PK information on the 3-5 year old group of the SRL + CsA arm will not be included in the label because there was an inadequate number (n = 3) of children with PK profiles comprising this particular age group. Thus, the reviewer proposes that the PK data only for pediatric patients from 6-11 and 12-18 years are to be included in the labeling.

The findings of the efficacy/safety study (#217) involving high-immunologic risk renal transplant patients between ages 2 to 20 years old showed that the efficacy failure rates were similar between the 'sirolimus + standard' treatment group and the standard therapy (control) group (45.3% versus 44.0%). Additionally, the incidence of urinary tract infections (UTI) was higher in the sirolimus combination group than in the control group (15% versus 1%). In the study, sirolimus doses were administered initially at about 3.0 mg/m^2 and were adjusted so as to achieve target sirolimus trough concentration range of 5 -15 ng/mL. The actual time-averaged sirolimus C_{min} values achieved in this study when sirolimus was administered with cyclosporine were 9.51 ± 3.19 ng/mL (2 to 5 years old), 11.89 ± 6.21 ng/mL (6 to 11 years old), 12.22 ± 5.22 ng/mL (12 to 17 years old), and 9.93 ± 6.79 ng/mL (18 to 20 years old). The calcineurin inhibitor (cyclosporine or tacrolimus) used as standard immunosuppressant therapy was also administered by concentration-control; cyclosporine C_{min} was generally within the targeted range. Although there appeared to be a trend of higher CsA trough concentrations in the control group

(versus the sirolimus combination group), a statistically significant difference was only found at months 10 and 18 to 24 after transplant.

Because the sponsor did not seek a specific pediatric indication for use of sirolimus for renal transplant, no dosage regimen will be recommended for pediatrics.

The PK information obtained mainly from pediatric renal transplant patients in Study #315 between the ages of 6-11 and 12-18 years, may be useful to the clinician considering sirolimus + CsA combination therapy for pediatric renal transplant patients. The data on sirolimus PK with concomitant tacrolimus (SRL + TAC) will not be included in the label because sirolimus is not currently approved for use with calcineurin inhibitors other than cyclosporine, and also because there was uncertainty regarding the dosing data on sirolimus (BID) + tacrolimus (BID).

Overall, the submission is acceptable from a clinical pharmacology perspective. The sponsor fulfilled the requirements of the pediatric written request from the perspective of the Clinical Pharmacology information.

B. Phase IV Commitments

None.

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Phil Colangelo

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