DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS HFD-590

NDA No. 21-083 (S-019) Rapamune® (sirolimus) Oral Solution
NDA No. 21-110 (S-024) Rapamune® (sirolimus) Tablets

PEDIATRIC EXCLUSIVITY DETERMINATION REQUEST
- PEDIATRIC STUDY REPORTS-

Medical Officer Executive Summary

1 SPONSOR IDENTIFICATION

Name: Wyeth Pharmaceuticals

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2 SUBMISSIONS /REVIEW DATES

Patent Expiration date: September 15, 2004

Date of Submission: September 13, 2004

CDER Stamp Date: September 15, 2004

Date of Pediatric Exclusivity Review Board Meeting: November 17, 2004

Date of Written Review completed: March 7, 2005

3 EXECUTIVE SUMMARY

The original Pediatric Written Request (WR) for Rapamune was issued on 15 Sep 1999 and addressed the fact that limited pharmacokinetic data were available in children.

Wyeth's response to the pediatric Written Request for Rapamune included two studies:

- Protocol 0468E1-217-US, "An Open-Label, Comparative Study of the Effect of Sirolimus versus Standard Treatment on Clinical Outcomes and Histologic Progression of Allograft Nephropathy in High Risk Pediatric Renal Transplant Patients,"
- Protocol 0468H1-315-US, "A Double-Blind Randomized Trial of Steroid Withdrawal in Sirolimus and Cyclosporine-Treated Primary Transplant Recipients." ***(pharmacokinetic portion)***

The WR was amended on 17 May 2004 (To include categorization of patients by race and ethnicity) and on 24 May 2004 (To allow to obtain pharmacokinetic (PK) profiles from patients across multiple studies).

Protocol 217 was a randomized study in high immunologic risk pediatric renal allograft recipients[1] that compared the safety and efficacy of sirolimus (SRL) plus a Calcineurin Inhibitor (C Inh)[2] and corticosteroids (CS) versus double therapy (CsA or tacrolimus and CS) or triple therapy (cyclosporine or tacrolimus plus azathioprine or mycophenolate mofetil and CS).

Efficacy was to be assessed by comparing the composite endpoint of the first occurrence of biopsy-proven acute rejection, graft loss, or death after 36 months of treatment.
Efficacy failure in the intention-to-treat (ITT) population (n=102) was numerically more frequent in subjects randomly assigned to receive the combination of sirolimus and a C Inh than in the subjects allocated to standard therapy (29/65, 44.6% versus 12/37, 32.4%, respectively). When comparing only subject 18 years old or younger (24/53, 45.3% versus 11/25, 44.0%, respectively) efficacy failure rates were similar.

Adverse events such as abdominal pain, fever, abnormal renal function, and urinary tract infection (UTI) were significantly more common in the sirolimus treatment cohort compared with standard therapy. UTI rates were 15% versus 1% in the sirolimus combination group versus the control group, respectively.
Overall, the remaining adverse event rates were numerically similar in both randomized groups.

Pharmacokinetics data were collected across studies 217 and 315. These studies targeted sirolimus whole blood concentrations from 5 to 15 ng/mL, and 10 to 20 ng/mL, respectively (chromatographic method).

Sirolimus and CsA Regimen:
Younger children had overall lower sirolimus dose normalized exposure apparently due to higher clearance.
A strong correlation at steady-state between whole blood sirolimus C_{min} and AUC values were observed for all treatments and regimens. We agree that these results indicate that sirolimus trough concentrations were adequate surrogates for sirolimus exposure. (See Section 7 of this review and Biopharmaceutics review for further details)

Conclusions:

- ***We agree with the sponsor that treatment of subjects with a prior history of acute rejection and/or chronic allograft nephropathy with the combination of sirolimus and a calcineurin inhibitor does not confer greater protection against recurrent acute rejection or progression of chronic allograft nephropathy than calcineurin inhibitor-based immunosuppression alone and may increase the risk for hyperlipidemia and faster renal function deterioration.***
- ***In the renal transplant population, the safety profile of sirolimus in children and adolescents appears to be similar to that for adults.***

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[1] Eligible subjects were those with ≥ 1 episode of acute rejection as well as those subjects with biopsy-proven chronic rejection.

[2] Cycolsporine (CsA) or Tacrolimus (TAC)

- ***The chronic use of cyclosporine together with Rapamune® as a maintenance regimen is no longer an acceptable in renal transplant recipients at low to moderate risk for rejection and the same statement appears to be true for children due to the resulting increased impairment in renal function.***
- ***The sponsor fulfilled the request for characterizing PK profiles of sirolimus in children and these studies qualify Rapamune for an extension of exclusivity under section 505A.***
- ***The results of these studies support the addition of information to the Rapamune labeling regarding safety and pharmacokinetics in children.***
- ***Information on the use of sirolimus in the children studied, and its potential hazards should be included in the label.***

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/s/

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