MEMORANDUM

DATE: December 28, 2001

TO: Antiviral Drugs Advisory Committee members

FROM: Marc Cavaillé-Coll, M.D.,Ph.D.
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SUBJECT: Clinical/Statistical Background Information for January 24, 2002 Advisory Committee Meeting

Drug name: Rapamune® (sirolimus) Oral Solution
NDA-21-083

Indication: Cyclosporine withdrawal at 2 to 4 months after transplantation

Applicant: Wyeth-Ayerst Laboratories

I. Introduction:

Rapamune® (sirolimus) Oral Solution was approved in 1999 for the prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that Rapamune be used in a regimen with cyclosporine and corticosteroids. A daily maintenance oral dose of 2 mg is recommended for use in renal transplant patients, with a loading dose of 6 mg. Although a daily maintenance dose of 5 mg, with a loading dose of 15 mg was used in clinical trials of the oral solution and was shown to be safe and effective, no efficacy advantage over the 2 mg dose could be established for renal transplant recipients. Patients receiving 2 mg of Rapamune Oral Solution per day demonstrated an overall better safety profile than did patients receiving 5 mg of Rapamune Oral Solution per day. In controlled clinical trials with concomitant cyclosporine, and corticosteroids, mean sirolimus whole blood concentrations, as measured by immunoassay, were 9 ng/mL (range 4.5-14 ng/mL [10^{th} to 90^{th} percentile]) for the 2 mg/day treatment group, and 17 ng/mL (range 10-28 ng/mL [10^{th} to 90^{th} percentile]) for the 5 mg/day dose. (See current approved package insert included in the Appendix to this memorandum).

A brief description of the phase III clinical trials that supported this approval is included in the Clinical Studies section of the approved package insert. More information on FDA's analyses of these studies is included in the July 19, 1999, memorandum to the Antiviral Drugs Advisory Committee, which is included in the Appendix to this memorandum. In phase III studies, mean serum creatinine was increased and mean glomerular filtration rate was decreased in patients treated with Rapamune and cyclosporine compared to those treated with cyclosporine and azathioprine or placebo controls (See Tables XII to XIX of the July 19, 1999 memorandum). It was observed in

those double blind studies that mean whole blood trough cyclosporine concentrations tended to remain at or above the upper limit of the protocol specified target concentrations ranges through the first 12 months post transplantation. However, there were no significant differences in cyclosporine doses or trough levels across the treatment groups.

II. Proposed Labeling Change

The applicant is proposing to modify this indication to allow consideration of cyclosporine withdrawal at 2 to 4 months after transplantation. To support the proposed change the applicant has submitted the results of two clinical studies that evaluated the safety and efficacy of cyclosporine withdrawal while using concentration-controlled sirolimus, study 310 and study 212. In study 310 the dosage of sirolimus was increased after cyclosporine withdrawal, and adjusted to maintain whole blood trough concentrations (measured by immunoassay) in the range of 20 to 30 ng/mL. In study 212 the dosage of sirolimus was increased after cyclosporine withdrawal, and adjusted to maintain whole blood trough concentrations (measured by immunoassay) in the range of 10 to 20 ng/mL. The applicant is recommending a target concentration range of 15 to 25 ng/mL (immunoassay) for concentration-controlled sirolimus, when used without cyclosporine. We are in general agreement with the applicant's description of these studies and the reported results in their Summary for the FDA Advisory Committee.

III. FDA Analyses

The analyses that we will present at the advisory committee meeting will focus on renal function (calculated glomerular filtration rate [GFR]), rates of acute rejection after cyclosporine discontinuation, patient and graft survival, as well as the safety profile of the regimens, with special emphasis on the types of adverse events that are associated with sirolimus or cyclosporine.

It is noted that the proposed therapeutic window for sirolimus is similar to the range of concentrations observed in the groups treated with 5 mg of sirolimus per day in the earlier phase III studies, and would represent a higher exposure to sirolimus than observed at the approved recommended dose of 2 mg per day (See Blood Concentration Monitoring in the DOSAGE AND ADMINISTRATION section of the appended approved package insert). Particular attention will be paid to decreases in platelets and hemoglobin and elevation of triglycerides and cholesterol that occurred in a dose related manner in patients receiving sirolimus in the earlier phase III studies.

The overall exposure to cyclosporine measured as whole blood trough concentrations was lower during the months prior to randomization and in patients randomized to cyclosporine maintenance in open-label studies 310 and 212 compared to the exposures observed in the earlier double blind phase III studies. In studies 212 and 310, the majority of the patients maintained whole blood cyclosporine concentrations within the targeted concentration range. Despite lower cyclosporine concentrations, the calculated GFR in the groups treated with sirolimus and cyclosporine were similar to those observed

in the earlier phase III studies (See Tables 6.4.4.2A and 6.4.4.2B in the applicant's summary).

The applicant's summary analyses of renal function include only observed mean values for on-therapy patients. Therefore patients who may have discontinued study drug or dropped out due to worsening renal function and/or rejection are not included in these analyses. Exploratory sensitivity analyses using standard approaches to account for missing observations will be presented.

Episodes of acute rejection are a potential concern after randomization to cyclosporine withdrawal. In both study 310, and 212 an excess of acute rejection episodes were observed in the first few months after cyclosporine withdrawal compared to those who remained on sirolimus, cyclosporine and corticosteroids. Lack of statistically significant differences in rates of acute rejection after randomization do not allow one to assume that the rates are equivalent or that one is not inferior to the other. There may have been insufficient power to exclude a clinically significant difference. Overall, one may not be able to reliably exclude that cyclosporine withdrawal was inferior to cyclosporine maintenance, with respect to occurrence of acute rejection, because of the multiple comparisons, the low rate of events and relatively small sample size. Analyses of the effect of rejection on renal function will be considered.

The open-label design creates a potential for bias in the assessment and comparison of rates of acute rejection, because the investigator who is informed of the treatment assignment may make treatment or diagnostic decisions that ultimately influence the rate of rejection. Thus, differences of rejection rates after randomization should be interpreted with caution.

Attention will be paid to the selection criteria, and what populations were chosen for randomization to cyclosporine withdrawal. Your advice will be sought to explore whether it is possible to define up-front which populations are likely to benefit from cyclosporine withdrawal with concentration-controlled sirolimus, and which ones would be placed at an unacceptable risk.

IV. Potential Questions to the Committee

Tentative draft questions to the committee are included in this briefing package. These reflect the areas where we will seek your advice and comment. Finally, this supplementary application following the large phase III development program, which was presented to the committee on July 27, 1999, provides the opportunity to reflect on endpoints for clinical trials in maintenance immunosuppression in renal transplantation. We look forward to your comments and recommendations.

APPENDIX

1. Approved package insert for Rapamune® (sirolimus) Oral Solution and Tablets
2. July 19, 1999 Memorandum to the Antiviral Drugs Advisory Committee members