WYETH-AYERST RESEARCH

ORIGINAL

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Division of American Home Products Corporation

S REGULATORY AFFAIRS

May 28, 1999

NDA No. 21-083

Response to FDA Request

ORIG AMENDMENT

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

B2

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to your May 3, 1999 facsimile in which Dr. Tiernan (Medical Reviewer) and Dr. Dixon (Statistical Reviewer) requested additional information regarding their review of the NDA.

The purpose of this submission is to provide the final response (Question 1) to the May 3 facsimile. Questions 2-8 were previously submitted to the Division on May 24, 1999. For the purpose of facilitating your review, FDA's comment is restated in bold with our response provided immediately thereafter as follows:

1. **Please provide us with a list, and summary tables, of all the patients who developed post-transplant diabetes mellitus (PTDM) in studies 301 and 302. Include the investigator number, patient identification number, study drug dose, the day the patient was diagnosed with PTDM (post-transplant), race and gender. The definition to be used for PTDM will be the same as that used in the European multicenter, phase III study of tacrolimus in renal transplantation. PTDM occurs in a patient without a prior history of insulin-dependent diabetes or non-insulin dependent diabetes and who requires the use of insulin for 30 or more consecutive days (with less than 5 days of interruption) to maintain a normal, fasting blood glucose concentration.**

For the purpose of this analysis, patients were regarded as having diabetes mellitus prior to transplant if any of the following were true: 1) etiology of renal failure was diabetes mellitus; 2) physician comments prior to transplant cited a history of diabetes; and 3) use of any glucose-lowering medication prior to transplant (and prior to use of sirolimus). Prior, concomitant, and after therapy use of glucose lowering agents was defined internally by algorithms which tie drug use to study drug medication start and stop dates. We interpreted "the day the patient was diagnosed with PTDM" to be day 1 of the 30 day insulin-use period.

Those patients not regarded as having diabetes mellitus prior to transplant were examined for insulin use 30 or more consecutive days (with less than five days interruption). Twenty seven patients met the 30 day use of insulin criteria defined in the request, and are included in the listings and summaries attached. The rates of insulin use for 30 or more consecutive days varied between 0% use in the placebo arm, 2.0% in the azathioprine arm, 3.0% in the combined sirolimus 2 mg/day arms, and 4.6% in the combined sirolimus 5 mg/day arms. Rates of insulin use in blacks exceeded that in non-blacks. There were no significant differences in the rates of PTDM between arms for all patients, blacks, or females. The rates the use of insulin for 30 or more consecutive days in the sirolimus trials are comparable to the rates of 2.2% and 4.0% reported for CsA-treated patients in the European and U.S. multicenter tacrolimus trials, and are lower than the rates reported for the tacrolimus arms (8.3% and 19.9%, respectively).

In addition to the patients described above, there were 8 patients who used insulin, but in whom there was insufficient data to determine the duration of insulin use. One patient (302-3528), randomized to sirolimus 5 mg/day, received insulin concomitantly with blinded therapy, (recorded on her final "Concomitant Treatment Record" case report form), with no further data available to determine whether insulin was used 30 or more consecutive days. Another 7 patients (5 patients randomized to sirolimus 5 mg/day and 2 randomized to azathioprine) began insulin after discontinuing blinded therapy (recorded on their final "Concomitant Treatment Record" case report form), with no further data available to determine whether insulin was used 30 or more consecutive days.

Accordingly, attached for your review is a list and summary tables of all the patients who developed post-transplant diabetes mellitus (PTDM) in studies 301 and 302. Please note that the tables contain information relative to the variables as requested in the May 3, 1999 facsimile. The following pages are organized as follows:

Please note that it is the understanding of Wyeth-Ayerst that this submission completes all responses to clinical safety questions which have been forwarded to us. We trust that this response adequately addresses the Division's comments. If you have any questions regarding this submission, please contact me at (610) 902-3798.

We request that this information be incorporated in the above-referenced NDA.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek. Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho with 2 desk copies
rbb/336.doc

WYETH-AYERST RESEARCH

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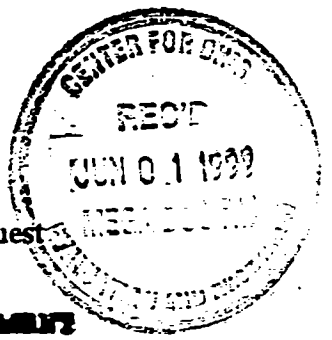
Division of American Home Products Corporation

REGULATORY AFFAIRS

ORIGINAL



May 28, 1999

NDA No. 21-083

Response to FDA Request

ORIG AMENDMENT

BP

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to our May 7, 1999 meeting which was held to discuss the re-analysis of the efficacy data relative to the pivotal Rapamune studies, studies 301 and 302. As a result of this meeting, Wyeth-Ayerst agreed to provide revised summaries containing the re-analysis of the efficacy data. Wyeth-Ayerst also stated that a revised pharmacokinetic/ pharmacodynamic analysis would be performed and submitted.

The purpose of this correspondence is to provide a report, GTR No. 37247, entitled, "*Updated Summary Report of Exploratory Pharmacodynamic Analysis of Sirolimus Based on Pooled Data of Protocols 301-US and 302-GL.*" As stated in this report, analyses were performed on the effect of drug concentrations on laboratory parameters (over 12 months) and acute rejection. The methods for safety assessments included descriptive frequency distribution analyses and stepwise linear mixed effect regression analyses of laboratory parameters verses drug (sirolimus and CsA) concentrations and demographic variables. The method for efficacy assessment included a stepwise logistic regression analysis of acute rejection verses drug concentrations and demographic variables. The analyses of safety and efficacy verses drug concentration were extended using a median-effect analysis. The clinical data used in the analyses were pooled from studies the Phase III safety and efficacy studies, studies 301 and 302.

Accordingly, attached please find GTR No. 37247 entitled, "*Updated Summary Report of Exploratory Pharmacodynamic Analysis of Sirolimus Based on Pooled Data of Protocols 301-US and 302-GL.*"

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho with 3 desk copies
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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

June 1, 1999

NDA No. 21-083

Response to FDA Request

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

DRUG AMENDMENT
AM

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to our May 7, 1999 meeting which was held to discuss the re-analysis of the efficacy data relative to the pivotal Rapamune studies, studies 301 and 302. Prior to the meeting, Wyeth-Ayerst informed the Division of a programming error which impacted the efficacy analyses. In the May 7 meeting, the Division suggested additional analyses which expanded the treatment window for acute rejection, a component of the composite primary efficacy endpoint. As a result of this meeting, Wyeth-Ayerst agreed to submit a revised Integrated Summary of Efficacy which would include the suggested re-analysis of the primary and secondary endpoints for studies 301 and 302.

The purpose of this correspondence is to provide the revised Integrated Summary of Efficacy. This document contains analyses based on databases reflective of the original 6 month database, identified as the prospective primary analysis, and a more extensive updated database, identified as the inclusive primary analysis. Furthermore, the inclusive analysis was conducted in accordance with the expanded treatment window analysis performed by Dr. C. Dixon, of your staff, as was discussed at the May 7 meeting and in follow-up teleconferences of May 13 and 14.

In summary, two analyses (prospective and inclusive) of the primary endpoint were performed that compared the incidence of the composite endpoint (efficacy failure) among treatment groups 6 months after transplantation. The composite endpoint was defined as the first occurrence of biopsy-confirmed acute rejection, graft loss or death. Biopsy-confirmed acute rejection was defined differently for the prospective and inclusive primary analyses; and each primary analysis used a different database: the prospective analysis used the original 6 month database and the inclusive analysis used the updated 6 month database.

The prospectively-defined primary analysis included patients with biopsy-confirmed acute rejection episodes that were treated within a 48 hour window from the time of renal biopsy; the data were taken from the original 6 month database and did not include any updated efficacy outcome data for any patient.

The inclusive primary analysis was based on a broader definition of biopsy-confirmed acute rejection (which included any patient with a biopsy positive for acute rejection, regardless of whether or not the rejection was treated) and a broader database that included verified updated 6 month efficacy outcome data.

The updated database was described in our April 30 letter and discussed at our May 7 meeting. In summary, the database was updated with information generated from queried efficacy endpoint designations to patients with missing efficacy data. For example, all patients identified as "lost to follow-up" in the original NDA, and declared as efficacy failures in the 12 month analysis of patient and graft survival, were located during the course of the NDA review. The endpoints of graft loss or death were verified for each of these patient and were included in the revised 12 month survival analyses. These analyses were previously submitted in our March 17, 1999 correspondence and are included in the six month efficacy analysis contained in the attached summary. Twenty-six (26) patients had updated information added to the 6 month database with regard to the 6 month efficacy outcome designation: ten (10) patients with missing efficacy data at 6 months who were initially counted as efficacy failures in the primary analysis subsequently had verification of the 6-month efficacy outcome as "no event" (n=9) or biopsy-confirmed acute rejection (n=1); 3 patients with an outcome of "biopsy-confirmed acute rejection" were subsequently found to have had graft loss before acute rejection; and 13 patients had an initial outcome of "no event" and were subsequently found to have had an episode of biopsy-confirmed acute rejection.

The inclusive analysis also permitted 24 patients who had biopsies positive for acute rejection to be represented after being excluded from the prospective primary analysis because treatment for acute rejection was not initiated within 48 hours of the biopsy procedure. Exclusion of these patients from the prospective primary analysis generated results that are incomplete because pertinent information relevant to an important efficacy variable (acute rejection) was suppressed as a result of the pre-defined definition of acute rejection in the prospective primary analysis. Although the prospective primary analysis was pre-defined and attempted to couple biopsy results and clinical symptoms/treatment, there are important factors that strongly argue to replace the original, narrowly-defined protocol definition of acute rejection with an inclusive definition (any biopsy that is histologically positive for acute rejection, regardless of treatment for acute rejection). These factors are discussed in detail in the attached integrated efficacy summary, section 8.7.4.6.2.

The revised Integrated Summary of Efficacy presents the results of both the prospective and inclusive primary analyses of studies 301 and 302. It is the inclusive analysis that is considered to be the most valid primary analysis of efficacy failure as it provides the most complete analysis of the efficacy of Rapamune. All secondary efficacy analyses were performed using the inclusive database. A brief summary of the pharmacokinetic and pharmacodynamic results based on the inclusive database is also provided.

Accordingly, we are submitting a revised integrated summary of efficacy which provides the re-analysis of the efficacy of studies 301 and 302 as described above. This revised summary concludes, as did the original NDA, that both the 2 mg/day and 5 mg/day doses are efficacious. It is recommended that the 2 mg/day be considered for the use in the majority of patients, and the 5 mg/day dose may provide an incremental benefit to patients at higher risk for acute rejection. It is anticipated that the two dose levels of Rapamune will adequately encompass the various clinical situations that are common in renal transplantation.

Finally, we are in the process of revising a risk/benefit to include further discussion of the utility of the 5 mg dose level. A revised Application Summary is also being prepared. These items will be submitted as discussed at our May 7 meeting.

Based on our discussions at the May 7 meeting, it is our understanding that this submissions is being considered a major clinical amendment. Please incorporate this information into the above referenced NDA.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho with 4 desk copies

bb/337.doc

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

June 4, 1999

NDA No. 21-083

Response to FDA Request

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to our May 7, 1999 meeting which was held to discuss the re-analysis of the efficacy data relative to the pivotal Rapamune studies, studies 301 and 302. As a result of this meeting, Wyeth-Ayerst agreed to provide revised summaries containing the re-analysis of the efficacy data. Wyeth-Ayerst also stated that a revised pharmacokinetic/ pharmacodynamic analysis would be performed and submitted.

The purpose of this correspondence is to provide a revised Item 6, Human Pharmacokinetic and Bioavailability Summary. Please note, the only change to this summary is section 6.1.10 entitled, "Brief Summary of PK and PD Conclusion." Section 6.1.10 has been replaced in its entirety and is a condensed summary of the pharmacokinetic/pharmacodynamic report previously submitted on May 28, 1999; GTR No. 37247, entitled, "*Updated Summary Report of Exploratory Pharmacodynamic Analysis of Sirolimus Based on Pooled Data of Protocols 301-US and 302-GL.*"

As stated in this summary, analyses were performed on the effect of drug concentrations on laboratory parameters (over 12 months) and acute rejection. The methods for safety assessments included descriptive frequency distribution analyses and stepwise linear mixed effect regression analyses of laboratory parameters verses drug (sirolimus and CsA) concentrations and demographic variables. The method for efficacy assessment included a stepwise logistic regression analysis of acute rejection verses drug concentrations and demographic variables. The analyses of safety and efficacy verses drug concentration were extended using a median-effect analysis. The clinical data used in the analyses were pooled from the Phase III safety and efficacy studies, studies 301 and 302.

Accordingly, attached please find the updated Item 6 to be incorporated into the above referenced NDA.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D Skowronek

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

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rbb/347.doc

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Division of American Home Products Corporation

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REGULATORY AFFAIRS

NEW CORRESP

NC

June 10, 1999

Response to FDA Request for Information

NDA No. 21-083

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to our April 13, 1999 teleconference with Drs. Cavaille-Coll, Tiernan, Mr Bacho, and representatives from Wyeth-Ayerst in which Dr. Cavaille-Coll encouraged Wyeth-Ayerst to submit an expanded discussion of the risk/benefit of Rapamune, particularly of the 5 mg group. The expanded risk/benefit was also briefly discussed at our May 7, 1999 meeting pertaining to the efficacy reanalyzes.

Accordingly, attached please find the revised Integrated Summary of Benefits and Risks. As discussed, the summary has been expanded overall, and includes a discussion of the benefits and risks of the 5 mg dose of Rapamune.

Please note that this document will also be part of the updated Application Summary which will be provided at a future date. Hence, the document is numbered as such.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

rbb/349.doc

cc. Mr. Matt Bacho with 4 desk copies

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Division of American Home Products Corporation

REGULATORY AFFAIRS

NEW CORRESP

NC

June 11, 1999

NDA No. 21-083

General Correspondence

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to our upcoming Subcommittee Meeting of the Antiviral Drugs Advisory Committee on Immunosuppressant Drugs, scheduled for Tuesday, July 27, 1999. In preparation for this meeting, we have prepared a briefing document summarizing key clinical pharmacokinetic, safety and efficacy data.

The purpose of the communication is to submit a draft of this briefing package for your review and comment. The attached briefing document contains: an executive summary followed by summaries of the clinical pharmacokinetic, safety, and efficacy data, and a risk/benefit discussion. Additionally a table of studies is provided. The summaries of the safety and efficacy of Rapamune primarily focus on our Phase III efficacy studies, studies 301 and 302.

We would appreciate receiving the Division's comments on the following topics:

1. Does FDA agree with the general presentation, organization, and content of the briefing document?

2. In reviewing the primary efficacy endpoint, we explain in section 7.2 (page 23) that the prospectively defined primary endpoint included a treatment window of 48 hours for acute rejection. However, as this definition resulted in an exclusion of a number of biopsy-confirmed acute rejections, we present the analysis which accounts for all biopsy-confirmed acute rejections, i.e. the "all-inclusive" analysis as presented in the revised integrated efficacy summary. We seek the Division's concurrence that the

presentation of the "all inclusive " analysis and all secondary analyses based on this definition is acceptable.

3. The safety summary discusses the cumulative safety data generated form studies 301 and 302, with supporting data from other sources presented in the context of selected safety topics. For example, the discussion of the effect of Rapamune on renal function (page 80) is presented in the context of the all the data that have been evaluated to date, including data from preclinical studies, Phase II studies, ongoing studies, and studies 301 and 302. Other safety topics are discussed in a similar manner. Does the Division agree with this approach?

We would appreciate receiving comments regarding the Advisory Committee Briefing Package by June 21, 1999. Your response by this timeframe will allow us to refine the document, as necessary, and forward copies to Ms. Rhonda Stover, Executive Secretary of the Antiviral Drugs Advisory Committee, by the date she has requested.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho with 11 desk copies

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Division of American Home Products Corporation

DRUG AMENDMENTS

B2

GULATORY AFFAIRS

June 14, 1999

NDA No. 21-083

Response to FDA Request

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
600 Fishers Lane
ockville, MD 20857

ear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, eviously submitted to your Administration on December 15, 1998.

Reference is also made to our May 7, 1999 meeting which was held to discuss the reanalysis the efficacy data relative to the pivotal Rapamune studies, studies 301 and 302. As a result of this eting, Wyeth-Ayerst agreed to provide a revised Application Summary incorporating the re-ılysis of the efficacy data.

The purpose of this submission is to provide the Division with a revised Application nmary. Many of the sections of the Application Summary were not affected by the efficacy ıalysis. As such, these sections are presented as originally submitted in our December 15, 1998 ıg. The remaining sections have been revised to reflect the reanalysis and/or to respond to :ific FDA requests. The updated sections are provided as follows:

Human Pharmacokinetics and Bioavailability Summary - The subsection 3.6.9 entitled, "Brief Summary of PK and PD Conclusions," has been updated as a result of the efficacy reanalysis. This updated summary was previously submitted in our correspondence of May 28, 1999 which provided the revised Item 6 Pharmacokinetic Summary. The PD summary in both the Application Summary and the Pharmacokinetic summary are the same aside from the differences ı the numbering of these documents.

Clinical Data Summary and Results of Statistical Analysis - The subsection 3.8.5 entitled, Integrated Summary of Efficacy," has been update to reflect the efficacy reanalysis. Aside om the numbering of this document, this summary is identical to the summary contained in the ıtegrated Summary of Efficacy which was previously submitted on June 1, 1999.

:lected Clinical Topics - This is a new section which was prepared to address a request of the ivision. This summary was previously submitted on May 21, 1999.

- Discussion of Benefit/Risk Relationship - This section, 3.10, has been revised to address the Division's request for an expanded discussion of the risk/benefit of Rapamune. This summary was previously submitted on June 10, 1999.

In addition, this application summary contains annotated labeling which was updated at the request of Dr. S. Bala and previously submitted on April 1, 1999. The section entitled, "Post Marketing Studies," is identical to that which was submitted in the original NDA, with the exception of the renumbering of the Application Summary. Finally, this Application Summary is provided in two volumes. These two volumes (volumes 2 and 2a) are meant to replace Volume 2 of the original application.

As discussed at our May 7 meeting, we in the process of revising our Package Insert to reflect the efficacy reanalysis and the long term safety data presented in our 3-month Safety Update. The revised Package Insert will be submitted in July.

It is our understanding that this submission fulfills our commitments made at our May 7, 1999 meeting. Please incorporate the attached volumes into the above referenced NDA.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

Mr. Matt Bacho with 10 desk copies
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WYETH-AYERST RESEARCH

Division of American Home Products Corporation

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US REGULATORY AFFAIRS

ORIGINAL

ORIG AMENDMENT

BM

June 14, 1999

Response to FDA Request

NDA No. 21-083

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to a June 11, 1999 request by Dr. Rosemary Tiernan regarding the supplemental volumes for the General Medical Reports (GMRs) for studies 301 and 302. Dr. Tiernan was inquiring about the location of supplemental volume 3 for each of these studies.

The purpose of this submission is to clarify that the information contained in supplemental volume 3 for each study is located in Item 11 (Case Report Tabulations). As a means of facilitating Dr. Tiernan's review, we are also providing the information on CD. This information is being provided on a single CD and is identical to the information presented in Item 11 of the NDA.

Accordingly, attached please find a single CD containing the following files:

- **301sv3.pdf** - Supplemental Volume 3 for Protocol 301.
- **301sv4.pdf** - Supplemental Volume 4 for Protocol 301. In order to be complete, this volume is being provided although not specifically requested
- **302sv3.pdf** - Supplemental Volume 3 for Protocol 302.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho
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WYETH-AYERST RESEARCH

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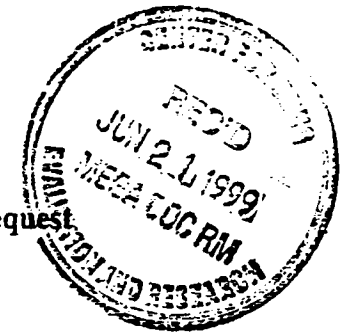
Division of American Home Products Corporation

REGULATORY AFFAIRS

BM



June 18, 1999

NDA No. 21-083

Response to FDA Request

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to a June 2, 1999 request by Dr. Marc Cavialle-Coll to provide Serum creatinine at 1 year on all patients, including those who did not remain on study drug. Along with this data, an analysis showing the proportion of patients with levels > 130 µm/L was also requested. The Division requested that this information be provided as a SAS dataset.

The purpose of this submission is to provide the requested datasets. The data are being provided on two disketes. The file names are CRE12_01 for Protocol 0468-E1-301 (Disk 1 of 2) and CRE12_02 for Protocol 0468-E1-302 (Disk 2 of 2).

The table in Attachment 1 provides a list of the variables included on the two diskettes. The window for 12 month visits is from Month 11 through 13. This was calculated as extending from Day 294 (28 days X 11 months - 14 days allowed for early visits) to Day 404 (30 X 13 +14). The study days are provided should the FDA wish to narrow the window. Not all patients have visits during Month 12. Where a patient is missing data, the SAS missing code, "." is provided.

Creatinine is provided in both international units and US units. The ratio of European values to US values is 88.4 for all values, the proper conversion factor.

ORIGINAL

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

June 21, 1999

NDA No. 21-083

Response to FDA Request

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to your May 28, 1999 request to provide additional data regarding the historical control data for the carcinogenicity studies in rats, which was previously submitted to the Division on April 1, 1999. In a June 7, 1999 teleconference, Dr. Kunder (Pharmacology/ Toxicology Reviewer) clarified that he wanted additional historical control data for the incidences of the individual diagnostic terms that comprised the general categories "degeneration" and "vascular mineralization." Although these individual diagnostic terms were listed in footnote "a" of Table 2.1 in the April 1999 submission, their respective incidences were not provided.

The purpose of this submission is to provide the historical control incidences of the individual diagnoses that were included in the general categories "degeneration" and "vascular mineralization." The requested information can be found in the attached document.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D Skowronek

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho
Rbb/356.doc

Rapamune (sirolimus) Oral Solution
NDA No. 21-083

In Protocol 301, 91.2% percent of patients had single values for the Month 12 observation. Of the remaining 8.8%, 44 patients had two values, 8 patients had three values, and 3 patients had four values. Since the existence of multiple values at 12 months may be informative, all values are provided for patients with multiple values as separate observations. A switch variable, VALUE_TO, is provided to indicate the number of multiple values a patient has. An index variable, VALUE_IN, indicates the number of the observation. Hence a patient with three observations will have a VALUE_TO of 3 and each value will be identified under VALUE_IN as 1, 2, or 3. A patient with a single observation will have the single value of 1 for both VALUE_TO and VALUE_IN.

Summary statistics of multiple observations are provided on each line for all patients. Thus, if a patient had three observations, the average, smallest, and largest of all observations is provided on each line. Patients with only one observation have these summary statistics as well; in the case of patients with one observation, each summary statistic is equal to the single value.

Additionally, SAS code is provided to extract SAS datasets from the dataset provided on the diskette, addressing the patients with multiple observations in three different ways. This code is provided in Attachment 2.

Accordingly, attached please find:

1. Diskette 1 of 2: CRE12_01 for protocol 301-US.
2. Diskette 2 of 2: CRE12_02 for protocol 302-GL.
3. Attachment 1: Table of variables.
4. Attachment 2: SAS code.
5. Attachment 3: PROC CONTENTS for CRE12_01.
6. Attachment 4: PROC CONTENTS for CRE12_02.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho
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Division of American Home Products Corporation

§ REGULATORY AFFAIRS

June 25, 1999

NDA No. 21-083

Response to FDA Request

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to your June 2, 1999 request to provide additional information specific to acute rejection data. Dr. Cavialle-Coll requested that Wyeth-Ayerst provide a dataset showing patients with biopsy confirmed acute rejection in the first six months, and how this relates to multiple rejection episodes. This should be demonstrated by showing the number of rejections episodes experienced after patients had a single episode. Additionally, he is interested in rejection episodes during months 7-12. Specifically, if patients with late rejection episodes have a worst prognosis than those with early rejection episodes.

The purpose of this submission is to provide the requested acute rejection information. This information is being provided as a single dataset on two diskettes. Studies 301 and 302 are presented separately.

Accordingly, attached for your review please find the following items:

- Diskette 1 of 2 - File AR_301 which contains acute rejection data for study 301.
- Diskette 2 of 2 - File AR_302 which contains acute rejection data for study 302.
- Table of Variables describing how the datasets are organized.
- PROC CONTENTS for AR_301.
- PROC CONTENTS for AR_302.

Ramapume (sirolimus) Oral Solution
NDA No. 21-083

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Mary D. Sucholl for

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho

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Division of American Home Products Corporation

REGULATORY AFFAIRS

June 29, 1999

NDA No. 21-083

Response to FDA Request

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

ORIG AMENDMENT

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to a June 21 telephone conversation held with Mr. Matt Bacho and Dr. Rose Tiernan of your staff and Ms. Maureen Skowronek of Wyeth-Ayerst Research, in which the Division requested additional safety data relative to Rapamune studies 301 and 302. Specifically, Dr. Tiernan requested that we provide a list of information containing the following parameters: patient ID; date of transplant; study treatment assignment; name of lipid lowering agent used during the study; and the start date for the lipid lowering agent.

The purpose of this submission is to provide the requested information. Attachment 1 contains the request listings for study 301, and Attachment 2 contains the requested listing for study 302. Please note that within each study, the entries are presented by treatment group and patient ID number.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho
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Division of American Home Products Corporation

REGULATORY AFFAIRS

July 9, 1999

NDA No. 21-083

Response to FDA Request

ORIG AMENDMENT

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to your June 22, 1999 facsimile which provided questions from Dr. Kofi Kumi (Clinical Pharmacology Reviewer) relative to his review of the NDA. For the purpose of facilitating your review, FDA requests are provided in bold with our responses provided immediately thereafter.

1. **Separate results of the pharmacokinetic/pharmacodynamic analysis for studies 301 and 302.**

   The individual pharmacokinetic/pharmacodynamic analyses for studies 301 and 302 will be provided under separate cover.

2. **Comparisons of whole blood sirolimus AUC, Cmax, and Cmin (24 hours) for individual patients among blacks and non-blacks from studies 301 and 302.**

   Provided for your review is a single CD containing 8 spreadsheet files containing the requested information. Results are broken out by study and the files are provided in two directories, S301 and S302. All files are formatted as Microsoft Excel spreadsheets. In order to facilitate the review of these files, Attachment 1 contains a table listing a description of the variables contained in the electronic files. Specifically, contained on the CD are the following files:

Directory	File	File Content
S301	S301_CON.XLS	Whole Blood SRL and CsA concentrations on PK days.
	S301_DEM.XLS	Demographic characteristics
	S301_PRM.XLS	Whole blood SRL and CsA PK parameters on PK days (C_{max}, t_{max}, $C_{min,ave}$, $C_{min,24h}$, AUC, CL/F/W)
	S301_TRG.XLS	Whole Blood SRL and CsA Trough Concentrations for individual patients over time
	S301_TRAG.XLS	Whole Blood SRL and CsA derived average trough concentrations ($C_{min,ave}$ and $C_{min,TN}$)
S302	S302_DEM.XLS	Demographic characteristics
	S302_TRG.XLS	Whole Blood SRL and CsA Trough Concentrations for individual patients over time
	S302_TRAG.XLS	Whole Blood SRL and CsA derived average trough concentrations ($C_{min,ave}$ and $C_{min,TN}$)

Please note that study 301 contains two files entitled S301_CON.XLS and S301_PRM.XLS that do not appear for study 302. These files contain the sirolimus and cyclosporine whole blood concentrations and PK parameters on sampling days and do not appear for study 302 because full PK analyses were not part of the protocol.

3. **Comparisons of whole blood cyclosporine AUC, Cmax, and Cmin (24 hours) for individual patients among blacks and non-blacks from studies 301 and 302.**

   Same response provided above for question 2.

4. **Include a graphical presentation as provided for the Cl/F in the NDA.**

   Attachment 2 contains 32 figures showing sirolimus and cyclosporine PK parameters and trough concentrations by race (blacks vs. non-blacks). As requested, the figures are broken out by study and compare results between blacks and non-blacks. A table showing the description of each figure can be found in the beginning of the attachment.

Accordingly, attached for your review are the following:

- CD containing the requested patient listings in Excel format.
- Attachment 1 – Description of variables contained in the electronic files.
- Attachment 2 – PK and trough sirolimus and cyclosporine figures.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy
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REGULATORY AFFAIRS

July 13, 1999

Response to FDA Request

NDA No. 21-083

CMC AMENDMENT

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to a July 6, 1999 request by Dr. Tiernan (Medical Reviewer) relative to her review of the NDA. Dr. Tiernan stated that she would like to better understand how patients were managed once their blood cell counts required dose adjustment or other management alternatives. As such, she requested that Wyeth-Ayerst provide patient line listing including the following parameters: patient ID, date of transplant, study treatment assignment, race, time to event, level of the change, level of the treatment dose reduction, time to recovery, length of time the patient was required to stay at the reduced treatment level. Dr. Tiernan advised the use of cutoff values of less than 75,000 for thrombocytopenia, and less than 3,000 for leukopenia.

The purpose of this submission is to provide the requested information. Attached are listings of patients who had either a platelet count of ≤75,000 or white blood cell count of ≤ 3000/mm^3. The listings include demographic information, date of transplant, study medication day, dosing history, listing of laboratory results by date and relative day (based upon day 1 being the first day of dosing study medication). The data represent ≥one-year results. Please note that the platelet results are reported in 10^9/L units and the WBC in 1000/mm^3 units.

Upon review of the data, it is notable that that decreases in platelet counts and decreases in WBCs are, for the most part, independent of one another. One can observe numerous examples of reduced platelet counts responding to Rapamune dose reduction, temporary discontinuation or permanent discontinuation. Reduced WBC below 3000/mm^3 occurred less frequently than reduced platelet counts. There are also illustrative cases demonstrating that reduced WBCs respond to Rapamune dose reduction or discontinuation.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek. Director
U.S. Regulatory Affairs

Mr. Matt Bacho with 1 desk copy
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Division of American Home Products Corporation

REGULATORY AFFAIRS

July 14, 1999

NDA No. 21-083

Response to FDA Request

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to your June 22, 1999 facsimile which provided questions from Dr. Kofi Kumi (Clinical Pharmacology Reviewer) relative to his review of the NDA. On July 13, 1999 responses to questions 2-4 were provided to the Division. The purpose of this submission is to provide the response to question 1. For the purpose of facilitating your review, FDA's request is provided in bold with our response provided immediately thereafter.

1. **Please separate the results of the pharmacokinetic/pharmacodynamic analysis for studies 301 and 302.**

   The individual pharmacokinetic/pharmacodynamic analyses for studies 301 and 302 are attached as follows:

   - Volume 1 - pharmacokinetic/pharmacodynamic analysis for study 301.
   - Volume 2 - pharmacokinetic/pharmacodynamic analysis for study 302.

This submission completes our response to all questions received to date.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy
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