WYETH-AYERST RESEARCH

BOX 8299 • PHILADELPHIA PA 19101-8299 • (610) 902-5710
FAX (610) 964-5973

Division of American Home Products Corporation

REGULATORY AFFAIRS

ORIGINAL

March 29, 1999

NDA No. 21-083

Response to Request for Information

NDA ORIG AMENDMENT

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration (HFD-590)
Center for Drug Evaluation and Research
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, Rapamycin) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to your facsimile dated February 4, 1999 in which Dr. Norman Schmuff and Dr. Mark Seggel requested specific information relative to the chemistry review of the NDA. On February 17, 1999 a portion of that request was submitted to the Division. At that time, the case for the syringe was not available. The purpose of this submission is to provide the outstanding information. In order to facilitate your review, FDA's comments have been stated in bold, with our responses immediately thereafter.

1) **Please provide us with samples of the drug product container/closure (i.e. 2 and 5 oz. bottles with closures, syringe adapters/bottle dosing inserts, disposable syringes and caps, case for syringe, and foil pouches).**

The following Rapamune Oral Solution packaging components are included with this submission in duplicate:

- Case for disposable syringes.

The following Rapamune Oral Solution packaging components were previously provided on February 17, 1999.

Rapamune Bottles

5 oz. and 2 oz. round

5 oz. and 2 oz. bottle inserts.

Child Resistant Closure for the 5 oz. and 2 oz. bottles.

3 mL amber syringe with

5 mL amber syringe with

Rapamune Foil Pouches

1 mL foil pouch with water.

2 mL foil pouch with water.

5 mL foil pouch with water.

If there are 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/296.doc

cc. Mr. Matt Bacho, Project Manager, with 1 Desk Copy

WYETH-AYERST RESEARCH

ORIGINAL

PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

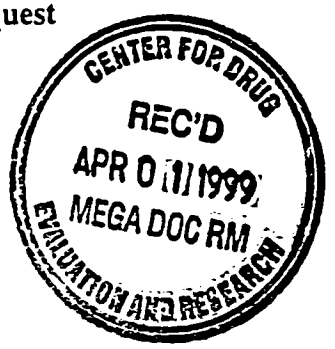
AFFAIRS

March 31, 1999

No. 21-083

Response to FDA Request

BS



Goldberger, M.D., Director
ion of Special Pathogens and Immunologic Drug Products
and Drug Administration
:r for Drug Evaluation and Research (HFD-590)
N: Document Control Room
Fishers Lane
:ville, MD 20857

: Dr. Goldberger:

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

The purpose of this submission to provide our response to a requests made during our rch 26, 1999 teleconference. Dr. Tiernan (Medical Reviewer) and Dr. Dixon (Statistician), uested that Wyeth-Ayerst provide a PROC CONTENTS for each dataset file contained within ISS database.

Accordingly, attached for your review is:

- PROC CONTENTS for all ISS dataset files.

We trust that our responses adequately address the Division's comments. If you have any iestions regarding this submission, please contact me at (610) 902-3798.

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

Sincerely,

WYETH-AYERST LABORATORIES

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

cc. Mr. Matt Bacho w/ 5 desk copies
rbb/300.doc

WYETH-AYERST RESEARCH

ORIGINAL

BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

REGULATORY AFFAIRS

April 1, 1999

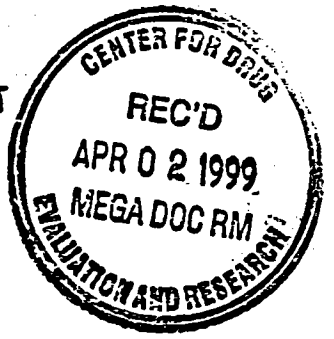
NDA No. 21-083

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

CDER AMENDMENT

BM



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.

The purpose of this submission to provide responses to requests made during the course of the Divisions review of our NDA. For the purpose of facilitating your review, FDA's comments are stated in bold, with our responses provided immediately thereafter. Responses are organized by the date they were received.

February 17, 1999 Teleconference:

1) **On February 17, a teleconference was held to discuss the 14 patients identified as lost to follow-up from the pivotal studies, Protocols 301 and 302. The Division requested graft and patient survival data be obtained for these 14 patients.**

Patient and graft survival data has now been obtained for all patients. These data are located in Attachment 1. These data were previously provided to the Division via facsimile on March 25, 1999.

larch 2, 1999 facsimile:

) **Wyeth-Ayerst is requested to provide historical control data on the incidence of testicular adenoma and related effects in rats.**

Our response is found in Attachment 2.

2) **Provide the following additional information regarding the safety report of increased incidence of hepatic thrombosis in liver transplant patients submitted in IND No. [redacted] (Serial No. 396).**

- **cold ischemia time for the donor liver**
- **age of the person who served as the liver donor**
- **type of surgical anastomosis used at the time of liver transplantation**

The requested information is provided in Attachment 3. Under separate cover, this information will be submitted to the IND for the sake of maintaining a complete file.

3) **As part of the review of NDA No. 21-083, the Division will consider the incidence of renal artery thrombosis, renal vein thrombosis, deep venous and superficial thrombosis in the renal transplant study patients on Rapamune® and cyclosporine with the azathioprine and placebo controls. Please summarize and submit this information for review.**

The summarized data is contained in Attachment 4.

) **Regarding the Advisory Committee Briefing Package, the Division suggests the following topics:**

a) **justification and rationale for dosing recommendations;**
b) **rationale for using a fixed dose of Rapamune, rather than adjusting the drug by monitoring blood levels;**
c) **discuss the efficacy and safety of Rapamune - especially in African-American patients.**

An outline of the Advisory Committee Briefing Package will be submitted under separate cover.

Although not considered a study endpoint, an issue of scientific interest is whether the incidence of rejection in the period 7-12 months post-transplantation may be predictive of chronic rejection. Data on rejection from study 301 and 302 during this time period, should be submitted, if available, for review.

The requested data on incidence of acute rejection in the period of 7-12 months is provided in Attachment 5.

March 11, 1999 Teleconference

1) **In a March 11, 1999 teleconference, the Division requested that Wyeth-Ayerst provide an updated label with the Mechanism of Action section annotated.**

Updated labeling including annotation of the Mechanism of Action section was sent to the Division via facsimile on March 25, 1999. Attachment 6 contains a copy of the updated label. No changes were made to the contents of the label.

March 26, 1999 Teleconference

) **Please provide the files "patlabs.xpt" as three separate transport files. The data should be organized by protocol; a file containing 301 data, a file containing 302 data, and a file containing all other protocol information.**

A tape containing the requested files was sent to the Division on March 31, 1999. Ms. D. Lorenz, FDA Information Technology, will receive the tape and transfer the files onto the Rapamune ERS.

In summary, attached are the following:

tle	Attachment
llow-up for patients in Protocols 301 and 302 who were originally identified lost to follow-up	1
storical control data on the incidence of testicular adenoma and related effects rats.	2
ormation regarding the safety report of increased incidence of hepatic mbosis in liver transplant patients filed to IND [redacted]	3
idence of renal artery thrombosis, renal vein thrombosis, deep venous and erficial thrombosis.	4
a on incidence of acute rejection in the period of 7-12 months.	5
lated label with the Mechanism of Action section annotated.	6

We trust that our responses adequately address the Division's comments. If you have any questions regarding this submission, please contact me at (610) 902-3798.

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

Sincerely,

WYETH-AYERST LABORATORIES

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

c. Mr. Matt Bacho w/ 5 desk copies

7297.doc

WYETH-AYERST RESEARCH

ORIGINAL

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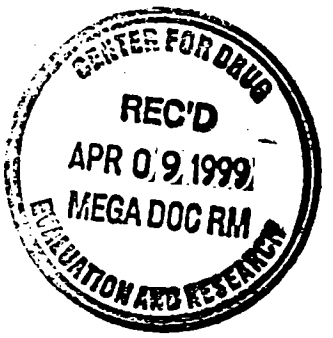
Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS



April 8, 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

NEW CORRESP
NC

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 March 31, 1999 request to provide Case Report Forms (CRFs) for patients who were lost to follow-up for studies 301 and 302. Data on graft and patient survival of the 14 patients lost to follow-up was submitted to the NDA on April 1, 1999. The purpose of this submission is to provide the request CRFs on a single CD ROM.

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

rbb.307.doc

WYETH-AYERST RESEARCH

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FAX: (610) 964-5973

Division of American Home Products Corporation

LEGAL AFFAIRS

April 8, 1999

IDA No. 21-083

Response to FDA Request

ORIG AMENDMENT

BI

lark Goldberger, M.D., Director
ivision of Special Pathogens and Immunologic Drug Products
ood and Drug Administration
enter for Drug Evaluation and Research (HFD-590)
TTN: 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, reviously submitted to your Administration on December 15, 1998.

Reference is also made to an April 2, 1999 telephone conversation with Mr. Bacho and r. Shukal Bala (microbiology reviewer). Dr. Bala stated that during her review, she came across a TR (GTR No. 23209; Volume 18 pg 276-294) which was missing the seven figures which should e appended to the GTR. This submission provides the GTR in its entirety, including the appended gures.

Additionally, in a March 29, 1999 telephone conversation with Mr. Bacho and Dr. Bala garding the annotations of the package insert reflective of the subsection entitled. "Mechanism of ction," Dr. Bala requested we provide reports for IL-7 and IL-4 studies. Further, she would like s to provide reports for studies pertaining to mTOR (mammalian Target of Rapamycin), and entify/provide the specific reports relative to the initial annotated review article.

In a March 26, 1999 communication, Mr. Bacho requested a listing of all the harmacology / Toxicology amendments which were filed to IND [redacted] Rapamune Oral.

Accordingly, attached please find the following attachments:

April 2, 1999 Telephone Conversation

1. **GTR 23209 (Volume 18 pg 276) - Rapamycin Inhibits Arterial Intimal Thickening Caused by Both Alloimmune and Mechanical Injury: Effect on Cellular, Growth Factor, and Cytokine Responses in Injured Vessels - with appended figures.**

March 29, 1999 Telephone Conversation

2. **IL-2 and IL-4 Double Knockout Mice Reject Islet Allografts: A Role for Novel T Cell Growth Factors in Allograft Rejection.**

   This paper defines the role of IL-7 in allograft rejection and the study demonstrates that Rapamune blocks IL-7 and IL-15 mediated graft rejection. Since graft rejection in mediated by T cell activation by IL-7 and IL-15 in absence of IL-2 and IL-4, it is shown that Rapamune has an effect on IL-7 induced T cell activation

3. **GTR 23220 (Volume 14; Page 123) - Anti-CD28 Antibody and IL-4 Induced Human T-Cell Proliferation is Sensitive to Rapamycin.**

4. **Mammalian Target of Rapamycin: Immunosuppressive Drugs Uncover a Novel Pathway of Cytokine Receptor Signaling.**

   This review describes the effects of mTOR in renal transduction and the blockage by Rapamune.

5. **Isolation of a Protein Target of the FKBP12-Rapamycin Complex in Mammalian Cells.**

   This paper reports the identification and isolation of mTOR.

The requested information pertaining to the initial review article is not provide in this submission. We are in the process of locating the 69 references and have noted in our review that many of them were included with the original NDA. A complete update regarding this information will be provided under separate cover.

March 26, 1999 Communication

6) **A report listing all of the pharmacology / toxicology amendments filed to IND Rapamune Oral.**

Accordingly, contained within this submission is:

Title	Attachment
TR 23209 (Volume 18 pg 276) - Rapamycin Inhibits Arterial Intimal Thickening aused by Both Alloimmune and Mechanical Injury: Effect on Cellular, Growth actor, and Cytokine Responses in Injured Vessels - with appended figures.	1
L-2 and IL-4 Double Knockout Mice Reject Islet Allografts: A Role for Novel Cell Growth Factors in Allograft Rejection.	2
Mammalian Target of Rapamycin: Immunosuppressive Drugs Uncover a Novel athway of Cytokine Receptor Signaling.	3
solation of a Protein Target of the FKBP12-Rapamycin Complex in Mammalian ells.	4
TR 23220 (Volume Page 123) - Anti-CD28 Antibody and IL-4 Induced Human T-Cell Proliferation is Sensitive to Rapamycin.	5
Complete Listing of Pharmacology / Toxicology Amendments Filed to IND	6

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

bev/304.doc
cc. Mr. Matt Bacho with 2 desk copies

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

ORIGINAL

April 12, 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
EM

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.

In a March 24 communication, Mr. Matt Bacho, Project Manager, conveyed the request of Dr. Rosemary Tiernan, medical reviewer, relative to the incidence of pneumonia in the Phase III studies, Protocols 301 and 302. In reviewing the 3 month safety update, Dr. Tiernan noted the higher incidence of pneumonia in the 5 mg sirolimus group. In order to have a better understanding of whether the cases of pneumonia represent community acquired pneumonia or opportunistic infections, information relative to the patient's treatment assignment, the type of pneumonia (bacterial, fungal, or parasitic), and the associated organism, if known, should be provided. Case Report Forms (CRFs) for these patients were also requested.

The purpose of this submission is to provide the requested pneumonia data. Attached are four tables in response to the FDA request for additional information regarding patients with pneumonia. Table 1 includes the investigator and patient number by treatment group for patients tabulated in Table 12 of the 90-day Safety Update.

Table 2 includes the additional information about patients which the reviewer requested. The reviewer should be reminded that Pneumocystis carinii pneumonia was tabulated separately in Table 12 of the 90-day Safety Update. The reviewer should also be advised that CMV pneumonia is a subset tabulated under CMV infection (tissue invasive) in the same table. The number of cases of CMV pneumonia were the following: sirolimus 2 mg/day - one case, sirolimus 5 mg/day - three cases, azathioprine - 0 cases and placebo-two cases.

Upon further review of the safety data it became clear that the guidelines for selecting patients for Table 12 in the 90-day Safety Update were very restrictive. Therefore the 12-month database was thoroughly reviewed and additional patients with documented pneumonia (or

systemic opportunistic infections which included lung involvement) were identified. These patients are listed in Table 3 by treatment group. The details of these cases are described in Table 4. The additional cases were tabulated in Table 11 of the 90-day Safety Update under a variety of COSTART terms such as infection, sepsis or pneumonia. Many of the patients are also listed in Table 28 of the 90-day Safety Update - Life-threatening events.

The combined data from Table 2 and Table 4 reveals that fungal and mycobacterial infections occurred in all treatment groups. Of the patients with mycobacterial infections involving the lungs, all but two patients in the sirolimus 2 mg/day treatment group had study drug discontinued at least fifty days before the event.

It should also be noted that one patient (30238-3815) in the 2 mg/day sirolimus group developed renal and pulmonary tuberculosis while on therapy in the second year of the trial.

Three additional patients had extra-pulmonary tuberculosis. Patient 30149-4903, who had been off sirolimus 2 mg/day for 326 days, developed tuberculosis arthritis. Patient 30153-5322 developed hepatic tuberculosis while receiving sirolimus 5 mg/day. Patient 30153-5313 developed tuberculosis osteomyelitis during the second year of treatment with sirolimus 5 mg/day.

In summary fungal, mycobacterial and other opportunistic pneumonias occurred in all treatment groups but represented a small percentage of the documented pneumonia. Mycobacterial infections of all types were observed, mostly in sirolimus-treated patients, but four of the nine sirolimus-treated patients were off drug for at least 50 days when the events occurred. None of the patients with mycobacterial infections in the first 12 months died as a result of their infection.

Please note, electronic Case Report Forms (CRFs) for these patients will be provided on CD ROM under separate cover.

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 2 desk copies
rbb/308 doc

WYETH-AYERST RESEARCH

ORIGINAL

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Division of American Home Products Corporation

REGULATORY AFFAIRS

NDA ORIG AMENDMENT

FM

April 13, 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.

In a March 24 communication, Mr. Matt Bacho, Project Manager, conveyed the request of Dr. Rosemary Tiernan, medical reviewer, relative to the incidence of pneumonia in the Phase III studies, Protocols 301 and 302. In reviewing the 3 month safety update, Dr. Tiernan noted the higher incidence of pneumonia in the 5 mg sirolimus group. In order to have a better understanding of whether the cases of pneumonia represent community acquired pneumonia or opportunistic infections, information relative to the patient's treatment assignment, the type of pneumonia (bacterial, fungal, or parasitic), and the associated organism, if known, should be provided. Case Report Forms (CRFs) for these patients were also requested.

An April 12, 1999 submission provided the requested pneumonia data. In summary, fungal, mycobacterial and other opportunistic pneumonias occurred in all treatment groups but represented a small percentage of the documented pneumonia. Mycobacterial infections of all types were observed, mostly in sirolimus-treated patients, but four of the nine sirolimus-treated patients were off drug for at least 50 days when the events occurred. None of the patients with mycobacterial infections in the first 12 months died as a result of their infection.

The purpose of this submission is to provide the electronic Case Report Forms (CRFs) for these patients. This information is being provided on a single CD ROM.

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

April 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

[redacted]

BM

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.

On April 13, 1999 a teleconference was held between Wyeth-Ayerst and the Division to discuss some of the technical issues relative to the SAS datasets and the ERS. During the teleconference, Dr. Tiernan, Medical Reviewer, asked if a case report tabulation (CRT) for transplant recipient listings could be provided. Specifically, Wyeth-Ayerst should provide panel reactive antibody listings by demographic analysis for study 301.

The purpose of this submission is to provide the requested case report tabulation for Protocol 301. This information is being provided on a single diskette which has been check for viruses and confirmed to be negative.

Additionally, in an April 8, 1999 teleconference, Dr. Cavaille-Coll requested that we provide demography and draft analyses by race data from Protocol No. 0468H1-309-US. Protocol 309 is the pivotal trial to support the NDA for Rapamune Oral Tablets. This study compares the 2 mg oral solution to the 2 mg tablet. The requested information is provided in Attachment 1 and was previously sent via facsimile to the Division on April 14, 1999.

Accordingly, this submission contains:

- Case Report Tabulation (CRT) for transplant recipient listings. This information is provided in a 3.5 inch diskette containing the file trnspln1.pdf.
- Preliminary results of demography and draft analysis by racy for Protocol 309.

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 w/ 1 desk copy

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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

April 26, 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
BC

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 February 4, 1999 facsimile received from Mr. Matt Bacho, Project Manager in you Division, which stated requests from the reviewing chemist, Dr. Mark Seggel. The requests were limited to Wyeth-Ayerst providing samples of the drug product container/closures and additional real time stability data to support the requested 24 month expiry dating. The requested container/closure materials were previously provided on February 17 and March 29, 1999.

In our February 17, 1999 submission we committed to providing 18 month stability data by April 30, 1999. Accordingly, the purpose of this submission is to provide the updated stability data. In the original filing of this NDA,

A

statistical analysis of the data is included in this report (please refer to page 73).

It is our understanding that with this response we have completely satisfied the Division's February 4, 1999 requests.

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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FAX: (610) 964-5973

Division of American Home Products Corporation

VP REGULATORY AFFAIRS

April 28, 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 April 16, 1999 teleconference relative to our revised efficacy analysis of studies 301 and 302, and our April 23, 1999 teleconference in which we discussed our plans to provide FDA with updated statistical datasets and programming code in order to verify the safety and efficacy analyses.

The purpose of this submission is to provide the Division with six revised statistical datasets. The revised datasets are being provided on two (2) diskettes. The first diskette contains three datasets for Protocol No. 0468E1-301-US and the second diskette contains the same three datasets for Protocol No. 0468E1-302-GL. The specific files contains on these diskettes are:

Dataset Name	Description
PRIMFLRV	Primary Endpoint Dataset
TRTFLSRV	Treatment Failure Endpoint Dataset
ARFILERV	"All" Rejection Endpoint Dataset

The primary endpoint of the study is a composite endpoint of, the first incidence of biopsy confirmed acute rejection, graft loss, or death. The treatment failure endpoint is the first of biopsy confirmed acute rejection or dose termination for any reason. The "all" rejection endpoint is the first of either biopsy confirmed or presumptive acute rejection; where patients had both of these endpoints, the endpoint indicates biopsy confirmed acute rejection.

Additionally, along with the two diskettes, you will find the PROC CONTENTS of these data files. The PROC CONTENTS documentation, provided in hard copy, gives the variable names in coding analyses, the description of the variables, and the format of the data (character, numeric, or date). In addition, a listing of the first ten cases of the data is also provided.

Accordingly, attached please find:

- Diskette containing three revised datasets for Protocol 301-US.
- Diskette containing three revised datasets for Protocol 302-GL.
- PROC CONTETS for each of the 6 revised datasets.

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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WYETH-AYERST RESEARCH

ORIGINAL

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FAX: (610) 964-5973

Division of American Home Products Corporation

S REGULATORY AFFAIRS

April 30, 1999

NDA No. 21-083

General Correspondence
Request for Meeting

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

BM

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 16, 1999 teleconference regarding the revised primary efficacy analysis for the Phase III studies, Protocols 301 and 302. Prior to the teleconference, the Division was contacted on April 14 and informed of an error in the analysis of rejections which impacts the composite primary endpoint. A tabular summary of the revised endpoint analyses (both ITT and on therapy analyses) was forwarded by fax on April 14, and on April 15 a written summary of the programming error was also forwarded, via fax.

The purpose of this submission is to provide a summary of the revised results of the primary and the most important secondary efficacy analyses for Protocols 301 and 302. The conclusion, after re-analysis of the efficacy data, continues to be that treatment of recipients of primary renal transplants with sirolimus (2 mg/day or 5 mg/day) and CsA/corticosteroids is effective for the prevention of acute rejection within the first 6 months of transplantation.

The attached summary also supports our April 27, 1999 facsimile in which we requested a meeting to discuss the revised efficacy analyses and our plans for submitting revised components of the NDA. The April 27 facsimile contained a response plan for amending the NDA; this plan is contained in the attached document, on page 31.

Accordingly, attached please find:

- Revised efficacy analyses results (Pages 1-30).
- Schedule of planned submission relative to the revised efficacy analyses (Page 31).

As discussed with Mr. Matt Bacho, of your staff, is our understanding that this meeting is scheduled for May 7, 1999. We appreciate the Division's responsiveness directed at our meeting request.

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

May 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

[redacted]
BS

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 23, 1999 teleconference which was held to discuss our plans to provide FDA with updated datasets and programming code in order to verify the safety and efficacy analyses. For the efficacy analysis, Dr. Dixon (Statistical Reviewer) requested a hard copy of the programming code which was used for the extraction of the efficacy data endpoints, not the efficacy analysis. Dr. Dixon specifically requested information to be provided individually for protocols 301 and 302, not for the group 1 integrated analysis.

This submission contains three program listings used to create three endpoints for Protocols 301 and 302. The endpoints are: 1) the primary endpoint of the two pivotal studies, 2) treatment failure, and 3) "all" acute rejection endpoints. The primary endpoint of the two pivotal studies is the first of biopsy confirmed acute rejection, graft loss, or death. The secondary endpoint, treatment failure, is the first of biopsy confirmed acute rejection, or discontinuation for any reason. The third endpoint, "all" acute rejection, is any rejection experienced by the patient, whether presumptive or biopsy confirmed. Presumptive rejections were rejections where therapy was initiated by the physician without confirming biopsy. Where the patient experienced both types, the biopsy confirmed acute rejection is taken as the endpoint type. The number of biopsy confirmed acute rejections on this file can exceed those on the primary endpoint file since the "all" rejection endpoint can include biopsy confirmed acute rejections following graft loss.

Each listing has internal documentation in the form of comments. Each program begins with a banner briefly describing the purpose of the program, with the original comments explaining major steps in the program. Additional comments have recently been added to indicate where the erroneous line of code is to be found, and describing how this code deleted valid endpoints from the analysis.

Throughout the course of development, the Division has emphasized the need for complete determination of the primary endpoint for all patients. In order to gather this information at the time of NDA filing, additional patient data not present on the six month database were "hard coded" at the time of the six month analysis into the program. Documentation pointing out and discussing the hard coded patient data has also ben inserted for both studies, Protocols 301 and 302.

For the safety analysis, Dr. Dixon requested a hard copy of the programming codes related to adverse events and laboratory data. Dr. Dixon requested that this information be presented for protocols 301 and 302 individually, and not for the group 1 integrated analysis. This information is being compiled and will be submitted to the Division at a later date under separate cover.

Accordingly, attached for your review are the hard copies of the following programs:

- Primary efficacy endpoint.
- Secondary efficacy endpoint of treatment failure.
- Secondary efficacy endpoint of "all" rejections.

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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WYETH-AYERST RESEARCH

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Division of American Home P[illegible]ation

REGULATORY AFFAIRS

NDA ORIG AMENDMENT May 7, 1999

NDA No. 21-083 BS **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 April 23, 1999 teleconference which was held to discuss our plans to provide FDA with updated datasets and programming code in order to verify the safety and efficacy analyses. For the safety analysis, Dr. Dixon requested a hard copy of the programming codes related to adverse events and laboratory data. Dr. Dixon requested that this information be presented for protocols 301 and 302 individually, and not for the group 1 integrated analysis.

The purpose of this submission is to provide the requested program listings for adverse events and laboratory determinations. The programs as presented are setup for Protocol 301. However, this code is identical to the code which would be used for Protocol 302. The only difference between the protocols is that the parameter selection files used by the three programs. The files GLOBPARM.SAS and GLOBPROT.SAS that are currently specifying Protocol 301 data would specify Protocol 302 data.

This information is being provided in three volumes and is organized as follows:

Report Number 5-5: Summary Tabulation and Analysis Among Treatment Groups of Adverse Events.	**Volume 1**
Report Number 6-3L: Analysis Within and Among Treatment Groups for Laboratory Determinations.	**Volume 2**
Report Number 6-4L-CS: Number (%) of patients with Laboratory Test Results of Potential Clinical Significance.	**Volume 3**
Macros	

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For the efficacy analysis, Dr. Dixon (Statistical Reviewer) requested a hard copy of the programming code which was used for the extraction of the efficacy data endpoints, not the efficacy analysis. This information was previously submitted to the Division on May 4, 1999.

We trust that our responses adequately address the Division comments. If you have any questions regarding this submission, please contact me at (610) 902-3798.

We request that his additional information be incorporated into the above-referenced NDA.

Sincerely,

WYETH-AYERST LABORATORIES

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

cc. Mr. Matt Bacho with 1 desk copy

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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

NDA ORIG AMENDMENT May 17, 1999

NDA No. 21-083 BS

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 with the Division to discuss the re-analysis of the efficacy data relative to the pivotal Rapamune studies, studies 301 and 302. At the meeting, Dr. C. Dixon, statistician, reviewed an analysis conducted by the Division which excludes the pre-specified (2 day) treatment window for acute rejection. The outcome of the pair wise analysis shows that both the 2 and 5 mg doses are statistically superior to the comparators. The Division recommended that the primary and secondary endpoints be re-analyzed by Wyeth-Ayerst to account for all rejections. As such, updated statistical datasets and PROC CONTENTS should be provided.

The purpose of this submission is to provide the Division with six revised statistical datasets. The revised datasets are being provided on two (2) diskettes. The first diskette contains three datasets for Protocol No. 0468E1-301-US and the second diskette contains the same three datasets for Protocol No. 0468E1-302-GL. The specific files contains on these diskettes are:

Dataset Name	Description
PRIBX301 and PRIBX302	Primary Endpoint Dataset
TRTFLSBX (301 and 302)	Treatment Failure Endpoint Dataset
ARFILEBX (301 and 302)	"All" Rejection Endpoint Dataset

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The primary endpoint of the study is a composite endpoint of, the first incidence of biopsy confirmed acute rejection, graft loss, or death. The treatment failure endpoint is the first of biopsy confirmed acute rejection or dose termination for any reason. The "all" rejection endpoint is the first of either biopsy confirmed or presumptive acute rejection; where patients had both of these endpoints, the endpoint indicates biopsy confirmed acute rejection.

For the acute rejection components, the biopsy is the sole basis for determining whether the patient had an acute rejection.

Additionally, along with the two diskettes, you will find the PROC CONTENTS of these data files. The PROC CONTENTS documentation, provided in hard copy, gives the variable names in coding analyses, the description of the variables, and the format of the data (character, numeric, or date). In addition, a listing of the first ten cases of the data is also provided.

Accordingly, attached please find:

- Diskette containing three revised datasets for Protocol 301-US.
- Diskette containing three revised datasets for Protocol 302-GL.
- PROC CONTENTS for each of the 6 revised datasets.

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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A Division of American Home Products Corporation

REGULATORY AFFAIRS

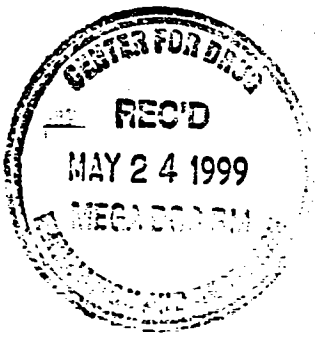
May 21, 1999

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

DRUG AMENDMENTS
BM



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.

In an April 14, 1999 teleconference, Dr. Cavaille-Coll suggested that it would be helpful if Wyeth-Ayerst submitted further interpretation of the safety of Rapamune. The summary should provide a more in depth discussion of potential safety issues.

Accordingly, we are providing a written summary addressing the relevant clinical topics. This summary discusses certain aspects of safety related to the use of Rapamune®: immunosuppression (infection and malignancy), effects on renal function, lipid levels, hematology, hemolytic-uremic syndrome (HUS), and other thrombotic events. In addition, the safety and efficacy of Rapamune in black patients is also discussed. This summary is based primarily on data gathered from the phase 3 clinical trials, as well as from phase 2 studies, preclinical studies, and the published literature on approved immunosuppressive agents. This summary clarifies the issues and, where appropriate, makes recommendations for patient management.

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

cc. Mr. Matt Bacho with 4 desk copies
rbb/329.doc

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

NDA ORIG AMENDMENT

BZ

May 24, 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 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 a response to the May 3 facsimile. For the purpose of facilitating your review, FDA's comments are restated in bold with our response provided immediately thereafter. Specifically, FDA requested:

1. **Please provide us with a list and summary tables of all patients who developed post-transplant diabetes mellitus (PTDM) in studies 301 and 302. Include investigator number, patient identification number, study drug dose, the day the patient was diagnosed with PTDM (post-transplant), race, and gender.**

   The response to this question is in preparation and will be provided under separate cover.

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2. **Please provide a list and summary tables, of all patients who developed grade 3 hypercholesterolemia, which should include investigator number, patient identification number, study drug dose, the day of diagnosis, race, gender, and the actual numerical value indicating that grade level.**

Enclosed in Attachment 1 are lists of all patients who developed elevations of cholesterol ≥240 mg/dl on therapy. The data are provided for each Phase III study (301 and 302) by treatment group. Race, gender and the remaining requested variables are identified for each patient. Additionally, summary tables which combine data from 301 and 302 are also provided as requested.

3. **Was hepatitis C status recorded in the patient demographic database and could a list of hepatitis C antibody-positive patients be provided?**

Hepatitis C status was not recorded in the patient demographic database and was not collected during the study.

4. **Please provide a list, and summary tables, of patients in studies 301 and 302 who developed:**

   a) **elevated ALT and/or AST at a level of ≥5 times normal and ≥10 times normal;**

   b) **eleveated T.Bili and ALK PHOS at a level of ≥5 times normal and ≥10 times normal.**

Include the investigator and patient identification numbers as well as the day these levels were reached (post-transplant), race, gender, and whether the study drug was discontinued temporarily or permanently.

Enclosed in Attachment 2 is a list of patients with liver enzyme elevations of 5 or 10 times normal for studies 301 and 302. The data are provided for each study with the requested variables presented. Additionally, summary tables which combine data from 301 and 302 are also provided. Please note that bilirubin was not collected in these studies.

5. **Please provide a list, and summary tables, of all patients who developed grade 3 rejection at any time post-transplant in Studies 301 and 302 (including their race and gender).**

Enclosed in Attachment 3 is a list of patients who developed a post-transplant grade 3 rejection in studies 301 and 302. The data are presented by study and treatment group. Race and gender are identified for each patient. Additionally, summary tables which combine data from 301 and 302 are also provided Please note that this represents data through month 12.

6. Please clarify Study 301 and 302's data cut-of date for datasets in the ISS database, which was submitted in December 1998

For Protocol 301 and 302, the SAS datasets in the ISS database for the original submission in December 1998 contains all data that was in-house on June 12, 1998. While not all of this data was edited, data up to the six month visit was, and the SAS programs selected only the six month data (210 days from the start of study medication) for the data report listings and tabulations.

7. Please explain how the biopsy-confirmed rejections for investigators 302D0, 302D1, 302D2, and 302D3 were included in the original submission when the error described affected alphanumeric investigator variables.

SAS treats these investigator identifiers as numbers in scientific (exponential) notation. For example, 302D1 (just like 302E1) is viewed as 302x10=3020; the "D" indicates the use of a double-precision format. The following simple program illustrates how SAS handles various alphanumeric investigator designations. The original program which extracted the primary endpoints for protocols 301 and 302 had an analogous problem. Investigator numbers with an embedded A, B, or C were inadvertently set to missing which resulted in their endpoints being dropped from the analysis. The embedded D did not cause the same problem (in neither study did the embedded character go beyond D).

Sample Program	Sample Output
data example; input inv pat; cards; 30201 001 30202 002 302A1 003 302B2 004 302C1 005 302D2 006 302E1 007 ; proc print; run;	The SAS System 08:21 Thursday, May 6, 1999 1 OBS INV PAT 1 30201 1 2 30202 2 3 . 3 4 . 4 5 . 5 6 30200 6 7 3020 7

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 2 desk copies
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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

ORIG AMENDMENT

BC

May 26, 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 May 21, 1999 request from Mr. Matt Bacho, Project Manager in your Division, which stated that the reviewing chemist, Dr. Mark Seggel, requested Wyeth-Ayerst to provide additional real time stability data of the Rapamune drug substance to support the requested 24 month expiry dating.

Accordingly, the purpose of this submission is to provide FDA with updated stability data to eighteen (18) months for three batches of sirolimus (rapamycin) drug substance. The primary packaging system used for these batches was double polyethylene bags inside an aluminum screw-cap can with desiccant.

In the original filing of this NDA, drug substance stability data were submitted in GTR 33490; Version 1.1. The attached report, GTR-33490; Version 1.2, presents updated stability data.

A statistical analysis of the data is included in this report.

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

[redacted]

It is our understanding that with this response we have completely satisfied Dr. Seggel's requests.

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

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