WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

EGULATORY AFFAIRS

July 28, 1999

ORIG AMENDMENT

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

REVISED DRAFT LABELING

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.

During the course of the NDA review for Rapamune®, additional safety and efficacy data have been submitted to the Division. As a result, Wyeth-Ayerst has undertaken a review of the package insert provided in the original NDA. We have made revisions to the document to include the additional data, which reflect our ongoing discussions with the Division.

The purpose of this communication is to provide a revised draft package insert for Rapamune® that includes additional safety and efficacy information, and addresses many of the comments made by the Division during the review of the NDA. Specifically, the package insert has been revised to include updated efficacy data, extended cumulative safety data (≥12 months) in the ADVERSE REACTIONS section, and an expanded PRECAUTIONS section reflective of the 12 month safety data. Several other editorial changes have been made for clarity. As requested by the Division, safety data are now presented by study, in contrast to the integrated presentation provided the original package insert. A glossary describing the specific revisions, and the rationale for making these revisions, is provided as Attachment 1. The revised package insert, with revisions presented in redline and strikeout, is provided as Attachment 2. Please note that the numerical identification in the left margin of the package insert corresponds to the glossary. Finally, a version of the package insert with the changes incorporated is provided in Attachment 3.

Please be advised that the changes to the package insert are not reflective of the discussions held at the July 27, 1999 meeting of the Subcommittee of the Antiviral Drugs Advisory Committee on Immunosuppressive Drugs. We anticipate that the issues raised at the Advisory Committee

ORIGINAL

meeting will be addressed in subsequent labeling negotiations between the Division and Wyeth-Ayerst.

To facilitate the review process and the labeling negotiations, we are also providing the revised package insert on disk in a Word 97 file.

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

ffdalet1.doc

c: Mr. Matt Bacho w/ 8 desk copies

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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

ORIG AMENDMENT
BL

August 5, 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.

The purpose of this submission is to provide the Division with our proposed container labels for Rapamune Oral Solution bottles and pouches. Rapamune Oral Solution is supplied as a concentrate of 1 mg/mL in amber glass bottles of 60 mL or 150 mL; and in unit-of-use laminated aluminum pouches of 1 mL, 2 mL, or 5 mL.

Please recall that the immediate container labels for the pouch were previously reviewed in a series of communications held in February 1999 with Dr. Mark Seggel, reviewing chemist. On February 25, Wyeth-Ayerst was notified that the immediate container labels for the 1 mL, 2 mL, 5 mL pouch presentations which were revised to incorporate the comments of Dr. Seggel, were acceptable. The Dr. Seggel's comments pertaining to the immediate container label for the pouch, i.e. the placement of generic name, listing of the percentage of alcohol, have been incorporated in remaining labels.

Accordingly, attached for your review are the corresponding container labels. Specifically we are providing the following labels:

60 mL Bottle	150 mL Bottle	1 mL pouch	2 mL Pouch	5 mL Pouch
Patient Kit	Patient Kit	Carton	Carton	Carton
PK 14084-1	PK 14085-1	UK 22622-1	UK 22623-1	UK 22624-1
Bottle Carton	Bottle Carton	Pouch Label	Pouch Label	Pouch Label
UK 22512-1	UK 22513-1	AN 674-1	AN 675-1	AN 676-1
Bottle Label	Bottle Label			
U1030-04-1	U1030-14-1			

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/378.doc

WYETH-AYERST RESEARCH

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FAX: (610) 964-5973

Division of American Home Products Corporation

REGULATORY AFFAIRS

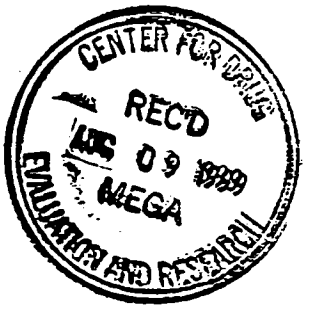
August 5, 1999

NDA No. 21-083

Response to FDA Request

GRAS AMENDMENT
BI

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.

The purpose of this submission is to provide copies of referenced literature that support our position that sirolimus has no effect on calcineurin activity. This literature was discussed in a teleconference held on August 5 with Dr. Shukal Bala and Mr. Matt Bacho, of the Division, and Dr. Suren Sehgal and Ms. Maureen Skowronek, of Wyeth-Ayerst. The teleconference related to suggested comments from Dr. Bala relative the mechanism of action section of the draft package insert.

In addition to providing the attached literature, we would like to provide the following comment relative to a report, GTR-23211, contained in the NDA.

GTR-23211, entitled, " Rapamycin Inhibits the *In Vitro* Release of Soluble IL-2 Receptor by Activated PBMC Independently of the Mode of Activation."

Ionomycin is a poor stimulator of T cells and generally is not used alone in cell cycle studies. However, ionomycin-induced stimulation also leads to expression of stimulatory proteins including IL-2 and IL-2-stimulated signal transduction pathways leading to DNA synthesis and cell proliferation.

Rapamycin blocks the T cell proliferation by inhibiting the response to the second signal (IL-2 stimulated cell cycle progression). Mitogenic stimuli activate T cell to produce stimulatory proteins including IL-2 which triggers signal transduction pathways that activate mTOR and result in the cell cycle progression leading to proliferation. Rapamycin therefore has an effect on mitogen-stimulated T cell proliferation. The results presented in this study are consistent with this and do not support an alternate mechanism.

ORIGINAL

Accordingly, attached are the following literature references:

1. Dumont, Francis J., et al; Distinct Mechanisms of Suppression of Murine T Cell Activation by the Related Macrolides FK-506 and Rapamycin.
2. Dumont, Francis J., et al; The Immunosuppressive Macrolides FK-506 and Rapamycin Act as Reciprocal Antagonists in Murine T Cells.
3. Liu, Jun, et al.; Calcineurin is a Common Target of Cyclophilin-Cylcosporin A and FKBP-FK506 Complexes.
4. Dumont, Francis J., et al; The Immunosuppressive and Toxic Effects of Fk506 are Mechanistically Related: Pharmacology of a Novel Antagonist of FK-506 and Rapamycin.
5. Sabers, Candace J., et al.; Isolation of a Protein Target of the FKBP12-Rapamycin Complex in Mammalian Cells.
6. Brown, Eric J., et al.; A Mammalian Protein Targeted by G1-Arresting Rapamycin-Receptor Complex.
7. Brown, Eric J., et al.; Control of p70 S6 Kinase by Kinase Activity of FRAP *In Vivo*.

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

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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

August 6, 1999

NDA No. 21-083

Draft Labeling

BL

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.

The purpose of this submission is to provide the Division with the most recent version of our draft labeling for Rapamune® (sirolimus) Oral Solution. The version of the label incorporates many of the recommendations received by FDA on August 3, 1999 and discussed in our August 4, 1999 teleconference. In order to facilitate the review of this submission, we are providing a key, which details the reason why changes were made.

Accordingly, attached for your review please find:

1. Key describing the changes that were made.
2. Rapamune draft labeling.

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 including electronic version

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WYETH-AYERST RESEARCH

AMENDMENT

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Division of American Home Products Corporation

REGULATORY AFFAIRS

August 6, 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.

The purpose of this submission is to provide a response to the July 29 facsimile which contained a request from the pharmacology and chemistry reviewers. The reviewers requested information relative to levels of seco-rapamycin in the batches used in pivotal toxicity studies (i.e., GTRs 25628, 32266, 23840, 22355, 24874, 22357, and 21942).

Accordingly, our response is as follows. The reports of these studies are listed below, along with the corresponding batch numbers of sirolimus drug substance lots used in those studies. The listed reports contain a description of the formulation evaluated in the study.

Toxicology Report No.	Drug Substance Batch No.
GTR-25628	0M 2695
	0M 3609
GTR-32266	0C 5634
GTR-23840	P-CFF
GTR-22355	P-CFF
GTR-24874	0M 2696
GTR-22357	P-CFF
GTR-21942	P-CFF

No detectable levels of seco-rapamycin have been found in these or any batches of sirolimus drug substance, [redacted] It has been for this reason that no test for seco-rapamycin has been applied to the specifications for sirolimus drug substance.

Please be advised that the NDA includes the results of 28 day study in rats in which seco-rapamycin levels were [redacted] of the formulation.

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

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ORIG AMENDMENT

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Division of American Home Products Corporation

REGULATORY AFFAIRS

BM

August 9, 1999

NDA No. 21-083

Response to FDA Request

CENTER FOR DRUG EVALUATION
REC'D
AUG 10 1999
MEGA DOC RM

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 July 29, 1999 facsimile in which the Division requested information specific to the drug-drug interaction between Rapamune and all formulations of cyclosporine. Specifically, the Division requested:

1. **Please submit all drug-drug interact information on sirolimus and all formulations of cyclosporine. This information or data could be from in-house data yet to be submitted to the FDA and/or from the scientific literature.**

   Attachment 1 contains a list of Rapamune® Clinical Trials in which cyclosporine was administered concomitantly. If a specific formulation was required by protocol, it is listed. If a route of administration was specified, it is listed. Please note that, except in two instances, we did not specify whether Sandimmune® or Neoral® was the solid or the liquid, nor did we collect the information on the case report forms (CRF).

   We are not aware of any patient receiving SangCya®. Specially, there were no pharmacokinetic studies done with that product.

2. Please send a list of all sirolimus-cyclosporine drug-drug interaction study reports that have been submitted to the FDA (IND and NDA).

Provided below is a list of study reports summarizing drug-drug interaction studies with Rapamune® and cyclosporine. All 5 reports listed below were provided as part of our NDA submission.

W-AR Studies Providing Evidence for a Pharmacokinetic Interaction Between Sirolimus and Cyclosporine (CsA) After the Administration of Rapamune® Oral Liquid and CsA Oral Formulations

Study	GMR	Subject Type	CsA Formulation	Section (s)
468E1-123-US	30212	Stable Renal Transplant	Neoral® (microemulsion)	Sections for Amend. XII only (7.1.3.3, 11.1.4 and 12.2)
468E1-163-US	31330	Healthy Volunteer	Neoral® (microemulsion)	Sections for 300-mg Neoral® cohort only (6.3.2, 6.5.2, 8.1, and 10.2)
468E1-206-EU	32070	Recalcitrant Psoriatic	Sandimmune® (oral liquid)	PK Sections only (4.6, 4.9.4, 4.13, 9.3, and 10.2.1)
468E1-301-US	32348	De-novo Renal Transplant	Neoral® (microemulsion)	PK Sections for CsA only (11.1.3, 11.1.8, 11.1.9, 12.2.2)
468E1-302-GL	33147	De-Novo Renal Transplant	Neoral® (microemulsion)	PK Sections for CsA only (11.1.2, 11.1.4)

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

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Division of American Home Products Corporation

REGULATORY AFFAIRS

August 19, 1999

BC

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 facsimile dated August 5, 1999 in which Dr. Norman Schmuff and Dr. Mark Seggel requested specific information relative to the chemistry review of the NDA. On August 17, 1999 responses to all but 1 comment (Comment 8) were provided to the Division.

[redacted] The complete response to comment 8 is provided as Attachment 1.

Also affected by this response is the post-approval stability protocol which was contained in our response to comment 12, submitted on August 17, 1999. The revised post-approval stability protocol now contains the updated drug product specification table. This table can be found in Attachment 2.

This submission completes our response to the above referenced facsimile. As requested in our August 17, 1999 submission, we would like to schedule a teleconference to discuss any issues regarding our response. 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 Copy
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Division of American Home Products Corporation

REGULATORY AFFAIRS

August 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

NDA 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 an August 19, 1999 telephone conversation between Wyeth-Ayerst and Dr. Tiernan, Medical Reviewer. Dr. Tiernan requested that we provide additional information relative to testosterone levels and GFR. For the purpose of facilitating your review, Dr. Tiernan's requests are provided in bold with our responses following immediately thereafter. This response was previously provided to the Division via facsimile on August 23. 1999.

1. **Confirm if an analysis of testosterone levels from males entered in study 301 were submitted in the NDA, identify the location, and/or provide the data.**

   Data were not submitted in the NDA as the data were not analyzable due to problems in standardizing the laboratories; reflective of the changes in methodology used across centers at the time of this study.

2. **Confirm if GFR [redacted] in selected centers for studies 301 and 302 have been submitted in the NDA, and provide the location of these data, and/or provide the data now.**

   Provided as Attachment 1 are the data collected in study 301. We do not believe that the data are valuable based on the few number of patients per group and that the mean values are inconsistent with serum creatinine and calculated creatinine clearance results previously submitted to the 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 1 desk copy

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Division of American Home Products Corporation

REGULATORY AFFAIRS

August 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

NDA 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 our August 20, 1999 teleconference in which we discussed FDA's fifteen chemistry comments contained in an August 5, 1999 facsimile. On August 17 and August 19, Wyeth-Ayerst provided responses to the 15 items contained in the facsimile.

As a result of the August 20, 1999 teleconference, Wyeth-Ayerst was asked to do the following:

- Include an additional test point for the fourth year testing plan in the post-approval stability protocol. It was agreed that the testing of accelerated conditions could be separated from the post-approval stability protocol and provided as its own protocol.

- Revise the drug product stability commitment to include in-use tests on three commercial batches. [redacted]. Please note, this request was also conveyed to us in writing on August 24, 1999.

Provided as Attachment 1 is the updated stability protocol (previously comment 12). The updated protocol includes the additional test in the fourth year testing plan and removes the accelerated testing from the routine market product stability commitment.

Provided as Attachment 2 are the protocols by which accelerated testing conditions and an in-use test for Rapamune are added. For the purpose of facilitating your review, this response has been term "Comment 16", as we view it as a continuation of the previous requests. As was discussed, these studies will be provided to FDA for comparison to data previously submitted to this 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 2 desk copies
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Division of American Home Products Corporation

REGULATORY AFFAIRS

August 24, 1999

NDA No. 21-083

Package Insert

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

RECD
AUG 25 1999

NDA 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 our August 17, 1999 submission in which we provided the Division with our previous version of the package insert. The purpose of this submission is to provide an updated version of the package insert. Due to our efforts to cleanup the label, minor editorial changes have occurred between versions. As a whole, the information contained within the label and the presentation of the data has not changed. The Division has been made aware of each change that has occurred.

We are aware that the nomenclature for cyclosporine is still under review by FDA's Office of Chief Counsel. Please note that our in house counsel has reviewed the label for the same reason and has added the word "Neroal®" to three places in the package insert. These changes occur twice on page 11 (lines 365 and 400) and once on page 19 (line 650).

Accordingly, attached for your review are the following:

1. The U.S. package insert for Rapamune®.
2. A diskette containing a Microsoft Word version of the package insert.

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 10 Desk Copies

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Division of American Home Products Corporation

REGULATORY AFFAIRS

NDA ORIG AMENDMENT

August 25, 1999

NDA No. 21-083

Package Insert

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 August 24 submission containing a revised package insert and our August 5 submission containing revised immediate container and carton labels for this product.

The purpose of this submission is to provide a revised package insert. The package insert has been amended with regard to the identity of our organization. This change is now consistent with the immediate container and carton labels.

Attached for your review are the following:

1. The revised package insert.

2. A diskette containing a Microsoft Word version of the package insert.

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 with 10 Desk Copies
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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

REGULATORY AFFAIRS

ORIGINAL
NC

NEW CORRESP

August 25, 1999

Elenita Yasana Ibarra-Pratt, R.N.
Division of Drug Marketing, Advertising and Communications
HFD-40, Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

RE: Rapmune® (sirolimus) Oral Solution
NDA 21-083, Launch Campaign

Dear Ms. Ibarra-Pratt:

Reference is made to NDA 21-083 for Rapamune (sirolimus) Oral Solution, and to our submission of August 24, 1999 wherein the proposed launch campaign for Rapamune was submitted.

Please replace the proposed press release in the August 24, 1999 submission with the attached version. The version submitted on August 24, 1999 had a minor error in the list of adverse reactions noted in the Clinical Trial Overview section. Minor punctuation changes have also been made.

We again appreciate your prompt review of the proposed Rapamune launch campaign. Please contact the undersigned at 610-902-3771 (fax 610-964-5972) with comments regarding this submission.

Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione

Diane Mitrione
Senior Director
U.S. Regulatory Affairs

cc: Dr. Mark Goldberger, Director, Division of Special Pathogens and Immunologic Drug Products

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WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

REGULATORY AFFAIRS

September 9, 1999

NDA No. 21-083

Package Insert

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 September 8, 1999 facsimile which provided additional comments relative to the US package insert for Rapamune Oral Solution. Specifically, the Division requested that all of the references be removed and provided suggested nomenclature for Neoral® within the label.

The purpose of this submission is to provide an updated version of the label. In addition to the changes referred to above, the agreed wording on the rifampin section of the Drug Interaction section of the label has been incorporated.

Accordingly, attached for your review are the following:

1. September 9, 1999 version of the US Package Insert.
2. Diskette containing a Microsoft Word version of the Package Insert.

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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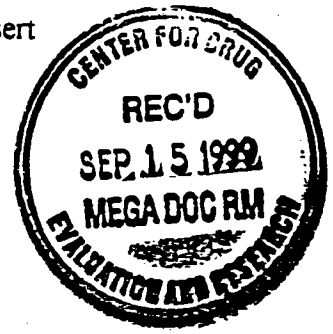
Division of American Home Products Corporation

REGULATORY AFFAIRS

September 14, 1999 ORIG AMENDMENT

NDA No. 21-083

Package Insert



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 September 13 and 14 facsimiles which provided additional comments relative to the US package insert for Rapamune Oral Solution and to a teleconference held on September 14 with representatives of your staff. As a result of the teleconference, all issues related to the package inserts were resolved.

The purpose of this submission is to provide an updated version of the label.

Accordingly, attached for your review are the following:

1. September 14, 1999 version of the US Package Insert.
2. Diskette containing a Microsoft Word version of the Package Insert.

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 with 3 desk copies

RSS-398.doc

HFD-590/M Dempsey

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Food and Drug Administration
Rockville MD 20857

DEC 28 1998

Wyeth-Ayerst
Attention: Maureen D. Skowronek
Director, US Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Skowronek:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Rapamune (sirolimus) 1 mg/ml oral solution

Therapeutic Classification: Priority (P)

Date of Application: December 15, 1998

Date of Receipt: December 15, 1998

Our Reference Number: 21-083

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 29, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 15, 1999.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

If you have any questions, contact Mary Dempsey, Project Manager, at (301) 827-2127.

Sincerely,

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECONFERENCE MINUTES

COPY

Meeting Date: April 16, 1999
Time: 10:00 a.m.
Location: U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
9201 Corporate Blvd., S400
Rockville, MD 20850

Application: NDA 21-083

Type of Meeting: Clinical Amendment Discussion/Type C

Meeting Recorder: Matthew Bacho, Regulatory Project Manager

FDA Attendees, titles, and Office/Division:
Mark Goldberger, M.D., M.P.H., DSPIDP Director
Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Rosemary Tiernan, M.D., Medical Officer
Nancy Silliman, Ph.D., Statistics Team Leader
Cheryl Dixon, Ph.D., Statistics Reviewer
Matthew Bacho, Regulatory Project Manager

External Constituent Attendees and titles:
Dr. Joseph Camardo, Senior Vice President of Clinical Research
Dr. Gary Littman, Senior Biostatistician
Ms. Maureen Skowronek, Director, U.S. Regulatory Affairs

Background: Wyeth-Ayerst Research requested, and was granted, a teleconference to discuss an error they found in the SAS program, which was used to create the datasets of endpoints for the statistical analysis of pivotal studies 301 and 302.

Meeting Objective: Wyeth-Ayerst wanted to make sure the FDA understood the error that was found in their NDA for Rapamune® Oral Solution and present their plan for submitting the necessary revisions.

Discussion Points:

1. Wyeth-Ayerst inquired whether their explanation of the error was clear and if the FDA had any further questions regarding its nature. *The FDA noted that no further explanation was needed. The FDA requested a revised list of all the derived variables and merged file datasets as well as the SAS programs used in compiling their safety and efficacy databases.*

2. Wyeth-Ayerst noted that a list of all efficacy analyses affected by the error, and an index of the revised tables, would be submitted for review in the near future. They also mentioned that their 12-month endpoint (patient and graft survival) analyses

were not affected because only biopsy-confirmed acute rejections were involved. *The FDA acknowledged these statements and reminded Wyeth-Ayerst that the Integrated Efficacy Summary, Integrated Safety Summary, and study reports for 301 and 302 need to be rewritten. It was also made clear that a total rewrite would not be necessary because Rapamune®'s safety profile was not greatly affected by the error. In light of the extensive revisions required to correct the material already reviewed, the FDA decided that they would constitute a major clinical amendment to the NDA. Under the Prescription Drug User Fee Act of 1997, the FDA noted that up to 90 extra days would be added to the review clock for this application. However, due to the nature of the error, not all of that time might be needed to complete the review. FDA also noted that the Advisory Committee meeting would have to be rescheduled for either late July or early August.*

3. FDA inquired whether this error would affect the efficacy datasets in Wyeth-Ayerst's proposed NDA for Rapamune® Tablets. *Wyeth-Ayerst explained that the error did not affect this NDA, however, the date for its submission would have to change to reflect the extra time FDA would need to review the current application's amendment.*

Action Items:

1. Wyeth-Ayerst intended to submit their revised SAS datasets and all case report forms that involved biopsy-confirmed acute rejections. They will also send a timeline for all subsequent amendment submissions.

2. The FDA requested a line listing of all discontinued patients with the following information: patient ID number, transplantation date, the dates upon which each patient started and stopped taking drug, and the reason(s) for discontinuation.

3. The FDA also requested a line listing of all hypercholesterolemia cases (i.e., a serum cholesterol value that is greater than 6.19mm/L), which should include the highest cholesterol test result for each patient.

Minutes Preparer: _____ _____

Meeting Chairperson: _____ _____