

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-110

CORRESPONDENCE

WORLDWIDE REGULATORY AFFAIRS

September 29, 2000

General Correspondence

NLA No. 21-110

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



AMENDMENT

XR

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-110 for Rapamune® (sirolimus) Tablets, previously submitted to your administration on October 29, 1999, and approved on August 25, 2000.

The purpose of this submission is to update the Patent Exclusivity Information found in Volume 1, on page 34. This update incorporates changes being made in both items 8 and 9 in the attached table.

Change to item 8): The claim of five years of patent exclusivity is being changed to three years in the following statement:

Pursuant to Section 505(j)(4)(D)(ii) and 505 (c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this NDA.

Change to item 9): U.S. patent 5,989,591 is being added to the list of applicable patents. This patent was previously submitted to this application on December 21, 1999, and is being provided again at this time for completeness.

If you have any questions regarding this submission, please contact me at (610) 902 - 3792.

Sincerely,

WYETH-AYERST LABORATORIES

Randall B. Brenner, Manager
Worldwide Regulatory Affairs

ORIGINAL

WORLDWIDE REGULATORY AFFAIRS

August 25, 2000

NDA No. 21-110

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. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

Reference is also made to Item 16, Debarment Certification, of this application. The purpose of this submission is to submit an updated Item 16, to certify that Wyeth-Ayerst did not use in any capacity the services of any person debarred under sections (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetics Act in connection with this application.

Accordingly, attached for your review is the updated Item 16, Debarment Certification. This certification is identical to the one provided in the original NDA with the exception of the word "knowingly" which has been removed.

If you have any questions regarding this submission, please contact me at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES



Randall B. Brenner, Manager
Worldwide Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy

WORLDWIDE REGULATORY AFFAIRS

August 21, 2000

NDA No. 21-110

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. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

The purpose of this submission is to provide the Division with our latest version of the US Package Insert for Rapamune Tablets. This version of the package insert incorporates the changes highlighted in the Division's August 18, 2000 facsimile.

Additionally, as requested by Mr. Matt Bacho, this version of the package insert also presents all of the changes made to the US Package Insert throughout the course of its review as redline and strikeout. The approved oral solution label was used as a starting document and all of the redline and strikeout text is added in support of the tablet application.

All of the changes incorporated into this version have been previously agreed to. This version of the package insert is identical to the version submitted on August 16, 2000 with the exception of the changes in the August 18 facsimile.

Accordingly, attached for your review are the following:

1. August 21, 2000 version of the US Package Insert with redline and strikeout.
2. August 21, 2000 version of the US Package Insert with changes incorporated.
3. Diskette containing two Microsoft Word version of the Package Insert
 - label8-21-redline.doc
 - label8-21-clean.doc

If you have any questions regarding this submission, please contact me at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES



Randall B. Brenner, Manager
Worldwide Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy
Ms. Ellen Frank with 1 desk copy

Rbb/475.doc

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

WORLDWIDE REGULATORY AFFAIRS

August 17, 2000

NDA No. 21-110

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. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

The purpose of this submission is to provide the Division with our final version of the print mat for the blister cards of Rapamune Tablets. This version of the print mat is identical to the one previously provided, via facsimile, for review by Dr. Seggel on July 18, 2000. No comments were received regarding this presentation and therefore, it has remained unchanged.

Accordingly, attached for your review please find the print mat for the blister card presentation of Rapamune Tablet. This print mat, combined with the blister card carton and bottle label that were previously submitted on August 17, 2000 are the only container labels for the 1 mg tablet.

If you have any questions regarding this submission, please contact me at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES



Randall B. Brenner, Manager
Worldwide Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy
Ms. Ellen Frank with 1 desk copy

Rbb476.doc

WORLDWIDE REGULATORY AFFAIRS

August 17, 2000

NDA No. 21-110

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

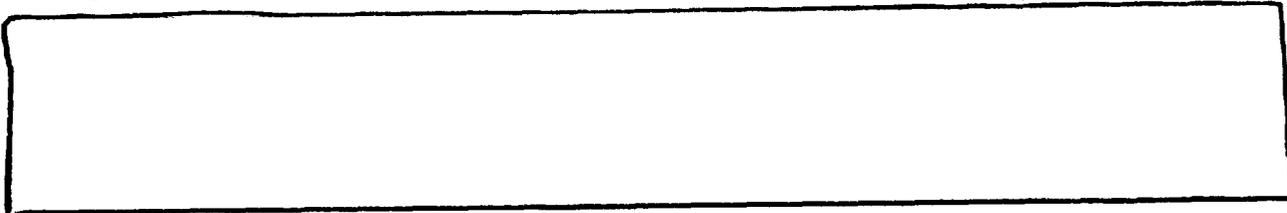
Dear Dr. Goldberger:

Reference is made to our NDA No. 21-110 for Rapamune® (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

Reference is also made to the August 16, 2000 request from Dr. Seggel, Chemistry Reviewer, and Dr. Kumi, Clinical PK Reviewer, to change the dissolution specification which is presented in the NDA. Specifically, the following change was requested:

Specification as Presented in NDA

Requested Updated Specification



The purpose of this submission is to confirm our acceptance of the proposed updated specifications. In order to support this change, attached please find the revised regulatory specifications for drug product and for the post-approval stability protocol.

If you have any questions regarding this submission, please contact me at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES

Randall B. Brenner, Manager
Worldwide Regulatory Affairs

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

August 17, 2000

NDA No. 21-110

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. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

Reference is also made to your July 28, 2000 and August 11, 2000 facsimiles that provided comments from Dr. Seggel, Chemistry Reviewer, and the Office of Postmarketing Drug Risk Assessment on our draft container labels. The purpose of this submission is to provide the Division with our updated container labels. Specifically, FDA requested the following changes regarding the carton labeling for Rapamune Tablets:

July 28, 2000 Facsimile:

- 1) Please revise the storage statement on the bottle and carton similarly: "Store at 20 to 25°C (68 to 77°F) [see USP Controlled room Temperature]."

August 11, 2000 Facsimile:

- 1) Please consider relocating the product strength to a position following the product name so that it is not confused with the net quantity.
- 2) We also ask that you consider putting just one statement of net quantity on the carton labeling because it distracts from the product strength.
- 3) We strongly recommend that you include a statement on the carton pertaining to whether or not the unit-dose package is child resistant. If it is not child resistant, you should add a statement along the lines of the following: "This unit-dose package is not child resistant. If dispensed for outpatient use, a child-resistant container should be utilized."

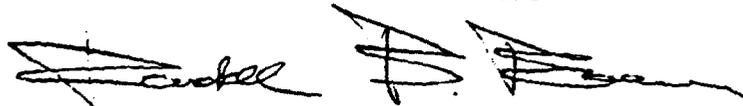
For consistency, where appropriate, changes that were recommended for the carton label have also been incorporated into the bottle label. Accordingly, attached for your review are the following product presentations. All of the changes requested in the August 11, facsimile have been incorporated. Please note that no changes were requested for the blister foil, and thus that presentation is not being provided with this submission.

- Carton label for hospital unit dose.
- Bottle label for the 100-count bottle.

If you have any questions regarding this submission, please contact me at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES



Randall B. Brenner, Manager
Worldwide Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy

Rbb/474.doc

APPEARS THIS WAY
ON ORIGINAL

WORLDWIDE REGULATORY AFFAIRS

August 16, 2000

NDA No. 21-110

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:

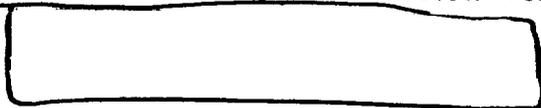
Reference is made to our NDA No. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

Reference is also made to our August 11 teleconference, your August 11 facsimile, and your August 16 facsimile, which provided additional comments relative to the US package insert for Rapamune tablets.

The purpose of this submission is to provide an updated version of the label. This version incorporates all of the changes agreed upon to date and presents the changes from the August 11 teleconference and facsimile as well as the August 16 facsimile as redline and strikeout.

Accordingly, attached for your review are the following:

1. August 16, 2000 version of the US Package Insert with redline and strikeout.
2. August 16, 2000 version of the US Package Insert with changes incorporated.
3. Diskette containing two Microsoft Word version of the Package Insert



If you have any questions regarding this submission, please contact me at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES

Randall B. Brenner, Manager
Worldwide Regulatory Affairs

Ms. Mary D... with...

WORLDWIDE REGULATORY AFFAIRS

A **AMENDMENT**

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August 15, 2000

NDA No. 21-110

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. 21-110 for Rapamune® (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

Reference is also made to your August 11, 2000 facsimile which provided comments from Drs. Seggel and Schmuff (Chemistry Team) and Drs. Kumi and Colangelo (Clinical Pharmacology and Biopharm Team). Additionally, the comments in the facsimile, along with our proposed responses were discussed during a teleconference, which was held on August 14, 2000.

The purpose of this submission is to provide the responses to the requests contained in the above referenced facsimile as well as two additional questions from the August 14 teleconference. For the purpose of facilitating your review, FDA's comments are restated in bold with our responses provided immediately thereafter.

Additionally, the following attachments are being provided. Each attachment was previously contained in NDA No. 21-110 and is being provided again for your convenience.

Attachment	Title	Location in NDA
1	GTR-35041 – Rapamycin: Development of an In Vitro/In Vivo Correlation for Rapamune (Rapamycin) Tablets	Vol. 13, Page 170
2	GTR-36642 – Justification for Biowaiver for Triangular Shaped Rapamune (Rapamycin) 1 mg Tablet	Vol. 13, Page 122

ORIGINAL

Question 1:

Please confirm that all of the formulation numbers used in study 309 are those provided in Table 6.1.12A in Volume 17 of the NDA.

Response:

Wyeth-Ayerst confirms that formulations 0930874B and 0930964B for the 1 mg tablet and formulations 0930346K and 0930840K for the oral solution as provided in Table 6.1.12A in Volume 17 of the NDA were the only formulations used in Study 309 US/CA/AU "A Comparative Study of the Effect and Equivalence of Sirolimus Oral Liquid Versus Sirolimus Tablets, Administered Concomitantly with Cyclosporine and Corticosteroids in Renal Allograft Recipients: 6-Month Report."

Question 2:

Please confirm all of the batch numbers of material used in Study 309.

Response:

Wyeth-Ayerst confirms the following batches of material were used in Study 309 "A Comparative Study of the Effect and Equivalence of Sirolimus Oral Liquid Versus Sirolimus Tablets, Administered Concomitantly with Cyclosporine and Corticosteroids in Renal Allograft Recipients: 6-Month Report."

1 mg tablet	1 mg/mL solution
R972973 (A97D086)	1998B0212
R979079* (A97D087)	9520080
1997B0110	9620810
1997B0139	9720002
1997B0141	1997B0046
1997B0140	1997B0104
	1997B0152
	1998B0320
	9710223
	9710228
	1998B0337*

* Used but not documented in NDA 21-110. These are additional batches that were used post date of cut-off.

Batches R972973 and R979079 were not printed and used in Study 309. Batches A97D086 and A97D087 are printed tablets which are part of the registration batches.

RESTRICTED

DRUG REGULATORY AFFAIRS

August 15, 2000

NDA No. 21-110

**Response to FDA Request
Phase IV Commitments**

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. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

The purpose of this submission is to formally submit Wyeth-Ayerst's plans for post-marketing commitments to the NDA for Rapamune Tablets. The plans for these studies were previously sent to the Division via facsimile on August 9, 2000 and were agreed upon during a teleconference on August 11, 2000.

Wyeth-Ayerst proposes that the following Phase IV commitments which were previously assigned to NDA No. 21-083 for Rapamune Oral Solution be completed with the Oral Solution or the Tablet formulation, thus becoming commitments for this application as well. They are as follows:

Clinical:

- 1) In order to evaluate the optimal dose of sirolimus in renal transplant patients, who are at high risk for acute rejection, Wyeth-Ayerst agrees to conduct a well-controlled, comparative study or studies, to further define the optimal dose or concentration in this patient population.

Patients from any or all of the following groups might be included:

- Black patients.
- Patients with retransplants.
- Patients with high panel-reactive antibodies.
- Patients with greater than or equal to 4 human leukocyte antigen mismatches.
- Patients with multiorgan transplants.

ORIGINAL

- 2) Wyeth-Ayerst Research agrees to conduct an appropriate study or studies to better define the type and duration of hyperlipidemia associated with the use of sirolimus. In particular, we will measure and analyze total fasting serum cholesterol and triglycerides, as well as high-density lipids/low density lipids, and lipoprotein A. Transplant recipients with and without a lipid disorder prior to transplant will be included, and the use of lipid-lowering agents and other specific interventions will be evaluated.
- 3) As part of the continuing development of sirolimus, we will evaluate the effect of long-term renal function using GFR in patients receiving kidney or other solid organ transplants.
- 4) In ongoing and future studies, we will evaluate the impact of the drug on liver function tests in recipients of kidney or liver transplants who may have hepatitis B virus and/or hepatitis C virus infection

Clinical Pharmacology:

- 5) Wyeth-Ayerst Research agrees to evaluate the optimum therapeutic concentration range for sirolimus and the value of reduced cyclosporine concentration in combination with sirolimus. We will employ therapeutic drug monitoring and logistic regression modeling in both high and low risk patients.
- 6) Wyeth-Ayerst Research will conduct a study or studies to evaluate the effect of ethnicity on the pharmacokinetics of sirolimus so as to facilitate the determination of the optimum dosing regimen among other ethnic origins. Such a determination will be made using a population pharmacokinetics analysis, preferably using mixed effects modeling.

In addition to those previously agreed upon commitments for the oral solution, Wyeth-Ayerst agrees to the following commitments specific to this application:

Clinical:

- 7) Wyeth-Ayerst Research agrees to collect and report 1 year follow-up safety data from the ongoing Phase 3 study, Protocol No. 0468H1-309-GL. Data pertaining to GFR and serum creatinine will be included as follow-up information. This will be available in March, 2001
- 8) Wyeth-Ayerst agrees to collect longer term data for Protocol No. 0468E1-306-US entitled, "*An Open-Label Extension Study of the Safety of Long-Term Administration of Sirolimus (Rapamune®) in Solid Organ Transplant Recipients,*" in which some patients have been on the tablet for several years. This data will be available in June 2001.

If you have any questions regarding this submission, please contact me at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES



Randall B. Brenner, Manager
Worldwide Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy

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APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

WORLDWIDE REGULATORY AFFAIRS

August 9, 2000

NDA No. 21-110

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. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

Reference is also made to your August 1, 2000 facsimile which provided recommendations from Dr. Kumi, clinical pharmacologist, on the proposed Rapamune package insert, which was submitted on July 26, 2000.

The purpose of this submission is to respond to comment number 6 from the referenced fax. For the purpose of facilitating your review, FDA's comment is restated in bold with our response provided immediately thereafter.

- 6) **Lines 155-7: Using table 11.1.4.1A from study 309, we think the whole blood sirolimus trough concentration (mean +/- SD) at 6 months from study 309 were 8.04 +/- 5.50 (n=114) and 8.85 +/- 4.54 ng/mL (n=106) for oral solution and oral tablets, respectively. Please provide a reference for the numbers in your proposed label.**

The average trough whole blood sirolimus concentrations listed in the in-text table 11.1.4.1A for study 309 were included to show the actual concentrations plotted in Supportive PK Figures S11-3 and S11-4. The average values in table 11.1.4.1A are based on available data on individual days up to 10 days and then for available data at ± 10 days for months 1, 2, 3, 4, 5, and 6. Using such data to determine an overall average trough sirolimus concentration among all individual patients would unfortunately exclude some of the available trough data and some patients. Therefore, we do not feel that the data in table 11.1.4.1A should be used to estimate the average concentrations over time. Instead, we feel that the time-normalized average trough concentration $C_{min,TN}$ should be used as defined by the relationship:

$$C_{min,TN} = AUC_{t1-t2}/(t2-t1) \quad (1)$$

In equation (1), t_1 and t_2 are the times for the first and last concentrations, respectively. Equation (1) should be applied to individual subjects, and an average among individual patients by treatment group should then be presented in the label. This approach was used for reporting the average trough sirolimus concentrations in both the GMR for study 301 and the label for Rapamune Oral Solution.

It should be pointed out that the pharmacokinetic analysis for study 309 was not entirely parallel to that for study 301. An analysis based on equation (1), was not reported in the GMR for study 309. Therefore, in order to maintain a parallelism between the solution and tablet formulations in the label for Rapamune Oral Solution and Tablets, $C_{min,TN}$ values were estimated for study 309 after the completion of the 6-month GMR. The mean \pm SD $C_{min,TN}$ among patients by treatment group are the values reported in the current draft label for Rapamune Oral Solution and Tablets. These data will be included in the 1-year 309 GMR as a permanent reference. In lieu of the 1-year GMR, SAS output are given in Tables 1 and 2 (see attached tables) that list the $C_{min,TN}$ for individual patients (and descriptive statistics) for the solution and tablet formulations, respectively.

Tables 1 and 2 also provide the time-normalized average doses ($Dose_{TN}$) and the dose-normalized average trough sirolimus concentrations ($DN-C_{min,TN}$) by treatment. A p-value for the statistical comparison of dose-normalized average trough concentrations for solution and tablet formulations is provided.

If you have any questions regarding this submission, please contact me at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES



Randall B. Brenner, Manager
Worldwide Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy

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WORLDWIDE REGULATORY AFFAIRS

July 24, 2000

NEW CORRESPONDENCE

NC

Response to FDA Request

NDA No. 21-110

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



Dear Dr. Goldberger:

Reference is made to our NDA No. 21-110 for Rapamune® (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

Reference is also made to your July 10, 2000 facsimile in which Dr. Mark Seggel, Chemistry Reviewer, requested information specific to his review of this NDA. The purpose of this submission is to provide complete responses to all of Dr. Seggel's questions.

Accordingly, please find our responses provided as Attachment 1. For the purpose of facilitating your review, FDA's questions are restated in bold with our responses provided immediately thereafter.

If you have any questions regarding this submission, please contact me at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES

Randall B. Brenner, Manager
Worldwide Regulatory Affairs

cc. Mr. Mati Bacho with 1 desk copy

ORIGINAL

WORLDWIDE REGULATORY AFFAIRS

NDA ORIG AMENDMENT

July 6, 2000

NDA No. 21-110

Request for Review and Comment

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

BL



Dear Dr. Goldberger:

Reference is made to our NDA No. 21-110 for Rapamune® (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

The purpose of this submission is to provide the Division with our draft Rapamune Tablet container labels (bottle label and carton). Please note that our current plans are to market the 1-mg tablets as bottles of 100 and as a hospital box containing 10 blister cards of 10 tablets each. The 30 pack (3 blister cards of 10 tablets each) which was presented in the original NDA has been removed from our initial launch plans because we do not plan to market the 1 mg tablet in this presentation.

Accordingly, attached for your review and comment please find the following:

- Hospital Carton (10 blister cards of 10 tablets each)
- Bottle Label (100 tablets)

If you have any questions regarding this submission, please contact our representative, Mr. Randall Brenner, at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES

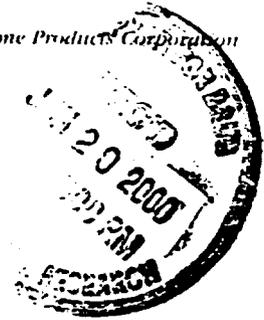
DUPLICATE

David K. Ellis, Ph.D., Director
Worldwide Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy
Rbb/458.doc

REGULATORY AFFAIRS

June 15, 2000



Wayne Smith
Food and Drug Administration
Philadelphia Science Branch
U.S. Customhouse, Room 900
Second and Chestnut Streets
Philadelphia, PA 19106

NEW CORRESP

NC

Dear Dr. Smith:

Reference is made to our NDA No. 21-110 for Rapamune Tablets, previously submitted to the Division of Special Pathogen and Immunologic Drug Products on October 29, 1999.

Reference is also made to your June 6, 2000 facsimile in which you requested specific samples and information in order to perform the necessary methods validation studies. The purpose of this submission is to provide you with details regarding the requested information. In order to facilitate FDA's review of this letter, FDA's requests are restated in bold, with our responses provided immediately thereafter.

Please note that the reference standard samples are being provided to you under frozen storage. Upon receipt, please assure that these samples remain stored in a freezer until time of assay (please be sure to allow the standards to warm to room temperature prior to opening their containers). Additionally, provided as Attachment 1 is an updated Table of Samples to be Submitted. This table has been revised since the original NDA to reflect the use of a new lot of seco-rapamycin reference standard (the inventory of the lot previously submitted has been exhausted).

1) Drug Product – Rapamune Tablets, 1 mg - 300 count

Due to the recommended storage conditions of Rapamune® tablets, the requested samples should be stored at controlled room temperature (20° to 25°C)

2) Rapamycin Reference Standard – 2 g

Due to the recommended storage conditions of the Rapamycin reference standard (RS 145-7, lot 0C6662), the requested samples should be stored frozen (-10° to -25° C) and protected from light. Additionally, as the period of use for this standard was recently extended, an updated Certificates of Analysis is provided as Attachment 2.

ORIGINAL

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

If you have any questions regarding this submission, please contact our representative
Mr. Randall Brenner at (610) 902-3792,

Sincerely,

WYETH-AYERST LABORATORIES

 *Per/*

David K. Ellis, Ph.D., Director
Worldwide Regulatory Affairs.

cc. Mr. Matt Bacho, Division of Special Pathogen and Immunologic Drug Products (letter only)

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APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

U.S. REGULATORY AFFAIRS

NDA ORIG AMENDMENT April 4, 2000

NDA No. 21-110

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. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

Reference is also made to a March 20, 2000 request by Dr. Cheryl Dixon, Statistical Reviewer, and Dr. Rose Tiernan, Medical Reviewer, to provide SAS datasets for the data contained in the 4-month safety update for Rapamune Tablets. Specifically, they requested the SAS datasets that were provided with the original NDA be provided again with the updated safety data.

Accordingly, attached for your review, on a single CD, are the requested datasets. Along with the datasets, the CD contains a Readme.txt file and a define.pdf file, which contain the PROC CONTENTS for the SAS datasets.

If you have any questions regarding this submission, please contact our representative, Mr. Randall Brenner, at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES



David K. Ellis, Ph.D., Director
Worldwide Regulatory Affairs

ORIGINAL

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

NDA ORIG AMENDMENT

June 5, 2000

NDA No. 21-110

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

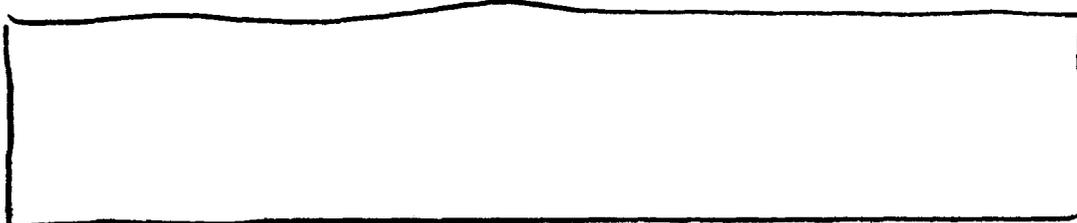
EC

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-110 for Rapamune® (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

Reference is also made to the Divisions May 31, 2000 request by Dr. Mark Seggel, Chemistry Reviewer, to provide an electronic Microsoft Word copy of the stability reports submitted to the NDA on March 30, 2000. These reports provided additional stability data of up to 12 months for the triangular shaped tablets and up to 24 months supportive stability data for the oval shaped tablets.

Accordingly, attached for your review is an electronic Microsoft Word copy of the following:



If you have any questions regarding this submission, please contact our representative, Mr. Randall Brenner, at (610) 902-3792.

Sincerely,

ORIGINAL

WYETH-AYERST LABORATORIES

David K. Ellis, Ph.D., Director
Worldwide Regulatory Affairs



cc. Mr. Matt Bacho

REGULATORY AFFAIRS

NDA OBSERVATION

March 30, 2000

NDA No. 21-110

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

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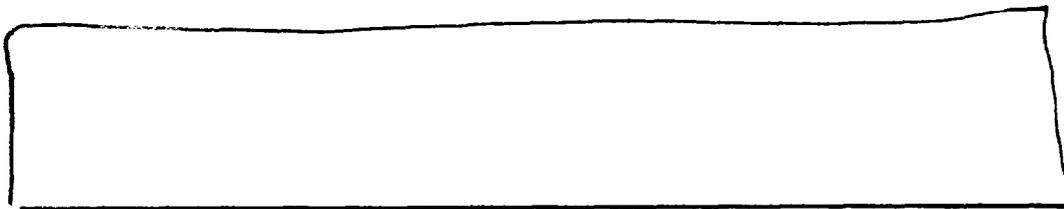
Dear Dr. Goldberger:

Reference is made to our NDA No. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

The purpose of this submission is to comply with Wyeth-Ayerst's commitment to provide the Division with additional stability data up to 12 months for the triangular shaped tablets and up to 24 months supportive stability data for the oval shaped tablets. This was agreed to during our pre-NDA meeting and is stipulated in Vol. 3, page 50 and Volume 4, page 414 of the above referenced NDA

Currently, the Rapamune Tablet NDA presents only 6 months of stability data for the triangular tablets, and 18 months for the oval tablets. These new reports extend those databases to 12 and 24 months respectively. For the triangular tablets, the 12-month strength values remained essentially unchanged from the 6-month values. Degradation levels increased slightly, but remained within specification. Dissolution values were also comparable. For the oval tablets, similar trends were noted. Based on statistical analyses of these data, these reports further confirm the stability of Rapamune[®] 1 mg tablets and the proposed expiration dating period of 18 months at controlled room temperature (20-25°C).

Accordingly, attached for your review are the following stability reports:



ORIGINAL

If you have any questions regarding this submission, please contact our representative,
Mr. Randall Brenner, at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES

A handwritten signature in black ink, appearing to read "David K. Ellis", with a stylized flourish at the end.

David K. Ellis, Ph.D., Director
Worldwide Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy

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REGULATORY AFFAIRS

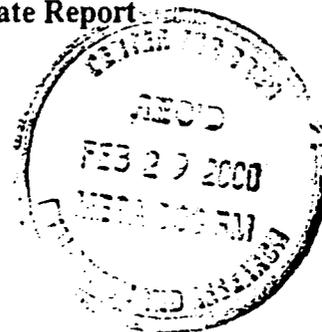
NDA 2110 A NDMENT

February 29, 2000

NDA No. 21-110

4-Month Safety Update Report

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. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

The purpose of this submission is to provide the 4-Month Safety Update Report for the above referenced new drug application. This report presents additional safety data. Emphasis is placed on data from the single, adequate and well controlled, pivotal trial, Protocol No. 0468H1-309-US. Data from four additional ongoing Rapamune Tablet studies are also reported in this safety update. They include 2 long-term extension studies (Protocols 306 and 311) and 2 additional ongoing controlled studies (210 and 310).

The data cutoff dates for this safety update were July 30, 1999 for all studies. The data for all studies were cumulative as of the cutoff date. Because differences in protocols, data from these studies were not integrated, rather they are presented individually.

Patient narratives and Case Report Forms (Item 12) are provided for all patients who died or discontinued due to adverse events. Case report forms are provided in electronic format only. Item 12 is provided per FDA's "Guidance for Industry: Providing Regulatory Submissions in Electronic Format-NDA." This item is being provided on two (2) CD-ROMs approximately 700 Mb in size, and is being submitted directly to the Central Electronic File Room for uploading onto the FDA network.

An electronic review aide consisting of the entire 4-month update as Portable Document Format (PDF) files is also provided with this submission on a single CD. Please note that all files were scanned for viruses using McAfee VirusScan 4.0.3 software and no viruses were detected.

ORIGINAL

Accordingly, we are pleased to provide herewith, in 1 volume, the 4-Month Safety Update Report for Rapamune Tablets.

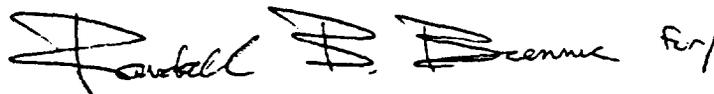
This submission is organized as follows:

1. Item 9: 4 Month Safety Update Report (paper-1 volume).
2. Item 12: Electronic CRFs for the all patients who died or discontinued due to adverse events.

If you have any questions regarding this submission, please contact our representative, Mr. Randall Brenner, at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES

Handwritten signature of Randall B. Brenner in black ink, followed by the initials "for/".

David K. Ellis, Ph.D., Director
Worldwide Regulatory Affairs

cc. Mr. Matt Bacho with 5 desk copy

Rbb/431.doc

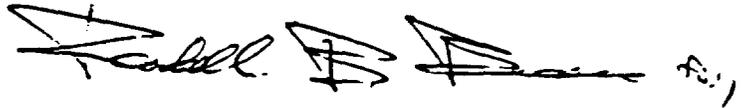
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- ATTACHMENT 5. A tabular presentation of clinical site information. The data are presented by investigator and by treatment group. The parameters are: number of patients enrolled; number of patients at the primary efficacy endpoint; number of discontinuations; and the number of serious adverse events. Please recall that the primary endpoint is defined as efficacy failure at six months; i.e., the composite of the first occurrence of acute rejection, death, or patient with graft loss. Serious adverse events are defined as deaths, graft loss, malignancies, and life-threatening events.

If you have any questions regarding this submission, please contact our representative, Mr. Randall Brenner, at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES



David K. Ellis, Ph.D., Director
Worldwide Regulatory Affairs

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NDA ORIG AMENDMENT

REGULATORY AFFAIRS

December 21, 1999

XR

NDA No. 21-110

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. 21-110 for Rapamune® (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

The purpose of this submission is to update the patent information contained within this application. The patent and exclusivity information along with the patent certification information can be found in Volume 1, pages 34-35. The reason for updating this information is that an additional patent has been approved since the filing date. The new patent is US Patent Number 5,989,591.

Accordingly, attached please find the updated:

- 1) Item 13: Patent and Exclusivity Information.
- 2) Item 14: Patent Certification with Respect to Any Patent Which Claims the Drug.

If you have any questions regarding this submission, please contact our representative, Mr. Randall Brenner, at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES

David K. Ellis, Ph.D., Director
Worldwide Regulatory Affairs

cc Mr. Matt Bacho with 1 desk copy
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ORIGINAL

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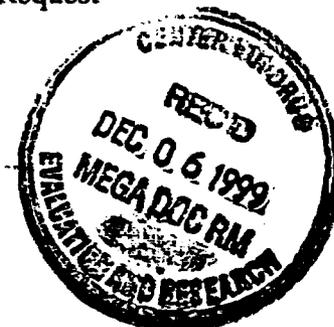
REGULATORY AFFAIRS

December 3, 1999

NDA No. 21-110

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. 21-110 for Rapamune® (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

Reference is also made to your November 22, 1999 facsimile in which you requested confirmation from Wyeth-Ayerst regarding the facilities and function with respect to the manufacturing, packaging, and controls of Rapamune Tablets.

The purpose of this submission is to provide the requested information. For the purpose of facilitating your review, FDA's comments have been restated in bold with our responses provided immediately thereafter.

1. **Please indicate if there are any facilities not listed below that are involved in the manufacture, packaging and control of Rapamune Tablets.**

Wyeth-Ayerst confirms that the facilities listed are a complete list, and that no other facilities are involved in the manufacture, packaging and control of Rapamune Tablets. Wyeth-Ayerst further confirms that [redacted] does not yet have a CFN number, although one has been requested.

2. **Please confirm the functions of each of the following facilities.**

Wyeth-Ayerst also confirms the functions of each facility as listed by the FDA, with the following exception: [redacted] site may serve to test the sirolimus dispersion for particle size, in addition to being the site of manufacture of the sirolimus dispersion.

Facility	Function
	Manufacture of sirolimus dispersion
	Sirolimus dispersion testing (appearance, particle size)
Wyeth-Ayerst Laboratories 64 Maple Street Rouses Point, NY 12979 CFN: 1310337	Sirolimus dispersion testing (Strength, identity, microbial content) manufacture of tablet core tablet manufacture alternative product testing site
	Sirolimus dispersion testing (microbial content)
Wyeth Pharmaceutical Company Highway No. 3, Km 142.1 Barrios Pozo Hondos and Jobos Guayama, Puerto Rico 00785 CFN: 2650135	Manufacture of tablet core Tablet branding, testing, packaging and release

3. Please confirm that the facilities are ready for pre-approval inspections.

The Wyeth-Ayerst Laboratories, Rouses Point, NY, and the Wyeth Pharmaceutical Company, Guayama, Puerto Rico, facilities are immediately ready for pre-approval inspection.

_____ sites are also currently ready for pre-approval inspection.

4. Please indicate where the primary drug product stability studies were conducted.

The primary drug product stability studies were conducted at Wyeth-Ayerst Research, 401 North Middletown Road, Pearl River, NY 10965.

5. Please indicate where the commercial drug product stability studies will be conducted.

The commercial drug product stability studies will be conducted at Wyeth Pharmaceutical Company (WPC), Highway No. 3, Km 142.1, Barrios Pozo Hondos and Jobos, Guayama, Puerto Rico, 00785. Analytical testing of the stability samples may be performed at WPC as well as the Rouses Point facility, as noted in the table in Comment 2.

If you have any questions regarding this submission, please contact our representative, Mr. Randall Brenner, at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES



Maureen D. Skowronek
Assistant Vice President
Worldwide Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy

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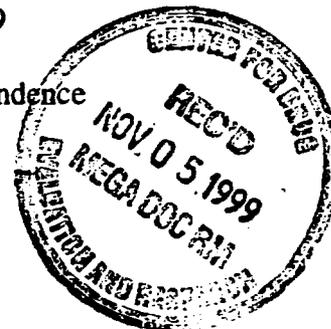
NEW CORRESP

NC

REGULATORY AFFAIRS

November 4, 1999

General Correspondence



NDA No. 21-110

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. 21-110 for Rapamune[®] (sirolimus) Tablets, previously submitted to your Administration on October 29, 1999.

As part of this NDA submission, Wyeth-Ayerst has agreed to provide the Division with a regulatory review aid, which will be loaded onto an FDA server. The purpose of this submission is to provide the noted review aid.

The review aid is being provided on a single CD. In this electronic review aid, the NDA paper volumes are being provided as PDF files with a detailed table of contents containing hyperlinks and bookmarks that will open the appropriate volume. Additionally, Excel files for the pharmacokinetic studies and SAS XPort files for the statistical data are being provided as well.

You will need Acrobat Exchange or Reader to read the PDF files. Reader is free software and the installation setup has been provided on this CD. Please call Wyeth-Ayerst Research in the USA with any technical questions or problems. The technical support number is 1-800-753-9757. Please note that the files have been tested with McAfee VirusScan (version 4.0.3a) and no viruses were discovered

Accordingly, attached please find:

1. A single CD containing the electronic regulatory review aid.
2. Electronic Regulatory Submission Manual.

If you have any questions regarding this submission, please contact our representative, Mr. Randall Brenner, at (610) 902-3792.

Sincerely,

WYETH-AYERST LABORATORIES



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

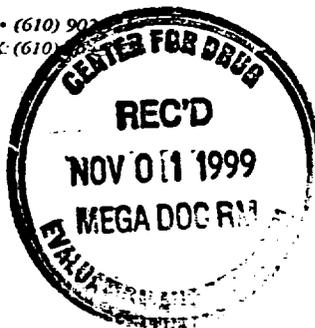
cc. Mr. Matt Bacho with 1 desk copy

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REGULATORY AFFAIRS



October 29, 1999

NDA No. 21-110

Original NDA

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:

Please find enclosed a new drug application, NDA No. 21-110 for Rapamune[®] (sirolimus) Tablets. The subject of this NDA is an alternative dosage form, tablet, of Rapamune[®] (sirolimus) Oral Solution, which was recently approved on September 15, 1999. Rapamune[®] Oral Solution has been shown to be safe and effective in the prevention of organ rejection in patients receiving renal transplants. This application seeks approval of the tablet dosage form for the same indication as the oral solution.

The tablet dosage form was developed with the intent of demonstrating equivalent safety and efficacy compared to the oral solution. The tablet formulation has several advantages over the oral solution formulation in terms of convenience for the patient. The oral solution formulation requires that the drug be mixed with orange juice or water before ingestion and that the solution be mixed in a glass or plastic container; refrigerated storage is also recommended. In contrast, the tablet formulation is easily administered without additional steps and it may be stored at room temperature. These improvements in the formulation should enhance patient acceptance in terms of ease of administration, storage, and compliance.

Regulatory History

The IND for Rapamune[®] Oral was filed on March 17, 1992 to the Division of Anti-Viral Drug Products. The development of Rapamune[®] was facilitated by the highly interactive relationship of FDA and Wyeth-Ayerst. Key issues relative to significant nonclinical and clinical development plans were discussed with FDA and resulted in agreements on the plans, the design of significant studies, and the dose selection of these studies. The development of the recently approved solution formulation preceded identification and selection of the tablet dosage form. The most significant of these interactions are summarized below:

- On June 27, 1997 a meeting was held with the Division to discuss the clinical development plan for Rapamune® Tablets. In general, the Division agreed with our plans to evaluate the two formulations (oral solution and tablet) clinically in Protocol 309. The time point for determining the incidence of acute rejection, three months, was considered acceptable provided the full efficacy analysis is a composite, i.e. incidence of acute rejection (3 months) and patient and graft survival at 12 months. It was agreed that the dose would be selected based upon Phase II data and preliminary estimates from blinded Phase III data (Protocols 301 and 302; pivotal studies for oral solution).
- On April 7, 1999, a pre-NDA teleconference was held in which the clinical and chemistry, manufacturing, and controls, sections of the NDA were discussed. In general, FDA concurred with the proposed content and format of the NDA. It was agreed that 3-month data could be presented in the initial tablet NDA with an analysis of 6-month efficacy data. Twelve-month patient and graft survival data for all patients could be presented in the 4-month safety update. Additionally, FDA agreed with the plans to provide appropriate pharmacokinetic data in addition to referencing data previously provided in the NDA for Rapamune® Oral Solution (NDA No. 21-083). References will also be made to NDA No. 21-083 for a majority of the preclinical data. Preclinical toxicology data specific to the tablet formation are limited to a study intended to qualify impurities.

Wyeth-Ayerst informed FDA of a change in the tablet shape late in the development plan. In order to set the product apart from other medications, the initial oval shape tablet was changed to a triangular shaped tablet. The two tablet shapes are identical in terms of components, composition, containers and closures. FDA agreed with the plans to seek approval on the triangular tablet.

With the filing of this submission we are requesting a waiver of a bioequivalence study. A justification for this waiver can be found in Item 4 (section 4.1.5.4) of the NDA. The justification is supported by an *in vitro/in vivo* correlation (multiple level C-IVIVC) which has been developed from available *in vitro* dissolution data and *in vivo* pharmacokinetic data gathered with the oval shape. Additionally, this is supported by dissolution profiles of the oval and triangular shape.

Additionally, FDA agreed that the amount of stability data at filing would be adequate, however, they would not support an expiry date of more than 6 months beyond the actual time studied for stability. Long-term stability data could be presented for the oval tablet, with 3-month data on three batches for the triangular shape. It was agreed that additional stability data could be provided during the review cycle as long as enough time is left to review it thoroughly.

Subsequent to our pre-NDA discussion, a decision was made to provide additional data in the original tablet NDA. This application contains longer term stability data (18 months oval, and 6 months triangular tablets) and complete 6 month safety and efficacy data. Twelve-month patient and graft survival data will be submitted during the course of the NDA review, at the time of the safety update.

Clinical Studies

The primary clinical evidence of the safety and efficacy focuses on a single Phase III study, 0468H1-309-GL. Study 309-GL was designed to compare the safety and efficacy, and to determine the pharmacokinetic profiles, of sirolimus oral solution and tablets in de novo renal transplant recipients. Study 309 is an open label, multi-center study which examined the safety and efficacy of a tablet formulation of sirolimus (2 mg/day) in combination with Neoral[®] and corticosteroids in recipients of primary or secondary, cadaveric or living, non-haploidentical renal allografts. The control group received concomitant immunosuppression consisting of the Neoral[®]/corticosteroids and recently approved Rapamune[®] Oral Solution. Patients were randomly assigned to treatment before transplantation. A single dose level of 2 mg/day was selected based upon both the results from Phase II studies and the observed overall rate of acute rejection while Phase III studies with the oral solution were still blinded. Standardized corticosteroid doses were mandated both for daily maintenance and for the treatment of rejection in both groups.

The results demonstrate that the efficacy of the sirolimus tablet formulation at a dose of 2 mg/day is equivalent to that of sirolimus oral solution at a dose of 2 mg/day in preventing efficacy failure (defined as the first occurrence of biopsy-confirmed acute rejection, graft loss, or death) during the first 3 months after transplantation. Additionally, there were no significant differences in; patient and graft survival, noted clinically important opportunistic infections, common transplant related infections, malignancy, or lymphoproliferative disease among the tablet and solution treatment arms. Thus, the results of study 309 demonstrate the clinical equivalence of the tablet and solution formulations of Rapamune[®].

NDA Content and Format

NDA No. 21-110 and User Fee ID No. 3815 have been pre-assigned to this application. The paper copy of this application contains a total of 59 volumes numbered consecutively. Included in these volumes are Items 1, 2, 3, 4, 5, 6, 8, 10, 13, 14, 16, 17, 18 and 19. Item 11 (case report tabulations) and Item 12 (case report forms) are provided in electronic form per FDA guidance (*Archiving Submissions in Electronic Format - NDAs*; issued January 1999). The archival copy of the electronic files is provided on tape with Digital Equipment Corporation DLT20/40 and 10/20 GB format using OPENVMS with VMS backup and will be loaded on FDA servers by FDA IT personnel per guidance. The files are organized in study directories; the two directories are entitled [REDACTED].

There is a table of contents file in each directory: [REDACTED] in [REDACTED] Indexes entitled [REDACTED] respectively, have been prepared for each directory and appear in the [REDACTED] directory. Please note that the submission files have been tested with McAfee VirusScan (version 4.0.3a) and no viruses were discovered. The electronic submission of Item 11 and Item 12, as compiled, is approximately .2 gigabytes and is provided on one tape in a separate binder accompanying the paper submission.

An electronic regulatory review aid will be provided using an FDA server located at the FDA Corporate Boulevard facility, Gaithersburg, MD. The review aid will be provided on a single CD and will be sent to the Central Documents Room approximately one week after the NDA submission. In this electronic review aid, the NDA paper volumes will be provided as PDF files with a detailed overall table of contents containing hyperlinks and bookmarks that will open the appropriate volume. Additionally, Excel files for the pharmacokinetic studies and SAS XPort files for the statistical data will be provided as part of the review aid.

In closing, if there are any questions concerning this application, please contact our representative Mr. Randall Brenner at (610) 902-3792

Sincerely,

WYETH-AYERST LABORATORIES



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

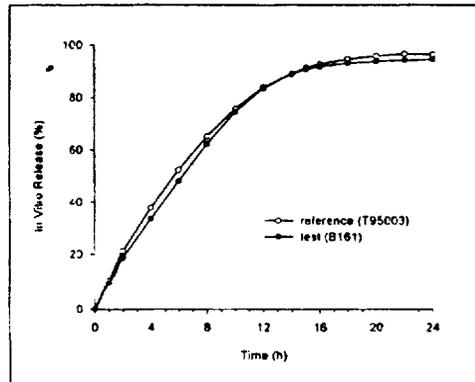
cc. Mr. Matt Bacho
BB/Rapamune/NDA No. 21-110

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Time (h)	Mean % Dissolved (Test)	Mean % Dissolved (Reference)
0	0	0
1	9.91	11.01
2	18.68	21.25
4	33.61	37.88
6	48.06	52.38
8	62.27	65.18
10	74.48	75.67
12	83.49	84.03
14	88.85	89.19
15	90.53	91.39
16	91.69	92.61
18	92.98	94.59
20	93.73	95.73
22	94.14	96.49
24	94.49	96.40

Figure 1 - Mean in vitro dissolution data for diltiazem for reference [redacted] and test [redacted] used in study [redacted]. USP Dissolution Apparatus II,



water, 100 rpm.

The biopharmaceutics reviewer calculated a similarity factor “f2” of 78.7 for the test and reference 240-mg Dilacor XR[®] capsules. The f2 value of 78.7 indicates similar dissolution between test and reference Dilacor XR[®] capsules.

BIOWAIVERS:

The sponsor has not submitted in vitro dissolution data for the lower strengths 120-mg and 180-mg supporting similarity in dissolution for products manufactured at the two sites.

COMMENTS:

1. The sponsor did not provide comparative dissolution data for the lower strengths, i.e. 120-mg and 180-mg, of Dilacor XR[®]. Comparative dissolution profiles are to be submitted in application/compendial medium and in 3 other media () to obtain an in vivo bioequivalence study waiver for the manufacturing site change for the 120-mg and 180-mg strengths.
2. The present bioequivalence study () was conducted in males only (inclusion criteria). The Agency discourages exclusion of subjects from studies solely based on gender except for potential safety concerns.

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics approves the manufacturing site change for the 240-mg dose strength of Dilacor[®] XR only. The sponsor did not provide comparative dissolution data supporting site change for the lower strengths of Dilacor[®] XR, 120-mg and 180-mg. Therefore, a bioequivalence study waiver cannot be granted for the 120-mg and 180-mg strengths of Dilacor[®] XR.

The Agency recommends the sponsor to submit comparative dissolution data for the 120-mg and 180-mg strengths of Dilacor XR[®] in application/compendial medium and in 3 other media () to obtain an in vivo bioequivalence study waiver for the manufacturing site change for the 120-mg and 180-mg strengths.

/s/

Gabriel J. Robbie, Ph. D.

RD/FT by Angelica Dorantes, Ph. D.

cc: NDA 20092, HFD 110, HFD 860 (Mehta, Robbie), CDER document room: Attn: Biopharm (CDER)



NDA 20-092/S-014

12/29/00

Watson Laboratories, Inc.
Attention: Dorothy Frank, M.S., RAC
Research Park
417 Wakara Way
Salt Lake City, Utah 84108

Dear Ms. Frank:

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

Name of Drug Product: Dilacor (Diltazem Hydrochloride) Extended Release Capsules

NDA Number: 20-092

Supplement Number: S-014

Date of Supplement: November 10, 2000

Date of Receipt: November 13, 2000

Unless we find the application not acceptable for filing, this application will be filed under section 505(b) of the Act on January 12, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Control Room 5002
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call:

Mr. John Guzman
Regulatory Project Manager
301-594-5312

Sincerely,

A stylized, handwritten signature in black ink, appearing to be the initials 'N.A.M.' or a similar representation of the sender's name.

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research