CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-110

ADMINISTRATIVE DOCUMENTS

Patent / Exclusivity Information

1)	Active ingredient(s)	Sirolimus
2)	Strength(s)	1 mg
3)	Trade Name	Rapamune®
4)	Dosage Form (Route of Administration)	Tablet in bottles of 100 tablets Blister packs of 30 tablets Redipak® of 100 tablets
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	21-110
7)	Approval Date	TBD
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	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.
9)	Applicable patent numbers and expiration date of each	U.S. Patent 5,100,899, Normal Expiration Date: June 6, 2009 U.S. Patent 5,212,155, Normal Expiration Date: May 18, 2010 U.S. Patent 5,308,847, Normal Expiration Date: May 3, 2011 U.S. Patent 5,403,833, Normal Expiration Date: April 4, 2012 U.S. Patent 5,989,591, Normal Expiration Date: March 11, 2018

NDA No. 21-110

PATENT INFORMATION UNDER SECTION 505(b)

The use of Rapamune® (Sirolimus; rapamycin) for inhibiting rejection in organ or tissue transplantation is covered by U.S. Patent 5,100,899, normal expiration date June 6, 2009.

The use of Rapamune® (Sirolimus; rapamycin) in combination with cyclosporin for inhibiting rejection in organ or tissue transplantation is covered by U.S. Patent 5,212,155, normal expiration date May 18, 2010.

The use of Rapamune® (Sirolimus; rapamycin) in combination with azathioprine for inhibiting rejection in organ or tissue transplantation is covered by U.S. Patent 5,308,847, normal expiration date May 3, 2011.

The use of Rapamune® (Sirolimus; rapamycin) in combination with a corticosteroid for inhibiting rejection in organ or tissue transplantation is covered by U.S. Patent 5,403,833, normal expiration date April 4, 2012.

An application for extension under the terms of the Drug Price Competition and Patent Term Restoration Act of 1984 will be filed upon approval of the NDA. Patent Information will be updated upon issuance of a certificate of patent term extension. The parent company of applicant is the exclusive licensee of this patent. In the opinion of applicant and to the best of applicant's knowledge, there is no other U.S. patent which claims the drug for which applicant has sought approval or which claims the use of the drug for which applicant has sought approval.

WYETH-AYERST LABORATORIES

By: _____

Arnold S. Milowsky
Senior Patent Attorney

EXCLUSIVITY SUMMARY for NDA # 21-110 **SUPPL #** _____

Trade Name Rapamune **Generic Name** Sirolimus

Applicant Name Wyeth-Ayerst Research **HFD-** 590

Approval Date August 25, 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/X/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /X/

   If yes, what type(SE1, SE2, etc.)? N/A

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   N/A

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical

data: N/A

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Wyeth-Ayerst requested 3 years of exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-083 Rapamune Oral Solution

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

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If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the

investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain: _____

_____

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 309-GL

Investigation #2, Study # 301

Investigation #3, Study # 302

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /X/ NO /___/

Investigation #3 YES /X/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 21-083 Study # 301
NDA # 21-083 Study # 302
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 309-GL

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # [redacted] YES /X/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____

_____	!	_____	
	!		
_____	!	_____	
	!		

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

/S/ 9/29/00

Signature of Preparer Date

Title: Regulatory Project Mngr

/S/ 9/29/00

Signature of Office of Division Director Date

cc:
Archival NDA
HFD- /Division File

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	021110	**Trade Name:**	RAPAMUNE (SIROLIMUS) 1MG TABLETS
Supplement Number:	000	**Generic Name:**	SIROLIMUS
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	THE PROPHYLAXIS OF ORGAN REJECTION IN PATIENTS RECEIVING RENAL TRANSPLANTS
Action Date:	10/29/99		

Indication # 1	Prophylaxis of acute rejection in renal transplant patients
Label Adequacy:	Inadequate for ALL pediatric age groups
Forumulation Needed:	NO NEW FORMULATION is needed
Comments (if any):	A Written Request letter for both the oral solution and tablet dosage forms of Rapamune for children 0-18 years of age was issued to Wyeth-Ayerst Research on September 15, 1999.

Lower Range	Upper Range	Status	Date
0 years	18 years	Deferred	12/31/04

This page was last edited on 8/16/00

/S/

Signature - ______ 8/16/00

Date

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Rapamune® (sirolimus) Tablets
NDA No. 21-110

Item 16 **Debarment Certification**

Wyeth-Ayerst hereby certifies that it did not and will 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 application No. 21-110 for Rapamune Tablets.

Signed: _____

Maureen D. Skowronek
Assistant Vice President
Worldwide Regulatory Affairs

Public Health Service
Food and Drug Administration

Expiration Date: XX/XX/XX

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkboxes.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator has a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators

Rapamune Tablet	Studies 210-EU, 306-US, 309-AU/CA/US
(See attached lists)	310-AU/CA/EU, 311-EU

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☒ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

Names	Titles
Joseph S. Camardo, M.D. Mr. Richard R. DeLuca	Senior Vice President - Clinical R&D Vice President - R&D Finance
Firm/Organization Wyeth-Ayerst Research	
Signature	**Date** 10/14/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

FORM FDA 3454 (10/98)

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Rapamune Tablet
Study 210-EU

Last Name	First	MI
Belgium		
Abramowicz	D	
Besse	T	
Eddour	D	Chaib
Malaise	J	
Nortier	J	
Squifflet	J	P
Vereerstraeten	P	
Wissing	K	M
Spain		
Campistol	Jose	Marie
Gil-Vernet	S	
Grinyo	Jose	Maria
Morales	Jose	Maria
Moreso	F	
Seron	D	
Vila	A	
France		
Bouloux		
Chong		
Kreis		
Mourad		
Germany		
Sohr		
Sweden		
Brattstrom	C	
Groth	C	G
Wrammer	L	

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Attachment to Section 1

Rapamune Tablet
Study 306 US

Last Name	First	MI
Abrams	Joan	
Adams	Mark	B
Adams	Patricia	L
Alfrey	Edward	J
Alveranga	Denise	
Anderson	Althena	
Aradhye	Shreeram	
Armstrong	Doug	
Arnaout	Walid	
Aswad	Saleh	
Badosa	Francisco	
Baker	A	L
Baliga	Prabhakar	
Barcenas	Camilo	
Barker	Catherine	
Barker	Clyde	
Bassadonna	Giacomo	P
Baxter	Joanne	
Bia	Margaret	J
Bilodeau	Kristen	
Bodziak	Kenneth	
Bogaard	Thomas	
Bohannon	Lawrence	L
Bowers	Victor	
Brayman	Kenneth	L
Bresnahan	Barbara	A
Brett	Myeva	
Brinker	Karl	
Brooks	Barbara	
Bruce	D	
Buell	J	
Burrows	Lewis	
Busuttil	Ashley	
Butt	Khalid	M
Charette	J	
Cibrik	Diane	
Cirulis	Connie	
Colquhoun	Steven	
Conjeevaram	H	
Conti	David	J
Crippin	Jeffrey	
Cromer	Deborah	T
Cronin	D	
Curtis	John	J

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Attachment to Section 1

Rapamune Tablet
Study 306 US

Last Name	First	MI
Dafoe	Donald	C
Dahlke	Linda	
Danovitch	Gabriel	
DeBernardi	Michael	
Deierhoi	Mark	A
Delaney	Vera	
Dunn	John	F
England	Brian	
Eskind	Lon	B
Esquenazi	Rafael	
Ettenger	Robert	B
Fairchild	Ralph	
Fernandez	Debbie	
Fernandez-Sloves	Idalia	M
Filo	Ronald	
Fotiadis	Chris	
Freeman	Richard	
Friedman	Amy	L
Fung	John	J
Gaboian	Karine	
Glisson	Susan	
Gloor	James	
Glowacki	Shannon	
Goldstein	[illegible]	
Gonwa	Thomas	
Gonzalez	Laura	
Goral	S	
Gores	Paul	
Gritsch	H	Albin
Groggel	Gerald	C
Grossman	Robert	
Gruber	Scott	
Hammeke	Michael	D
Hannon	G	
Hariharan	Sundaram	
Hart	George	M
Hayes	Daniel	
Hays	Steve	
Helderman	J	H
Hricik	Donald	E
Inokuchi	Sharon	
Iskandar	Samy	
Jabs	Kathy	
Jagadeesan	Muralidharan	
Johnson	Christopher	P
Johnson	Stephanie	
Josephson	M	
Julian	Bruce	

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Rapamune Tablet
Study 306 US

Last Name	First	MI
Kahana	Lawrence	
Kaplan	Bruce	
Katz	Stephen	
Katznelson	Steve	
Kerr	Stephen	
Khalil	Kassem	
Khetan	Umakant	
Kliger	Alan	S
Klintmalm	Goran	
Knight	Richard	
Knight	Thomas	F
Krauss	Thomas	C
Kronson	Jeffrey	
Kumar	Anil	
Lake	Kathy	
Lakkis	Fadi	
Larson	Timothy	
Launiat	Sandra	
Leapman	Stephen	B
Leichtman	Alan	B
Leone	John	P
Levin	Barry	S
Levy	Freda	
Levy	Marlon	
Lingelbach	Susan	
Lorber	Marc	I
Mai	Martin	
Marterre	William	F
Martinez	Arturo	
Matas	Arthur	J
McHugh	Lois	
McNaughton	M	
Mead	J	
Melton	Larry	
Mendez	Rafael	G
Mendez	Robert	
Mielke	Brandon	
Milgrom	Martin	L
Millis	J	Michael
Millos	Budisavljevic	
Monaco	Anthony	P
Mulloy	Laura	L
Munson	Jennifer	
Murphy	Barbara	
Myhre	Kari	

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Attachment to Section 1

Rapamune Tablet
Study 306 US

Last Name	First	MI
Naji	Ali	
Naraghi	Robert	
Nesser	David	
Netto	Georges	J
Newell	K	
Neylan	John	F
Nyberg	Scott	
Ojo	Akinloku	
O'Laughlin	R	
Pankewycz	Oleh	
Pavlakis	Martha	
Pescovitz	Mark	D
Raja	Rasib	
Rajagopalan	P	R
Richie	R	
Rohr	Michael	S
Rohrer	Richard	
Roza	Allan	M
Sabastian	Lisa	
Sabawi	Mazen	
Salley	Marsha	
Sanders	Charles	
Scandling	John	D
Schiano	T	D
Schulak	James	A
Schwab	Thomas	
Seaman	Mary	
Shapiro	Michael	E
Shen	Gary	
Shidban	Hamid	
Siegel	C	
Simpson	Mary Ann	
Singh	Tejinder	P
Small	Marjorie	
Someren	Ayten	
Spira	Moses	
Stack	Austin	
Stegall	Mark	
Steinberg	Steven	
Sterioff	Sylvester	
Strom	Terry	B
Sudan	Debra	L
Sunga	Victor	
Taylor	Rodney	
Thistlethwaite	J	R
Tillery	G	Weldon
Toto	Robert	

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Attachment to Section 1

Rapamune Tablet
Study 306 US

Last Nam	First	MI
Van Buren	Charles	
Van Buren	David	
Velez	Ruben	
Velosa	Jorge	
Vergne-Marini	Pedro	
Walker	Phillip	
Warvariv	Vasyl	
Weigel	Kelly	A
Weinberg	Joel	
Weinstein	Samuel	
Wiesner	Russell	
Wiggins	Roger	C
Wilkinson	Alan	H
Woodle	E	S
Wright	Charles	
Wright	Francis	H
Yang	Shuin-Lin	
Yoshida	A	
Yum	Moo-Nahm	
Zapanta, Jr.,	Ramulfo	F

APPEARS THIS WAY
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Attachment to Section 1

Rapamune Tablet
Study 309-AU

Last Name	First	MI
Allen	R	D M
Bannister	K	
Burke	John	
Campbell	Scott	
Carney	G	
Cass	A	
Chapman	Jeremy	
Charlesworth	J	A
Clarkson	T	
Collett	P	
de Jersey	Peter	
Duggin	G	
Eris	Josette	
Falk	Michael	
Fassett	Robert	
Faull	R	
Fraser	Ian	
Freeman	John	
Furlong	Tim	
Gallagher	M	
Gillin	A	
Greenstein	J	
Griffin	Anthony	
Hawley	Carmel	
Healy	Helen	
Herzig	Karen	
Horvath	J	
Hurley	B	
Hutchison	Brian	
Isbel	Nicole	
Jardine	Meg	
Johnson	David	
Johnson	J	
Jones	Emlyn	
Kainer	G	
Kalowski	S	
Lau	H	
Lawrence	J	
Lonergan	M	
Luxton	Grant	
Macdonald	G	J

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Attachment to Section 1

Rapamune Tablet
Study 309-AU

Last Name	First	MI
MacGinley	Robert	
Mackie	J	
Mathew	Timothy	
Moody	Harry	
Nankivell	B	J
Nicholls	Kathleen	
Nicol	David	
O'Connell	P	J
Petrie	Jim	
Pussell	Bruce	A
Rigby	Russell	
Robertson	M	R
Rosenberg	A	
Roy	L	P
Russ	G	
Saltissi	David	
Tiller	David	
Walker	Rowan	G
Wyndham	R	

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Attachment to Section 1

Rapamune Tablet
Study 309-CA

Last Name	First	MI
Baltzan	Marcel	A
Busque	Stephan	
Daloze	Pierre	
Girardin	Catherine	
Leveille	Michel	
Mongrain	Sylvie	
Saint-Louis	Gilles	
Shoker	Ahmed	S
Smeesters	Christian	

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FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Rapamune Tablet
Study 309 US

Last Name	First	MI
Adams	Mark	B
Alfrey	Edward	J
Amos	Randolph	C
Asai	Paul	
Aswad	Saleh	
Baillie	G	Mark
Baliga	Prabhakar	
Basadonna	Giacomo	Paul
Batiuk	Thomas	
Ben-Haim	Menachem	
Bertolatus	J	Andrew
Bia	Margaret	J
Bodziak	Kenneth	
Bogaard	Thomas	
Bresnahan	Barbara	A
Brett	Myeva	
Bunke	C	Martin
Burrows	Lewis	
Butt	Khalid	M H
Cirulis	Connie	
Conti	David	J
Corwin	Claudia	
Curtis	John	J
Dafoe	Donald	C
Danovitch	Gabriel	
Deierhoi	Mark	A
Delaney	Vera	
Downs	Robert	
Dunn	John	F
Facciuto	Marcello	
Fairchild	Ralph	
Fernandez-Sloves	Idalia	M
Filo	Ronald	
Fishbein	Thomas	
Fisher	Robert	A
Freeman	Richard	
Friedman	Amy	L
Gaboian	Karine	
Gaston	Robert	S
Gehr	Todd	
Genyk	Yuri	
Gores	Paul	F
Groggel	Gerald	C
Gruber	Scott	
Guasch	Antonio	

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Rapamune Tablet
Study 309 US

Last Name	First	MI
Guy	Stephen	
Ham	John	M
Hammeke	Michael	D
Hariharan	Sundaram	
Hart	George	M
Hatch	Julie	
Hayes	Daniel	H
Hunsicker	Lawrence	
Jagadeesan	Murlidharan	
Jindal	Rahul	M
Johnson	Christopher	P
Julian	Bruce	A
Katz	Stephen	
Kelly	Dympna	
Kew	Clifton	E
Khetan	Umakant	
King	Anne	L
Kliger	Alan	S
Knight	Richard	
Knight	Thomas	F
Kraus	Michael	
Lakkis	Fadi	G
Larsen	Christian	P
Leapman	Stephen	B
Leiberman	Kenneth	
Leone	John	P
Lorber	Marc	I
Marcos	Amadeo	
Martinez	Arturo	G
Mendez	Robert	
Mendez	Rafael	G
Milgrom	Martin	L
Millos	Budisavljevic	
Mulloy	Laura	L
Murphy	Barbara	
Neylan	John	F
O'Brien	David	P
Pavlakis	Martha	
Pearson	Thomas	C
Perrone	Ronald	
Pescovitz	Mark	
Posner	Marc	P

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Rapamune Tablet
Study 309 US

Last Name	First	MI	
Rajagopalan	P	R	
Rayhill	Stephen		
Rodgers	Crystal		
Rodriguez-Laiz	Gonzalo		
Rohrer	Richard		
Roza	Allan	M	
Sabawi	Mazen		
Scandling	John	D	
Shen	Gary		
Shidban	Hamid		
Singh	T	Paul	
Small	Marjorie		
Spira	Moses		
Steinberg	Steven		
Steiner	Robert	W	
Sudan	Debra	L	
Sunga	Victor		
Taylor	Rodney		
Thomas	Christie		
Tomasula	John		
Ucci	Angelo		
Van Buren	Charles		
Verani	Regina		
Walker	Phillip	J	
Wilkinson	Alan	H	
Wu	You	Min	
Wynn	James	J	
Young	Carlton	J	
Yum	Moo-Nahn		
Zapanta	Ramulfo		

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FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Rapamune Tablet
Study 310-AU

Last Name	First	MI
Allen	R	D M
Augustson	B	
Bannister	K	
Barrat	L	
Burke	John	
Campbell	Scott	
Carney	G	
Caterson	Robyn	
Chapman	Jeremy	
Charlesworth	J	A
Clarkson	T	
Collett	P	
Disney	Alex	
Dogra	G	
Duggin	G	
Eris	Josette	
Falk	Michael	
Fassett	Robert	
Faull	R	
Fraser	Ian	
Freeman	John	
Gallagher	M	
Gillin	A	
Greenstein	J	
Griffin	Anthony	
Harris	D	C
Hawley	Carmel	
Healy	Helen	
Herzig	Karen	
Horvath	J	
Hurley	B	
Hutchison	Brian	
Jardine	Meg	
Johnson	J	
Johnson	David	
Jones	Emlyn	
Kainer	G	
Kalowski	S	
Kirkland	Geoff	
Lau	H	
Lawrence	J	
Lawrence	S	

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Rapamune Tablet
Study 310-AU

Last Name	First	MI
Lim	Wai	
Lonergan	M	
Luxton	Grant	
Mackie	J	
Mahony	J	
Mathew	Tim	
Moody	Harry	
Nankivell	B	J
Nicholls	Kathleen	
Nicol	David	
O'Connell	P	J
Petrie	J	
Pussell	Bruce	
Rigby	Russell	
Robertson	M	R
Rosenberg	A	
Roy	L	P
Russ	G	
Saltissi	David	
Tiller	David	
Walker	Rowan	
Wyndham	R	

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Rapamune Tablet
Study 310-CA

Last Name	First	MI
Cole	Edward	H
Daloze	Pierre	
Halloran	Philip	
Landsberg	David	N
Lawen	Joseph	
Ludwin	David	
Shoker	Ahmed	S
Zaltzman	Jeffrey	S

Last Name	First	MI
Belgium		
Kuypers	D.	
Maes		
Messiaen	T.	
Vanrenterghem	Yves	
France		
Akposso		
Baron		
Bedrossian	J.	
Berhery	L.	
Bourbigot	Bernard	
Costa		
Dantal		
Deteix		
Fournier		
Giral		
Heyman		
Hourmant		
Jacobs		
Jambon	Henri	
Kreis		
Lahlou		
Legendre		
Mazouz		
Moal		
Morelon		
Peraldi		
Pruna		
Rondeau	Jean	Paul
Souliliou	Jean	Daniel
Sraer	E.	
Thervet	Paul	
Viattel		
Westeel		
Zaoui		
Germany		
Arns	W.	
Aust		
Gerold		
Haufe	U	
Heemann		
Keller		
Kohnle		
Luetkes		
Manwald	H	
Sperschneider		

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Last Name	First	MI
Italy		
Altieri	Paolo	
Ancona	Giusto	
Boschiero	Luigi	
Branca	Gianfranco	
Carmellini	Mario	
Castagneto	Marco	
Cossu	Maria	
Di Paolo	Salvatore	
Foco	Maurizio	
Maiorca	Rosario	
Mosca	Franco	
Murgia	Maria	Gavina
Nanna	Giuseppe	
Nanni	Giuseppe	
Onano	Bruno	
Piredda	Gianbenedetto	
Sanorini	Silvio	
Satta	Renza	
Schena	Francesco	P
Schena	Antonio	
Setti	Gisella	
Sorba	Gianbattista	
Stallone	Giovanni	
Torini	Michele	
Valente	Umberto	
Netherlands		
Hilbrands	L.	B.
Hoitsma	A.	J.
Koene	R	A.P.
Norway		
Bentdal	Oystein	
Hartman	Anders	
Poland		
Oldakowska-Jedynak	U.	
Paczek		
Senotorski	G.	
Portugal		
Dias	Jose	Silva Coelho
Ferreira	Carlos	Bastos
Figueredo	Arnaldo	J
Henriques	Castro	
Lobos	Ana	Vila
Mota	Alfredo	
Oliveira	Helena	
Pataca	Isabel	
Pena	Joao	Rodrigues
Pinto	Reimao	
Remedio	Francisco	
Roseiro	Antonio	
Segueindo	Arnaldo	
Silva	Maria	Fernandez

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FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Rapamune Tablet
Study 311-EU

Last Name	First	MI
Belgium		
Besse	Totiane	
Eddour	Chaib	
Kuypers		
Maes	B.	
Malaise	Jaques	
Squifflet	J.	P.
France		
Bouloux		
Bruneel	Mamzer	
Chong		
Durand	F	
Jacobs		
Kreis		
Lang	P	
Mourad		
Peraldi		
Touraine		
Germany		
Loss	Martin	
Winkler	Michael	
Spain		
Campistol		
Gil-Vernet	S	
Grinyo	Jose	Maria
Morales	Jose	Maria
Moreso	F	
Seron	D	
Vila	Ana	

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FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 3

Rapamune Tablet
Study 210-EU

Letters requesting Financial Disclosure were sent to the Clinical Investigators listed below. If no response was received from the initial request, additional attempts were performed (such as mail, phone, fax, e-mail) in order to meet the Financial Disclosure requirement. See comments below for explanation of why Financial Disclosure forms could not be obtained.

Last Name	First	MI	Comments
Belgium			
Fernez	P		No longer at site. Cannot be located.
Germany			
Land	W.		Has not responded to several requests.
Zanker			Has not responded to several requests.
France			
Legendre			Has not responded to several requests.
Rostaing			Has not responded to several requests.

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APPEARS THIS WAY
ON ORIGINAL

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 3

Rapamune Tablet
Study 306 US

Letters requesting Financial Disclosure were sent to the Clinical Investigators listed below. If no response was received from the initial request, additional attempts were performed (such as mail, phone, fax, e-mail) in order to meet the Financial Disclosure requirement. See comments below for explanation of why Financial Disclosure forms could not be obtained.

Last Name	First	MI	Comments
Appel	Richard	G	Has not responded to several requests.
Asai	Paul		Has not responded to several requests.
Ayala	Janie		Has not responded to several requests.
Banowsky	Lynn		Has not responded to several requests.
Bertolatus	J	Andrew	Has not responded to several requests.
Bleyer	Anthony	J	Has not responded to several requests.
Buckalew	Vardaman		Has not responded to several requests.
Buckart	John	M	Has not responded to several requests.
Busuttil	Ronald	W	Has not responded to several requests.
Chavin	Kenneth		Has not responded to several requests.
Chen	Pauline	W	Has not responded to several requests.
Cortina	G		Has not responded to several requests.
Dawson	Sherfield		Has not responded to several requests.
Dikman	Steven	H	Has not responded to several requests.
Facciuto	Marcello		Has not responded to several requests.
Farmer	Douglas	G	Has not responded to several requests.
Fishbein	Thomas		Has not responded to several requests.
Freedman	Barry	I	Has not responded to several requests.
Ghobrial	Rafik	M	Has not responded to several requests.
Goldstein	Leonard	I	Has not responded to several requests.
Gonin	Joyce		No longer at site. Cannot be located.
Hoard	Peggy		Has not responded to several requests.
Holt	Curtis		Has not responded to several requests.
Jindal	Rahul	M	No longer at site. Cannot be located.
Johnson	K		Has not responded to several requests.
Kikeri	Deepak		No longer at site. Cannot be located.
Lassman	C		Has not responded to several requests.
Lieberman	Kenneth		Has not responded to several requests.
Martin	Paul		Has not responded to several requests.
McDiarmid	Sue		Has not responded to several requests.
Nylander	W		Has not responded to several requests.
Rocco	Michael	V	Has not responded to several requests.
Rodrigues-Laiz	Gonzalo	P	Has not responded to several requests.
Romani	Levio		Has not responded to several requests.
Siegel	Deborah	S	Has not responded to several requests.
Sindhi	Rakesh		Has not responded to several requests.
Stahl	Vicky		Has not responded to several requests.
Steiner	Robert	W	Has not responded to several requests.
Sullivan	M		Has not responded to several requests.
Ynares	C		Has not responded to several requests.

APPEARS THIS WAY
ON ORIGINAL

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 3

Rapamune Tablet
Study 309-AU

Letters requesting Financial Disclosure were sent to the Clinical Investigators listed below. If no response was received from the initial request, additional attempts were performed (such as mail, phone, fax, e-mail) in order to meet the Financial Disclosure requirement. See comments below for explanation of why Financial Disclosure forms could not be obtained.

Last Name	First	MI	Comments
George	C		Refused to complete Financial Disclosure form.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
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FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 3

Rapamune Tablet
Study 309 US

Letters requesting Financial Disclosure were sent to the Clinical Investigators listed below. If no response was received from the initial request, additional attempts were performed (such as mail, phone, fax, e-mail) in order to meet the Financial Disclosure requirement. See comments below for explanation of why Financial Disclosure forms could not be obtained.

Last Name	First	MI	Comments
Ashton	Kay		Has not responded to several requests.
Barker	Catherine	V	Has not responded to several requests.
Busuttil	Ashley		Has not responded to several requests.
Fabrega	Alfredo		Has not responded to several requests.
Gurken	Alihan		No longer at site. Cannot be located.
Kitabayashi	Kazuo		No longer at site. Cannot be located.
Laftavi	Mark	Reza	Has not responded to several requests.
Lingelbach	Susan		No longer at site. Cannot be located.
Sindhi	Rakesh		No longer at site. Cannot be located.
Whelchel	John	D	No longer at site. Cannot be located.

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FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 3

Rapamune Tablet
Study 310-AU

Letters requesting Financial Disclosure were sent to the Clinical Investigators listed below. If no response was received from the initial request, additional attempts were performed (such as mail, phone, fax, e-mail) in order to meet the Financial Disclosure requirement. See comments below for explanation of why Financial Disclosure forms could not be obtained.

Last Name	First	MI	Comments
George	C		Refused to complete Financial Disclosure form.

APPEARS THIS WAY
ON ORIGINAL

Letters requesting Financial Disclosure were sent to the Clinical Investigators listed below. If no response was received from the initial request, additional attempts were performed (such as mail, phone, fax, e-mail) in order to meet the Financial Disclosure requirement. See comments below for explanation of why Financial Disclosure forms could not be obtained.

Last Name	First	MI	Comments
Austria			
Mayer	G		Has not responded to several requests.
Oberbauer	R		Has not responded to several requests.
France			
Blancho			Has not responded to several requests.
Cantarovitch			Has not responded to several requests.
Durand			Has not responded to several requests.
Germany			
Lutz	J.		Has not responded to several requests.
Merkel			Has not responded to several requests.
Reimer	J.		Has not responded to several requests.
Richter			Has not responded to several requests.
Zimmermann	U.		Has not responded to several requests.
Italy			
Cortesini	Raffaello		Has not responded to several requests.
Segoloni	Giussepe		Has not responded to several requests.
Spain			
Blanco	J.		Has not responded to several requests.
Sweden			
Claesson	Kerstin		Has not responded to several requests.
Wilczek	H.		Has not responded to several requests.

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 3

Rapamune Tablet
Study 311-EU

Letters requesting Financial Disclosure were sent to the Clinical Investigators listed below. If no response was received from the initial request, additional attempts were performed (such as mail, phone, fax, e-mail) in order to meet the Financial Disclosure requirement. See comments below for explanation of why Financial Disclosure forms could not be obtained.

Last Name	First	MI	Comments
France			
Dahmane			Has not responded to several requests.
Galland			Refused to complete Financial Disclosure form.
Lefrancois	N		Refused to complete Financial Disclosure form.
Spain			
Segura	J.		Has not responded to several requests.
Sweden			
Backman	L		Has not responded to several requests.
Brattstrom	C.		Has not responded to several requests.
Claesson			Has not responded to several requests.
Ostman	A.		Has not responded to several requests.
Ostrtatt	O.		Has not responded to several requests.
Wrammer	L.		Has not responded to several requests.

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Public Health Service
Food and Drug Administration

Expiration Date: XX/XX/XX

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Barry Kahan, M.D. (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study Rapamune Tablet (*Name of clinical study*), Study 306-US, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

Name Joseph S. Camardo, M.D. Richard R. DeLuca	Title Senior Vice President-Clinical Research Vice President-R&D Finance
Firm/Organization Wyeth-Ayerst Research	
Signature	Date 10/14/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

<- Please DO NOT RETURN this form to this address.

FORM FDA 3455 (10/98)

Attachment

FDA Form 3455
Disclosure: Financial Interests and Arrangements of Clinical Investigators

Rapamune Tablet
Study 306-US

Barry D. Kahan, Ph.D., M.D., the principal investigator at Hermann Hospital, the University of Texas School of Medicine, Houston, Texas, has received from Wyeth-Ayerst Research approximately [redacted] for honoraria and reimbursement of business expenses. The University of Texas School of Medicine, Houston, Texas, has received from Wyeth-Ayerst Research, an educational grant of approximately [redacted] Dr. Kahan's specific role in the clinical program is outlined below.

Dr. Kahan's primary role in the Rapamune Tablet program as it relates to this current NDA for the tablet formulation is as a clinical investigator, holding primary responsibility for the conduct of clinical Study 306-US. In this capacity, Dr. Kahan oversees clinical care and management of renal transplant patients. His center enrolled a total of 87 patients into this specific study, and patients continue to be followed for long term safety at this time. The study required an evaluation of safety and efficacy parameters which were objective (i.e. patient and graft survival). The study required the assessment of other health care professionals in determining biopsy-confirmed acute rejection, lipid and renal effects. Furthermore, Dr. Kahan was not involved in the analysis of any safety and/or efficacy data obtained from Rapamune Tablet treated patients in this study, and is not anticipated to directly benefit from the sale of this product. Therefore, the financial assets received by Dr. Kahan were not likely to have influenced his medical assessment of the long term safety endpoints of the study (i.e., patient death, graft survival, and biopsy-confirmed acute rejection), or his assessment of key objective laboratory parameters (i.e., lipid and renal effects).

Public Health Service
Food and Drug Administration

Expiration Date: XX/XX/XX

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Barry Kahan, M.D. (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study Rapamune Tablet (*Name of clinical study*), Study 309-US, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

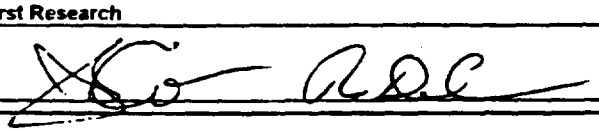
☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

Name	Title
Joseph S. Camardo, M.D. Richard R. DeLuca	Senior Vice President-Clinical Research Vice President-R&D Finance
Firm/Organization Wyeth-Ayerst Research	
Signature 	**Date** 10/14/98

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

<- Please DO NOT RETURN this form to this address.

FORM FDA 3455 (10/98)

Attachment

FDA Form 3455
Disclosure: Financial Interests and Arrangements of Clinical Investigators

Rapamune Tablet
Study 309-US

Barry D. Kahan, Ph.D., M.D., the principal investigator at Hermann Hospital, the University of Texas School of Medicine, Houston, Texas, has received from Wyeth-Ayerst Research approximately [redacted] for honoraria and reimbursement of business expenses. The University of Texas School of Medicine, Houston, Texas, has received from Wyeth-Ayerst Research, an educational grant of approximately [redacted] Dr. Kahan's specific role in the clinical program is outlined below.

Dr. Kahan's primary role in the Rapamune Tablet program as it relates to this current NDA for the tablet formulation is as a clinical investigator, holding primary responsibility for the conduct of clinical Study 309-US. In this capacity, Dr. Kahan oversees clinical care and management of renal transplant patients. His center enrolled a total of 32 patients into this specific study, and patients continue to be followed for long term safety at this time. The study required an evaluation of safety and efficacy parameters which were objective (i.e. patient and graft survival). The study required the assessment of other health care professionals in determining biopsy-confirmed acute rejection, lipid and renal effects. Furthermore, Dr. Kahan was not involved in the analysis of any safety and/or efficacy data obtained from Rapamune Tablet treated patients in this study, and is not anticipated to directly benefit from the sale of this product. Therefore, the financial assets received by Dr. Kahan were not likely to have influenced his medical assessment of the primary endpoint of the study (i.e., patient death, graft survival, and biopsy-confirmed acute rejection), or his assessment of key objective safety parameters (i.e., lipid and renal effects).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Wyeth-Ayerst Laboratories	8/25/2000
TELEPHONE NO. *(Include Area Code)* (610) 902-3792	FACSIMILE (FAX) Number *(Include Area Code)* (610) 964-5973

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

P.O. Box 8299
Philadelphia, PA 19101-8299

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-110

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Sirolimus	Rapamune

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
See Attachment 1 to Form 356h	Rapamycin, AY-022989

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	1 mg	Oral

(PROPOSED) INDICATION(S) FOR USE: The prophylaxis of organ rejection in patients receiving renal transplants

APPLICATION INFORMATION

APPLICATION TYPE (check one)
- ☒ NEW DRUG APPLICATION (21 CFR 314.50)
- ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
- ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE
- ☒ 505 (b) (1)
- ☐ 505 (b) (2)
- ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
- ☐ ORIGINAL APPLICATION
- ☐ AMENDMENT TO A PENDING APPLICATION
- ☐ RESUBMISSION
- ☐ PRESUBMISSION
- ☐ ANNUAL REPORT
- ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT
- ☐ SUPAC SUPPLEMENT
- ☐ EFFICACY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
- ☒ OTHER

REASON FOR SUBMISSION: Response to FDA Request

PROPOSED MARKETING STATUS (check one)
- ☒ PRESCRIPTION PRODUCT (Rx)
- ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____

THIS APPLICATION IS
- ☒ PAPER
- ☐ PAPER AND ELECTRONIC
- ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attachment 2 to Form 356h

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☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
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☐	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
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☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (k) (3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. OTHER (Specify) DMF Information, Financial Disclosure Information, Pediatric Rule

CERTIFICATION

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7. Local, state and Federal environmental impact laws.

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The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Randall B. Brenner, Manager Worldwide Regulatory Affairs	8/25/2000

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
170 Radnor Chester Road St. Davids, PA 19087	(610) 902-1792

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Wyeth-Ayerst Laboratories	8/21/2000
TELEPHONE NO. *(Include Area Code)* (610) 902-3792	FACSIMILE (FAX) Number *(Include Area Code)* (610) 964-5973

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

P.O. Box 8299
Philadelphia, PA 19101-8299

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-110

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Sirolimus	Rapamune

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* See Attachment 1 to Form 356h

CODE NAME *(If any)* Rapamycin, AY-022989

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	1 mg	Oral

(PROPOSED) INDICATION(S) FOR USE: The prophylaxis of organ rejection in patients receiving renal transplants

PLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

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TYPE OF SUBMISSION (check one)
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☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Response to FDA Request

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Randall B. Brenner, Manager Worldwide Regulatory Affairs	8/21/2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
170 Radnor Chester Road St. Davids, PA 19087	(610) 902-3792

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

FORM FDA 356h (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Wyeth-Ayerst Laboratories	8/18/2000
TELEPHONE NO. *(Include Area Code)* (610) 902-3792	FACSIMILE (FAX) Number *(Include Area Code)* (610) 964-5973

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

P.O. Box 8299
Philadelphia, PA 19101-8299

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-110

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Sirolimus	Rapamune

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
See Attachment 1 to Form 356h	Rapamycin, AY-022989

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	1 mg	Oral

(PROPOSED) INDICATION(S) FOR USE: The prophylaxis of organ rejection in patients receiving renal transplants

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

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Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
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☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION: Response to FDA Request

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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CERTIFICATION

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Randall B. Brenner, Manager Worldwide Regulatory Affairs	8/18/2000

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DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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FORM FDA 356h (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT: Wyeth-Ayerst Laboratories	DATE OF SUBMISSION: 8/17/2000
TELEPHONE NO. *(Include Area Code)*: (610) 902-3792	FACSIMILE (FAX) Number *(Include Area Code)*: (610) 964-5973
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: P.O. Box 8299 Philadelphia, PA 19101-8299	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued): 21-110

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*: Sirolimus	PROPRIETARY NAME *(trade name)* IF ANY: Rapamune
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: See Attachment 1 to Form 356h	CODE NAME *(If any)*: Rapamycin, AY-022989

DOSAGE FORM: Tablet	STRENGTHS: 1 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE: The prophylaxis of organ rejection in patients receiving renal transplants

APPLICATION INFORMATION

APPLICATION TYPE (check one): ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE: ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

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Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one): ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION: Response to FDA Request

PROPOSED MARKETING STATUS (check one): ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

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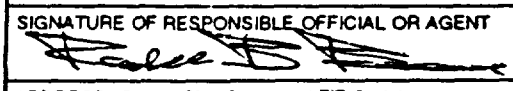
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Randall B. Brenner, Manager Worldwide Regulatory Affairs	8/17/2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
170 Radnor Chester Road St. Davids, PA 19087	(610) 902-3792

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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FORM FDA 356h (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Wyeth-Ayerst Laboratories	8/17/2000
TELEPHONE NO. *(Include Area Code)* (610) 902-3792	FACSIMILE (FAX) Number *(Include Area Code)* (610) 964-5973

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

P.O. Box 8299
Philadelphia, PA 19101-8299

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-110

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Sirolimus	Rapamune

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
See Attachment 1 to Form 356h	Rapamycin, AY-022989

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	1 mg	Oral

(PROPOSED) INDICATION(S) FOR USE: The prophylaxis of organ rejection in patients receiving renal transplants

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION: Response to FDA Request

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attachment 2 to Form 356h

oss References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
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☐	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
☐	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
☐	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
☐	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
☐	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (k) (3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. OTHER (Specify) DMF Information, Financial Disclosure Information, Peditric Rule

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

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The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Randall B. Brenner, Manager Worldwide Regulatory Affairs	8/17/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
170 Radnor Chester Road St. Davids, PA 19087	(610) 902-3792

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Hubert H. Humphrey Building, Room 531-H
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Washington, DC 20201

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FORM FDA 356h (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-110

APPLICANT INFORMATION

NAME OF APPLICANT: Wyeth-Ayerst Laboratories	DATE OF SUBMISSION: 10/29/99
TELEPHONE NO. *(Include Area Code)*: (610) 902-3798	FACSIMILE (FAX) Number *(Include Area Code)*: (610) 964-5973
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued)*: P.O. Box 8299, Philadelphia, PA 19101-8299	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, Telephone & FAX number)* IF APPLICABLE

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D OCT 29 1999 CDR

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued): 21-110

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*: Sirolimus	PROPRIETARY NAME *(trade name)* IF ANY: Rapamune
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: See Attachment 1 to Form 356h	CODE NAME *(If any)*: Rapamycin, AY-022989
DOSAGE FORM: Tablet	STRENGTHS: 1 mg
ROUTE OF ADMINISTRATION: Oral	

(PROPOSED) INDICATION(S) FOR USE: The prophylaxis of organ rejection in patients receiving renal transplants

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D NOV 01 1999 MEGA DOC RM

APPLICATION INFORMATION

APPLICATION TYPE (check one)
- ☒ NEW DRUG APPLICATION (21 CFR 314.50)
- ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
- ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE
- ☒ 505 (b) (1)
- ☐ 505 (b) (2)
- ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
- ☐ ORIGINAL APPLICATION
- ☐ AMENDMENT TO A PENDING APPLICATION
- ☐ RESUBMISSION
- ☐ PRESUBMISSION
- ☐ ANNUAL REPORT
- ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT
- ☐ SUPAC SUPPLEMENT
- ☐ EFFICACY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
- ☐ OTHER

REASON FOR SUBMISSION: New Submission

PROPOSED MARKETING STATUS (check one)
- ☒ PRESCRIPTION PRODUCT (Rx)
- ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 59

THIS APPLICATION IS
- ☐ PAPER
- ☒ PAPER AND ELECTRONIC
- ☐ ELECTRONIC

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See Attachment 2 to Form 356h

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Maureen D Skowronek	Maureen D. Skowronek Director, U.S. Regulatory Affairs	10/29/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
170 Radnor Chester Road St. Davids, PA 19087	(610) 902-3798

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH

EVALUATION OF CLINICAL INVESTIGATOR INSPECTIONS.

DATE: September 20, 2000

NDA 21-110

HFD 590

SPONSOR: Wyeth-Ayerst Research.

Product: Rapamune (Rapamycin), sirolimus oral liquid.

Indications: THE PROPHYLAXIS OF ORGAN REJECTION IN PATIENTS RECEIVING RENAL TRANSPLANT.

Project Manager: Mathew Bacho

Medical Officer: Rosemary Tiernan

I. Background:

These routine inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which NDA 21-110 approval may be based and to assure that the rights and welfare of the human subjects of those studies were protected. These inspections were conducted in accordance with CP 7348.811, Clinical Investigators, in addition to concentrate in comparing source documents, case report forms (CRFs), and data listings in regard to primary endpoints, adverse drug events reporting and discontinued subjects in these protocols. Sites selected in corroboration between HFD-590 Division medical officer, Dr. Tiernan and DSI reviewer, Dr. Jose Carreras.

Name	City	Protocol	CL
Sundaram Hariharan, M.D.	Milwaukee, Wisconsin	#0468H1-309-US	VAI
Charles T. Van Buren, M.D.	Houston, Texas	#0468H1-309-US	NAI

Key to Classifications
NAI = No deviation from regulations
VAI = Minor Deviation(s) from regulations

Site #1
Sundaram Hariharan, M.D.

This investigator enrolled twenty-six subjects in the study. Seventeen subjects completed the 6 months. The field investigator conducted a comprehensive review of fourteen subject's records. Data audit did not reveal significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appear acceptable.

Site #2
Charles T. Van Buren, M.D.

This investigator enrolled forty subjects in the study. Thirty-four subjects completed the study. Four subjects died of transplant complications. Two subjects were discontinued due to transplant complications. The field investigator conducted a comprehensive review of eight subject's records. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appear acceptable.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS :

No objectionable conditions were found in the above sites which would preclude the use of their data submitted in support of pending NDA.

Jose A. Carreras, M.D.

cc:
NDA 21-110
Division File
HFD-47/Currier

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation IV/ Division of Special Pathogens and Immunologic Drug Products

DATE: August 18, 2000

TO: Reanata Albrecht, M.D.
Acting Division Director, HFD-590

FROM: Marc W. Cavaillé-Coll, M.D., Ph.D. 8/18/00
Medical Officer Medical Team Leader, HFD-590

SUBJECT: NDA 21-110 for Rapamune® (sirolimus) Tablet for the prophylaxis of organ rejection in allogeneic renal transplantation.

The major issues of this NDA have been thoroughly discussed in the pre-clinical, statistical and clinical reviews. I concur with the consensus of the reviewers that NDA 21-110 for Rapamune® (sirolimus) Tablet, should be approved for the indication of prophylaxis of organ rejection in patients receiving allogeneic renal transplants, to be used concomitantly with cyclosporine and corticosteroids. This memorandum will briefly comment on a few areas that have been discussed at some length during the review process.

Rapamune®(sirolimus) Oral Solution was approved on September 15, 1999 for the prophylaxis of organ rejection in allogeneic renal transplantation (NDA 21-083). A solid table formulation has been developed, but was found to be 27% more bioavailable than the approved oral solution. Thus, a clinical study was conducted to assess whether 2 mg of Rapamune® administered as a tablet would be clinically equivalent to 2 mg administered as a solution, meaning that the tablet would have comparable efficacy without increased toxicity.

Overall, when used at doses of 2mg /day with cyclosporine and corticosteroids, Rapamune® tablet is as effective as Rapamune® oral solution, in preventing graft rejection in renal transplant recipients. Rates of adverse events known to be associated with sirolimus in previous clinical studies, including hyperlipidemia, hypercholesterolemia, increased serum creatinine, thrombocytopenia, and anemia, were comparable. There were no increased rates of infections associated with the use of the tablet. The relative efficacy and safety of Rapamune® tablet, compared to Rapamune® oral solution has not been evaluated at doses higher than 2mg per day.

The clinical development of Rapamune® continues to be a global project involving clinical centers in the US, Canada, Europe and Australia. The US regulatory action would represent the first approval for this new formulation in the world. Availability of a solid tablet formulation is expected to meet the needs of patients who have difficulty in using the oral solution, and should enhance compliance.

Post marketing safety of Rapamune® oral solution has also been examined during the review of this NDA. Cases of pneumonitis with no identified infectious etiology, sometimes with an interstitial pattern, have occurred in patients receiving immunosuppressive regimens including Rapamune®. In some cases the pneumonitis has resolved upon discontinuation of Rapamune®. This represents a new safety concern that has emerged since the approval of Rapamune® in the U.S. and has been added to the adverse event section of the package insert under the heading "Other Clinical Experience".

Several clinical issues await further resolution in proposed phase 4 post-marketing studies. These include: the evaluation of the optimal dose of sirolimus in renal transplant patients who are at high risk for acute rejection; the evaluation of the effect of sirolimus on long term renal function; and studies intended to define the type and duration of hyperlipidemia associated with the use of sirolimus. Further information is also needed on use in pediatric populations.

NDA 21-110
Division file
HFD-590/Cavaillé-Coll
HFD-590/Tiernan
HFD-590/Bacho

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: August 23, 2000

TO: Randy Brenner
Manager of Worldwide Regulatory Affairs
Wyeth-Ayerst Research
(610) 902-3792
(610) 964-5972 (fax)

FROM: Ellen C. Frank, R.Ph., Chief, Project Management Staff for Matthew A. Bacho, Regulatory Project Manager

THROUGH: Arzu Selen, Ph.D., Deputy Division Director, DPEIII
Funmi Ajayi, Ph.D., Clin. Pharm. & Biopharmaceutics Team Leader
Kofi A. Kumi, Ph.D., Clin. Pharm. & Biopharmaceutics Reviewer

NDA: 21-110 (Rapamune® Tablets)

SUBJECT: Biowaiver and Dose Proportionality Study

Please refer to your NDA 21-110 for Rapamune® Tablets:

1) We are granting a waiver of a bioequivalence study comparing the Rapamune® 1-mg triangular tablet to the oval-shaped tablet. This decision was based on:
   a) Similarity factor (f2) determinations of the dissolution profiles of the oval- and triangular-shaped tablets, and
   b) The small difference in surface area between the oval- and triangular-shaped tablets.

2) The [redacted] *in vitro* and *in vivo* correlation (IVIVC) that you submitted is inadequate and unacceptable. Therefore, the IVIVC you submitted cannot be used as the basis of granting waivers for pre-approval and post-approval changes in the tablet dosage formulation. The rationale behind this decision is that the IVIVC was developed using three data points, one of which was obtained from the oral solution formulation. IVIVC cannot be developed with information obtained from an oral solution. A minimum of three solid oral dosage formulations (preferably more than three) is needed to attempt a [redacted] correlation.

3) We recommend that future development plans for Rapamune® tablets include an evaluation of the dose proportionality of sirolimus over a dose range that includes 2 mg and 5 mg.

telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

/S/

Ellen C. Frank for Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: August 18, 2000

TO: Randy Brenner
Manager of Worldwide Regulatory Affairs
Wyeth-Ayerst Research
(610) 902-3792
(610) 964-5972 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Rosemary Tiernan, M.D., Medical Officer
Kofi A. Kumi, Ph.D., Acting Clin. Pharm. & Biopharm. Team Leader
Kenneth L. Hastings, Ph.D., Pharmacology/Toxicology Team Leader

NDA: 21-110 (Rapamune® Tablets)

SUBJECT: Label Comments

With reference to NDA 21-110, our reviewing clinical pharmacologist, toxicologist, and medical officer would like to make the following changes to the proposed Rapamune® package insert (clean version, August 16, 2000):

1) Lines 85, 761 and 763: Please replace the terms "therapeutic equivalence" and "therapeutically equivalent" with "clinical equivalence" and "clinically equivalent," respectively.

2) Lines 87-8: This sentence should read as follows: "Sirolimus concentrations <u>following administration of oral solution to</u> ~~in~~ stable renal transplant patients are dose proportional between 3 and 12 mg/m^2."

3) Lines 90-1: In order to be consistent with the sentence located in lines 94-6, the word "breakfast" should be replaced with "meal."

[redacted]

6) Line 736: Please insert a space between the words "disorder" and "in."

We are providing the above information via telephone facsimile for your convenience. Please feel

free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

/S/

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DSPIDP/HFD-590 • 5600 Fishers Lane • Rockville, MD 20857 • (301) 827-2127 • Fax: (301) 827-2475

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: August 16, 2000

TO: Randy Brenner
Manager of Worldwide Regulatory Affairs
Wyeth-Ayerst Research
(610) 902-3792
(610) 964-5972 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Kenneth L. Hastings, Ph.D., Pharmacology/Toxicology Team Leader
Steve Kunder, Ph.D., Pharmacology/Toxicology Reviewer

NDA: 21-110 (Rapamune® Tablets)

SUBJECT: Label Comments

With reference to NDA 21-110, our reviewing pharmacology/toxicology reviewer would like to make the following changes to the **WARNINGS: Carcinogenesis, Mutagenesis, and Impairment of Fertility** section (lines 584-95) of the proposed Rapamune® package insert (August 10, 2000):

> Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at dosages of 0, 12.5, 25 and 50/6 (dosage lowered from 50 to 6 mg/kg/day at week 31 due to infection secondary to immunosuppression) there was a statistically significant increase in malignant lymphoma at all dose levels (approximately 16 to 135 times the clinical doses adjusted for body surface area) compared with controls. In a second mouse study at dosages of 0, 1, 3 and 6 mg/kg (approximately 3 to 16 times the clinical dose adjusted for body surface area), hepatocellular adenoma and carcinoma (males were considered Rapamune related. In the 104-week rat study at dosages of 0, 0.05, 0.1, and 0.2 mg/kg/day (approximately 0.4 to 1 times the clinical doses adjusted for body surface area), there was a statistically significant increased incidence of testicular adenoma in the 0.2 mg/kg/day group.

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/S/

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: August 11, 2000

TO: Randy Brenner
Manager of Worldwide Regulatory Affairs
Wyeth-Ayerst Research
(610) 902-3792
(610) 964-5972 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Norman R. Schmuff, Ph.D., Chemistry Team Leader
Mark Seggel, Ph.D., Chemistry Reviewer
Philip M. Colangelo, Pharm.D., Ph.D., Clin. Pharm. & Biopharm. Team Leader
Kofi A. Kumi, Ph.D., Clin. Pharm. & Biopharm. Reviewer

NDA: 21-110 (Rapamune® Tablets)

SUBJECT: Dissolution Information Request

With reference to NDA 21-110, our reviewing chemist and clinical pharmacologist would like to request the following information:

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 NDA 21-110.

2) Please confirm all of the batch numbers of material used in study 309.

3) Please provide all of the dissolution data and/or profiles using the proposed dissolution test method for those batches used in study 309.

4) Finally, please provide the dissolution profile comparison between the lots used in study 309 and the to-be-marketed triangular 1-mg tablets.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

/S/

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: August 11, 2000

TO: Randy Brenner
Manager of Worldwide Regulatory Affairs
Wyeth-Ayerst Research
(610) 902-3792
(610) 964-5972 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Norman R. Schmuff, Ph.D., Chemistry Team Leader
Mark Seggel, Ph.D., Chemistry Reviewer
Carol Holquist, R.Ph., Safety Evaluator, OPDRA

NDA: 21-110 (Rapamune® Tablets)

SUBJECT: Carton Labeling Recommendations

With reference to NDA 21-110 and your documents dated July 6 and July 18, 2000, our colleagues in the Office of Postmarketing Drug Risk Assessment and the reviewing chemist have the following comments and recommendations regarding the carton labeling for Rapamune® Tablets:

1) Please consider relocating the product strength to a position following the product name so that it is not confused with the net quantity statement.

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."

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

/S/

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: August 10, 2000

TO: Randy Brenner
Manager of Worldwide Regulatory Affairs
Wyeth-Ayerst Research
(610) 902-3792
(610) 964-5972 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Philip M. Colangelo, Pharm.D., Ph.D., Clin. Pharm. & Biopharm. Team Leader
Kofi A. Kumi, Ph.D., Clin. Pharm. & Biopharm. Reviewer

NDA: 21-110 (Rapamune® Tablets)

SUBJECT: Label Comments

With reference to NDA 21-110 and your memorandum of August 8, 2000, our reviewing clinical pharmacologist has the following recommendations concerning the **CLINICAL PHARMACOLOGY:** ***Special Populations:*** *Gender and Race* subsections of the proposed Rapamune® package insert (July 26, 2000):

1) Lines [redacted]: Please replace the last two sentences in this paragraph with: "A similar trend in the effect of gender on sirolimus oral dose clearance and $t_{1/2}$ was observed after the administration of Rapamune Tablets. Dose adjustments based on gender are not recommended."

   The mean oral clearance is about 21% lower in males compared to females after tablet administration. There were relatively fewer females (n=29) compared to males (n=111) and large variability (%CV= 40.6% for males and 60.8% for females) in the data which make interpretation difficult. But we agree that dosage adjustment should not be recommended.

2) Lines [redacted]: Please modify this sentence as follows: "Similarly, after administration of Rapamune Tablets (2mg/day) in a phase III trial, mean sirolimus trough concentrations over 6 months were not significantly different among black (n=51) and non-black (n=128) patients."

   We believe these are trough concentrations over 6 months.

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... at (301) 827-2127 if you have any questions regarding the contents of this transmission.

/S/

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: August 1, 2000

TO: Randy Brenner
Manager of Worldwide Regulatory Affairs
Wyeth-Ayerst Research
(610) 902-3792
(610) 964-5972 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Marc Cavaille-Coll, M.D., Ph.D., Medical Officer Team Leader
Rosemary Tiernan, M.D., Medical Officer
Funmilayo O. Ajayi, Ph.D., FCP, Clin. Pharm. & Biopharm. Team Leader
Kofi A. Kumi, Ph.D., Clin. Pharm. & Biopharm. Reviewer

NDA: 21-110 (Rapamune® Tablets)

SUBJECT: Label Comments

With reference to NDA 21-110, our reviewing clinical pharmacologist has the following recommendations concerning the proposed Rapamune® package insert that you submitted on July 26, 2000:

1) Lines 83-6: Please make the following changes: "The systemic availability of sirolimus was estimated to be approximately 14% after the administration of Rapamune Oral Solution. [redacted] The mean bioavailability of sirolimus after administration of the tablet relative to the oral solution [redacted] Sirolimus oral tablets are not bioequivalent to the oral solution; however, therapeutic equivalence has been demonstrated at the 2-mg dose level. (See Clinical Studies and Dosage and Administration) Sirolimus concentrations following administration of the oral solution [redacted] stable renal transplant patients are dose proportional between 3 and 12 mg/m^2.

[redacted]

The t_{max} information is already provided in the table on line 153 and the dose proportionality information does not include a recommended dose range (2 – 5 mg).

might not produced differences in the two formulations with respect to rate of absorption but not in extent of absorption. Evidence from a large, randomized, multicenter, controlled trial comparing Rapamune Oral Solution to Tablets, supports that the differences in absorption rates does not effect the efficacy of the drug. (See Clinical Studies: Study 3)

It is not known whether in Study 309, patients took the dose with or without food. Also, there was not sufficient statistical power to detect a significant difference in AUC and C_{max}. The statistical power for detecting a 20% difference in treatment at the α level of 0.05 was 50% for C_{max} and 39% for AUC.

4) Line 149-51: Please delete the line, "There were no significant differences in any of these parameters with respect to treatment group or month."

There was insufficient statistical power to make such a definitive statement. The statistical power for detecting a 20% difference in treatment at the α level of 0.05 was 50% for C_{max} and 39% for AUC.

[redacted]

7) Lines 189-211: Please provide the references for the new data presented in these three sections.

8) Lines 463-5: Please change the phrase "...6.1-fold and 2.5-fold..." into percentages (i.e., ...mean C_{max} and AUC were increased by 512% and 148%, respectively, relative to administration of sirolimus alone).

9) Lines 469-71: Please delete this statement from your label: "In a large, randomized, multicenter, controlled trial in renal transplant recipients (See Clinical Pharmacology), there was no significant difference in either sirolimus tablets or oral solution for C_{max} and AUC when sirolimus was administered 4 hours after CsA."

There wasn't sufficient statistical power to make such a definitive conclusion (see the comments for point #3 above).

10) Lines 507-8: Please change this sentence in the following manner: "It is recommended that sirolimus oral solution and oral tablets should not be administered with ketoconazole."

11) Lines 761-2: Please make the following changes to this paragraph: [redacted] Two-mg Rapamune oral solution has

bioequivalent. However, it is not known whether higher doses of Rapamune oral solution are [redacted] equivalent to higher doses of the tablets on a mg to mg basis. (See Clinical Pharmacology: Absorption)

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/S/

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: July 28, 2000

TO: Randy Brenner
Manager of Worldwide Regulatory Affairs
Wyeth-Ayerst Research
(610) 902-3792
(610) 964-5972 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Marc Cavaille-Coll, M.D., Ph.D., Medical Officer Team Leader
Rosemary Tiernan, M.D., Medical Officer
Karen Higgins, Sc.D., Statistics Team Leader
Cheryl Dixon, Ph.D., Statistics Reviewer
Mark Seggel, Ph.D., Chemistry Reviewer

NDA: 21-110 (Rapamune® Tablets)

SUBJECT: Label Comments

With reference to NDA 21-110, our reviewing medical officer, statistician, and chemist have the following recommendations concerning the proposed Rapamune® package insert:

1) Please revise the list of inactive ingredients for Rapamune® Tablets, located in the DESCRIPTION section, by including the statement, "...and other ingredients." This covers proprietary information on the printing ink not available to Wyeth-Ayerst.

2) Please revise the storage statement, located in the HOW SUPPLIED section, to maintain consistency with the USP in the following manner: "Rapamune Tablets should be stored at 20 to 25°C (USP Controlled Room Temperature)."

3) [redacted]

should be formatted in the same manner as the table in point #7.

7) Please insert the following sentence and table at line 294: "The table below summarizes the results of the primary efficacy analysis at 6 months after transplantation."

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 6 MONTHS: STUDY 3[a]

	Rapamune® Oral Solution (n=238)	Rapamune® Tablets (n=239)
Efficacy failure at 6 months	26.1	27.2
Components of efficacy failure		
Biopsy-proven acute rejection	21.0	19.2
Graft loss	3.4	6.3
Death	1.7	1.7

a: Patients received cyclosporine and corticosteroids.

8) In line 295, please replace "secondary" with "co-primary" so that the sentence would read, "Graft and patient survival at 12 months were co-primary efficacy endpoints."

9) The percentages you state in line 297 should be replaced with [redacted] so that the statement would read, "Graft survival was [redacted] for the oral solution and tablet treatment groups, respectively."

[redacted]

11) At line 303, please insert the following: "The table below summarizes the mean GFR at one-year post-transplant for all subjects in Study 3 who had serum creatinine measured at 12 months."

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (CC/MIN) BY NANKIVEL EQUATION AT 12 MONTHS POST TRANSPLANT: STUDY 3

	Rapamune® Oral Solution	Rapamune® Tablets
Mean (SE)	58.3 (1.64) n=166	58.5 (1.44) n=162

[redacted]

13) In lines 730-1, you stated that adverse events which occurred with an incidence of ≥3% and <20% in either treatment group in Study 3 were similar to those in Studies 1 and 2, however, hypotonia was seen more frequently in the solution than in the tablet (p=0.037).

14) In line 769, please insert the phrase "of the oral solution" after "clinical trials" so that this statement would read as follows: "Although a daily maintenance dose of 5 mg, with a loading dose of 15 mg, was used in clinical trials of the oral solution and was shown to be safe and

patients."

15) In lines 771-2, please insert "oral solution" after the word "Rapamune" so that the sentence would read as follows: "Patients receiving 2 mg of Rapamune oral solution per day demonstrated an overall better safety profile than did patients receiving 5 mg of Rapamune oral solution per day."

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/S/

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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