05-19-09

CASE 100-7932/PCT

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV 706065247 US — Express Mail Label Number

May 18, 2009 — Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT No. 5,665,772
ISSUED: SEPTEMBER 9, 1997.
INVENTORS: SYLVAIN COTTENS AND
RICHARD SEDRANI
FOR: O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS

MS: Patent Ext.
Director for Patents
PO Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Sir:

Enclosed in triplicate is an application for the extension of U.S. Patent No. 5,665,772 under 35 U.S.C. §156.

The Director is hereby authorized to charge the Application Fee of $1,120.00 prescribed by 37 C.F.R. §1.20(j)(1), as well as any additional fees which may be required in connection with the filing of this Application for Patent Term Extension, to Applicant's Deposit Account No. 19-0134 in the name of Novartis. Two additional copies of this transmittal letter are being submitted for charging purposes.

Respectfully submitted,

Gregory C. Houghton

Gregory C. Houghton
Attorney for Applicants
Reg. No. 47,666

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 101
East Hanover, NJ 07936-1080
(862) 778-2614
Date: 5/18/09

CASE 100-7932

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV706065242US
Express Mail Label Number

May 18, 2009
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,665,772

ISSUED: September 9, 1997

INVENTORS: Sylvain Cottens and Richard Sedrani

FOR: O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS

MS Patent Ext.
Director for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C.§156

Sir:

Pursuant to 35 U.S.C.§156 and 37 C.F.R.§1.710 *et seq.*, Novartis AG ("Applicant"), a Corporation organized under the laws of Switzerland, hereby requests an extension of the patent term due to regulatory review of U.S. Patent No. 5,665,772, which was granted on September 9, 1997.

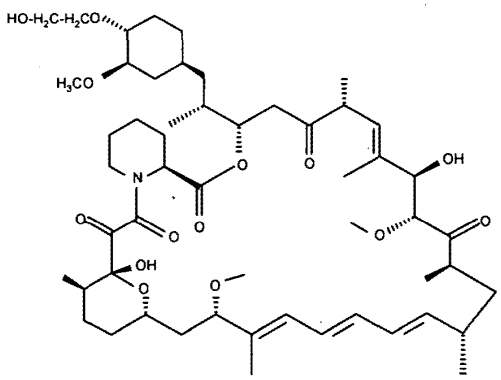
Applicant asserts that it is the owner of the entire right, title and interest in U.S. Patent No. 5,665,772 by virtue of an assignment from the inventors, Sylvain Cottens and Richard Sedrani, to Sandoz LTD, which later changed its name to Novartis AG. The assignment and name change to Novartis AG is recorded in the U.S. Patent and Trademark Office at Reel 008422, Frame 0042 on March 24, 1997. A copy of the assignment is attached hereto as Appendix A. A copy of the Power of Attorney evidencing that Novartis AG being the owner of the entire right, title and interest in and to U.S. Patent No. 5,665,772 appoints Gregory C. Houghton as its agent to act in its interest in this matter is attached hereto as Appendix B.

In accordance with 35 U.S.C.§156 and 37 C.F.R.§1.740, Applicant provides the following information in support of its request for a patent term extension. The following sections are numbered analogously to 37 C.F.R.§1.740.

05/19/2009 NHGUYEN1 00000008 190134 5665772
01 FC:1457 1120.00 DA

(1) Identification of the Approved Product

The approved product is Afinitor®, which contains the active ingredient everolimus, having the chemical name 40-O-(2-hydroxyethyl)-rapamycin and having the chemical structure



2. Identification of the Federal Statute under which Regulatory Review Occurred

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505 (New Drugs).

3. The Date of Permission for Commercial Marketing

The approved product received permission for commercial marketing under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C.§355(c)) on March 30, 2009. A copy of the FDA approval letter is attached hereto as Appendix C.

4. Active Ingredient Statement

The sole active ingredient in Afinitor® is everolimus, which has not been previously approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act prior to the approval of NDA 22-334 by the United States Food and Drug Administration on March 30, 2009.

A medical device known as The XIENCE™ V Everolimus Eluting Coronary Stent System, which may also be distributed as the PROMUS™ Everolimus Eluting Coronary Stent System, was approved by the Federal Food, Drug and Cosmetic Act under the authority of Section 515 on July 8, 2008. This medical device is indicated for improving coronary luminal diameter in patients with symptomatic heart disease. A copy of the of the FDA's premarket approval letter (PMA) is attached hereto as Appendix D.

5. Statement of Timely Filing

The last day on which this application could be submitted is May 29, 2009, which is 60 days after the approval of NDA 22-334 on March 30, 2009. This application is timely filed on or prior to May 29, 2009.

6. Identification of Patent for which Extension is Sought

This application seeks to extend the term of U.S. Patent No. 5,665,772, which issued September 9, 1997 to Sylvain Cottens and Richard Sedrani, the term of which would otherwise expire on September 9, 2014.

7. Patent Copy

A complete copy of U.S. Patent No. 5,665,772, identified in paragraph 6 above, is attached as Appendix E.

8. Post-Issuance Activity Statement

No Reexamination certificate, no terminal disclaimer, or Reissue has been issued or requested with respect to U.S. Patent No. 5,665,772. Two maintenance fees have become due since the patent has issued and both have been paid in a timely manner. Copies of the maintenance fee statements received by the United States Patent & Trademark Office indicating that the respective maintenance fees were timely paid, are attached hereto as Appendix F.

A Request for a Certificate of Correction for U.S. Patent No. 5,665,772 was mailed to the United States Patent and Trademark Office on March 30, 1998. A copy of the Request is attached hereto as Appendix G. The United States Patent and Trademark Office issued the Certificate of Correction for U.S. Patent No. 5,665,772 on June 30, 1998. A copy of the Certificate of Correction is attached hereto as Appendix H.

9. Statement Showing How the Claims of the Patent for which Extension is Sought Cover the Approved Product

Claims 1, 2 , 3 and 10 of U.S. Patent No. 5,665,772 claim compounds which include the approved product, Afinitor®.

Claims 1-3 claim compounds, including everolimus, the active ingredient in the approved product. The active ingredient, everolimus, is the compound of claim 1 wherein R_1 is hydroxy(C_1-$_6$)alkyl. Further, the active ingredient, everolimus, is the compound of claims 2 and 3, wherein R_1 is hydroxy(C_1-$_3$)alkyl.

Claim 10, as corrected by the Certificate of Correction, claims everolimus by its chemical name, which is 40-O-(2-hydroxyethyl)-rapamycin. The Certificate of Correction is attached hereto as Appendix H.

Claim 7 claims pharmaceutical compositions containing a compound of claim 1, which as shown above, includes everolimus, the active ingredient of the approved product. Claim 7 claims a pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier therefor.

10. Statement of the Relevant Dates to Determine the Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C.§156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) The patent for which extension of the term thereof is sought claims a human drug product. The human drug product is a composition containing everolimus.

(A) An Investigational New Drug Application for everolimus as an antiproliferative drug with an application as an anti-cancer agent was submitted on November 22, 2002. This was assigned IND 66,279. A request was made to cross-reference a previously filed Investigational New Drug Application for everolimus' use as an immunosuppressant. This cross-reference was to include safety data such as carcinogenicity data to support IND 66,279. The previously filed Investigational New Drug Application for everolimus as an antiproliferative drug with an application as an immunosupressant was submitted on November 15, 1996, was received by the Department of Health and Human Services on November 19, 1996, was assigned IND No. 52,003, and became effective on December 19,1996.

A copy of the IND letter, dated Dec. 18, 2002, to the FDA regarding IND 66,279 and a fax communication, dated Dec. 18, 2002, to the FDA regarding the cross–referencing of IND 52,003, and a fax communication, dated Dec. 19, 2002, from the FDA regarding IND 66,279 are attached as Appendix I. A copy of the IND application cover letter and table of contents, dated Nov. 15, 1996, concerning IND 52,003 and a copy of the acknowledgement letter, dated Nov. 26, 1996, from the FDA concerning IND 52,003 are attached as Appendix J. A copy of the IND application cover letter and table of contents, dated Nov. 22, 2002, concerning IND 66,279 and a copy of the acknowledgment/approval fax, dated Dec. 19, 2002 (copy also included in Appendix I), from the FDA concerning IND 66,279 are attached as Appendix K.

(B) A New Drug Application for Afinitor® was received by the Department of Health and Human Services on June 30, 2008 and granted NDA No. 22-334.

(C) NDA No. 22-334 was approved on March 30, 2009.

11. Brief Description of Activities Undertaken During the Regulatory Review Period

As a brief description of the activities undertaken during the applicable regulatory review period, attached hereto as Appendix L is a chronology of the major communications between the U.S. Food and Drug Administration and the Applicant in IND No. 66,279 and NDA No. 22-334 and in IND 52,003 (the cross-referenced IND).

12. Opinion of Eligibility for Extension

Applicant is of the opinion that U.S. Patent No. 5,665,772 is eligible for extension under 35 U.S.C.§156 and 37 C.F.R.§1.720 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C.§156(a) and 37 C.F.R.§1.720(a)

U.S. Patent No. 5,665,772 claims, everolimus, the active ingredient of a human drug product and pharmaceutical compositions containing the active ingredient. MPEP 2751 states:

> "A patent is considered to claim the product at least in those situations where the patent claims the active ingredient per se, or claims a composition or formulation which contains the active ingredient(s) and reads on the composition or formulation approved for commercial marketing or use"

As pointed out in Section 9 of this Patent Term Extension Application, U.S. Patent No. 5,665,772 claims both the active ingredient per se (claims 1-3 and 10) and a composition containing the active ingredient (claim 7).

(b) 35 U.S.C.§156(a)(1) and 37 C.F.R.§1.720(g)

The term of U.S. Patent No. 5,665,772 (expiring September 9, 2014) has not expired before the submission of this application.

(c) 35 U.S.C.§156(a)(2) and 37 C.F.R.§1.720(b)

The term of U.S. Patent No. 5,665,772 has never been extended.

(d) 35 U.S.C.§156(a)(3) and 37 C.F.R.§1.720(c)

The application for extension of the term of U.S. Patent No. 5,665,772 is submitted by the authorized attorney of the owner of record thereof in accordance with the requirements of 35 U.S.C.§156(d) and 37 C.F.R.§1.740.

(e) 35 U.S.C.§156(a)(4) and 37 C.F.R.§1.720(d)

The approved product, Afinitor®, has been subjected to a regulatory review period under 35 U.S.C. § 156(g)(1) before its commercial marketing or use.

(f) 37 C.F.R.§1.720(h)

No other patent has been extended for the same regulatory review period for the approved product, Afinitor®.

(g) 35 U.S.C.§156(a)(5)(A) and 37 C.F.R.§1.720(e)(1)

The permission for the commercial marketing or use of the approved product, Afinitor® is the first received permission for commercial marketing or use of Afinitor® under Section 505, the provision of law under which the applicable regulatory review occurred.

As set forth in paragraph 4 above, a medical device known as The XIENCE™ V Everolimus Eluting Coronary Stent System, which may also be distributed as the PROMUS™ Everolimus Eluting Coronary Stent System, was approved by the Federal Food, Drug and Cosmetic Act under the authority of Section 515 on July 8, 2008. This medical device is indicated for improving coronary luminal diameter in patients with symptomatic heart disease.

13. Length of extension claimed under 37 C.F.R.§1.740(a)(12)

The length of extension of the patent term of U.S. Patent No. 5,665,772 requested by Applicant is 1,826 days (5 years), which length was calculated in accordance with 37 C.F.R.§1.775 as follows:

(a) The regulatory review period under 35 U.S.C.§156(g)(1)(B) began on December 19, 1996 (the effective date of the cross-referenced IND 52,003) and ended on March 30, 2009, amounting to a total of 4,484 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C.§156(g)(1)(B)(i), the "Testing Period," began on December 19, 1996 and ended on June 30, 2008 which is 4,211 days;

(ii) The period for review under 35 U.S.C.§156(g)(1)(B)(ii), the "Application Period," began on June 30, 2008 and ended on March 30, 2009, which is 273 days;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in subparagraph (13)(a) above (4,484 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (Sept. 9, 1997), i.e., 264 days, and

(ii) The number of days during which the Applicant did not act with due diligence, i.e., zero days, and

(iii) One-half of the number of days remaining in the period in subparagraph (13)(a)(i) after subtracting the number of days in subparagraphs (13)(b)(i) and (13)(b)(ii), which is one-half of (4211 - [264 + 0]) or 1974 days;

which results in a period of 4,484 -[264 + 0 + 1974 days] = 2,246 days.

(c) The number of days as determined in subparagraph (13)(b), when added to the original term (September 9, 2014), would result in the date of October 19, 2020.

(d) Fourteen (14) years when added to the date of the NDA Approval Letter (March 30, 2009) would result in the date of March 30, 2023.

(e) The earlier date as determined by subparagraphs (13)(c) and (13)(d) is October 19, 2020.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five (5) years. Five years, when added to the original expiration of U.S. Patent No. 5,665,772 (September 9, 2014), results in the date September 9, 2019.

(g) The earlier date as determined in subparagraphs (13)(e) and (13)(f) is September 9, 2019.

14. Duty of Disclosure Acknowledgement Under 37 C.F.R.§1.740(a)(13)

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

15. Fee Charge

The prescribed fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account No. 19-0134 as authorized in the attached transmittal letter, submitted in triplicate.

16. Correspondence Address Required by 37 C.F.R.§1.740(a)(15)

All correspondence relating to this application for patent term extension should be addressed to:

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 101
East Hanover, NJ 07936-1080

17. Certification Under 37 C.F.R.§1.740(b)

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted as one original and two copies thereof in accordance with 37 C.F.R.§1.740(b).

Respectfully submitted,

Gregory C. Houghton

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 101
East Hanover, NJ 07936-1080

Gregory C. Houghton
Attorney for Applicant
Reg. No. 47,666
(862) 778-2614

Date: 5/18/09

FORM PTO-1595
(Rev. 6-93)
OMB No. 0651-0011 (exp. 4/94)

Tab settings ⇨ ⇨ ⇨ ▼

MAY 1 8 2009

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Appendix A

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

SYLVAIN COTTENS, RICHARD SEDRANI

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: NOVARTIS AG (formerly SANDOZ LTD

Internal Address: CH-4002

Basle, Switzerland

Street Address:

City: State: ZIP:

Additional name(s) & address(es) attached? ☐ Yes ☐ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other

Execution Date: MARCH 13, 1995

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

Case 100-7932/PCT
Serial No. 08/416,673
Filed 4/7/95

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Robert S. Honor

Internal Address: NOVARTIS CORP.

Patent and Trademark Dept.

Street Address: 59 Route 10

City: E. Hanover State: NJ ZIP: 07936

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40.00

☐ Enclosed

☒ Authorized to be charged to deposit account

8. Deposit account number:

19-0134

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Linda C. Rothwell
Name of Person Signing

Linda C. Rothwell
Signature

3/20/97
Date

Total number of pages including cover sheet, attachments, and document: 2

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

A S S I G N M E N T

I/We Sylvain Cottens and Richard Sedrani

for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to SANDOZ LTD. (also known as SANDOZ AG), a Company organised under the laws of the Swiss Confederation, of 4002 Basle, Switzerland, its successors and assigns, all my/our right, title and interest, in and for the United States of America, in and to the O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS invented by me/us and described in the specification for United States Letters Patent therefor, executed on even date herewith, and all United States Letters Patent which may be granted therefor, and all divisions, reissues, continuations and extensions thereof, the said interest being the entire ownership of the said Letters Patent when granted, to be held and enjoyed by the said SANDOZ LTD., its successors, assigns or other legal representatives, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held and enjoyed by me/us if this assignment and sale had not been made;

And I/we hereby authorize and request the Commissioner of Patents to issue said Letters Patent to the said SANDOZ LTD.

Signed this day of March 13 1995 Cottens S.

Sylvain Cottens

Signed this day of March 13 1995 Richard Sedrani

Richard Sedrani

Signed this day of 19

Signed this day of 19

Appendix B

Case No. 100-7932/PCT

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS

the specification of which

[ ] is attached hereto.

[ ] was filed on 19 as application Serial No. 0/
and, if these brackets contain an X [ ], was amended on 19

[X] was filed as Patent Cooperation Treaty internation application No. PCT/EP93/02604
on September 24 , 19 93 , if these brackets contain an X [ ], was amended under Patent Cooperation Treaty Article 19 on , 19
and, if these brackets contain an X [ ], was amended on , 19

[ ] entered the national stage in the United States and was accorded Serial No.
on , 19 , and if these brackets contain an X [ ]
was amended on

I hereby state that I have reviewed and understand the contents of the above-identified specifiction including the claims, as amended by any amendment(s) referred to above.

I acknowledge my duty to disclose all information which is known by me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim the benefit under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate indicated below and of any Patent Cooperation Treaty international application(s) designating at least one country other than the United States indicated below and have also identified any foreign application(s) for

patent or inventor's certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application for said subject matter the priority of which is claimed:

Country:	Number:	Filing Date:	Priority Claimed:
Great Britain	9221220.8	October 9, 1992	[X] Yes[ ] No
			[ ] Yes[ ] No
			[ ] Yes[ ] No
			[ ] Yes[ ] No
			[ ] Yes[ ] No
			[ ] Yes[ ] No

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and of any Patent Cooperation Treaty international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of Title 35, United States Code, §112, I acknowledge my duty to disclose all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date(s) of the prior application(s) and the national or Patent Cooperation Treaty international filing date of this application:

Application Serial No.	Filed	Status (Pending, Abandoned, Patented)
none		

Case No. 100-7932/PCT

I hereby appoint the following:

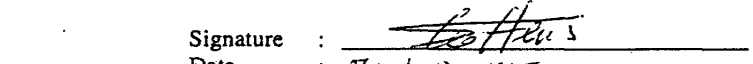
ROBERT S. HONOR	Reg. No. 22,801
THOMAS O. MCGOVERN	Reg. No. 25,741
MELVYN M. KASSENOFF	Reg. No. 26,389
JOSEPH J. BOROVIAN	Reg. No. 26,631
DIANE E. FURMAN	Reg. No. 31,104
CARL W. BATTLE	Reg. No. 30,731
ANDREW N. PARFOMAK	Reg. No. 32,431
JOHN L. CHIATALAS	Reg. No. 31,818
CAROL A. LOESCHORN	Reg. No. 35,590
MICHAEL P. MORRIS	Reg. No. 34,513
THOMAS C. DOYLE	Reg. No. 22,340

respectively and individually, as my attorneys and/or agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademarks Office connected therewith. Please address all communications to ROBERT S. HONOR, SANDOZ CORPORATION, 59 Route 10, East Hanover, New Jersey 07936-1080, whose telephone number is 201-503-8485.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issuing thereon.

Sole inventor or
first joint inventor:

Full name : Sylvain Cottens

Signature : 

Date : March 18, 1995

Citizenship : Switzerland

Residence : In den Reben 12, CH-4108 Witterswil, Switzerland

P.O. Address: same as above

IMPORTANT: Before this declaration is signed, the patent application (the specificateion, the claims and this declarations) must be read and understood by each person signing it, and no changes may be made in the application after this declaration has been signed.

Second joint inventor, if any:

Full name : Richard Sedrani
Signature : Richard Sedrani
Date : Nov 13 1995
Citizenship : Luxembourg
Residence : Herrengrabenweg 15, CH-4054 Basle, Switzerland
P.O. Address : same as above

Third joint inventor, if any:

Full name :
Signature : _____
Date :
Citizenship :
Residence :
P.O. Address:

Fourth joint inventor, if any:

Full name :
Signature : _____
Date :
Citizenship :
Residence :
P.O. Address:

Fifth joint inventor if any:

Full name :
Signature : _____
Date :
Citizenship :
Residence :
P.O. Address:

PTO/SB/81 (01-09)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	08/416673
Filing Date	April 7, 1995
First Named Inventor	Cotten, Sylvain
Title	O-ALKYLATED RAPAMYCIN
Art Unit	1202
Examiner Name	Bond, Robert
Attorney Docket Number	100-7932

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

01095

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature	Gregory C. Houghton	Date	4/21/09
Name	Gregory C. Houghton	Telephone	862 778-2614
Title and Company	Patent Attorney, Novartis		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/96 (03-09)
Approved for use through 04/30/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Novartis AG

Application No./Patent No.: 08/416,673 / 5,665,772 Filed/Issue Date: April 7, 1995 / September 9, 1997

Titled: O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS

Novartis AG , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 008422, Frame 0042, or for which a copy therefore is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Gregory C. Houghton — Signature
4/21/09 — Date
Gregory C. Houghton — Printed or Typed Name
Patent Attorney — Title

Appendix C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-334

NDA APPROVAL

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

RECEIVED 4/2/09

Attention: Sibylle R. Jennings, Ph.D.
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Jennings:

Please refer to your new drug application (NDA) dated June 27, 2008, received June 30, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afinitor® (everolimus) tablets 5 mg and 10 mg.

We acknowledge receipt of your submissions dated July 29, August 4, 20, 21 (2), 26, 29, September 5 (2), 9, 11, 25 (2), 29 (2), 30 (2), October 14, 17, 20, 21, 24, 28, 31, November 11, 19, 26, December 5, 10, 22, 2008, January 12, 20, 30, February 5, 10, 17, 18, 20, 23 (2), 25, 26, 27, March 3, 10, 11, 12, 20, 25, and 27, 2009.

This new drug application provides for the use of Afinitor® (everolimus) tablets for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

An expiration dating period of 24 months is granted when stored as recommended in the approved product labeling. You may extend the expiration dating based on accrual of real-time stability data and report this in an annual report for this NDA.

This application was not taken to a meeting of the Oncologic Drugs Advisory Committee (ODAC) because the application is based on a trial demonstrating a clinically and statistically significant improvement in progression-free survival with an acceptable benefit/risk ratio. Progression-free survival has previously been used as the basis for approval of drugs for the treatment of advanced renal cell carcinoma and the safety profile is similar to that of other drugs approved for this indication.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since this disease does not occur in the pediatric population.

POSTMARKETING REQUIREMENTS UNDER 505 (o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Trial A2303 evaluated everolimus in patients with moderate hepatic impairment (Child Pugh Class B) and due to increases in everolimus exposure, a dose reduction is needed in these patients. No exposure data are available for patients with severe hepatic impairment and current labeling recommends that Afinitor® (everolimus) should not be used in these patients.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of increased drug exposure when Afinitor® (everolimus) is administered to patients with severe hepatic impairment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the unexpected serious risk of increased drug exposure when Afinitor® (everolimus) is administered to patients with severe hepatic impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to complete the following postmarketing clinical trial:

1. Conduct a trial in patients with severe hepatic impairment (Child Pugh Class C). This trial need not be conducted in patients with cancer and a single dose evaluation will be appropriate. The protocol should be submitted prior to initiation for review and concurrence.

   The timetable you submitted on March 3, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	May 14, 2009
Trial Start Date:	October 14, 2009
Final Report Submission:	April 14, 2011

Submit protocols to your IND 66,279, with a cross-reference letter to this NDA 22-334. Submit all final report(s) to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing requirement as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We remind you of your postmarketing commitments in your submission dated March 27, 2009. These commitments are listed below.

2. Submit the final, per-protocol overall survival analysis of protocol C2240 which was to be conducted 2 years after randomization of the last patient.

Protocol Submission:	July 27, 2006
Trial Start Date:	December 6, 2006
Final Report Submission:	June 2010

3. Develop a 2.5 mg dosage form (tablet) to allow for proper dose reductions when Afinitor® (everolimus) is co-administered with moderate CYP3A4 inhibitors. The 2.5 mg dosage form should be sufficiently distinguishable from the 5 mg and 10 mg tablets. Full chemistry, manufacturing and controls (CMC) information for the 2.5 mg dosage form including batch and stability data, updated labeling, and an updated environmental assessment should be submitted as a prior approval supplement.

Protocol Submission Date:	May 14, 2009
Final Report Submission:	January 14, 2010

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical trials number of patients entered into each trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence**."

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-334."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-334.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFINITOR safely and effectively. See full prescribing information for AFINITOR.

AFINITOR (everolimus) tablets for oral administration
Initial U.S. Approval: 2009

INDICATIONS AND USAGE

AFINITOR is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. (1)

DOSAGE AND ADMINISTRATION

- 10 mg once daily with or without food. (2.1)
- Treatment interruption and/or dose reduction to 5 mg once daily may be needed to manage adverse drug reactions. (2.2)
- For patients with Child-Pugh class B hepatic impairment, reduce dose to 5 mg once daily. (2.2)
- If strong inducers of CYP3A4 are required, increase AFINITOR dose in 5 mg increments to a maximum of 20 mg once daily. (2.2)

DOSAGE FORMS AND STRENGTHS

5 mg and 10 mg tablets with no score. (3)

CONTRAINDICATIONS

Hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS

- Non-infectious pneumonitis: Monitor for clinical symptoms or radiological changes; fatal cases have occurred. Manage by dose reduction or discontinuation until symptoms resolve, and consider use of corticosteroids. (5.1)
- Infections: Increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly. (5.2)
- Oral ulceration: Mouth ulcers, stomatitis, and oral mucositis are common. Management includes mouthwashes (without alcohol or peroxide) and topical treatments. (5.3)
- Laboratory test alterations: Elevations of serum creatinine, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter. (5.4)
- Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines. (5.7)
- Use in pregnancy: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus. (5.8, 8.1)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥30%) are stomatitis, infections, asthenia, fatigue, cough, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Strong and moderate CYP3A4 or PgP inhibitors: Avoid concomitant use. (5.5, 7.1)
- Strong CYP3A4 inducers: Avoid concomitant use. If combination cannot be avoided, increase dose of AFINITOR. (2.2, 7.2)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or nursing, taking into consideration the importance of drug to the mother. (8.3)
- Hepatic impairment: AFINITOR should not be used in patients with Child-Pugh class C hepatic impairment. For patients with Child-Pugh class B hepatic impairment, reduce dose to 5 mg daily. (2.2, 5.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 03/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

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2 DOSAGE AND ADMINISTRATION
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2.2 Dose Modifications
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
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* Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AFINITOR® is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of AFINITOR for treatment of advanced renal cell carcinoma is 10 mg, to be taken once daily at the same time every day, either with or without food *[see Clinical Pharmacology (12.3)]*. AFINITOR tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

2.2 Dose Modifications

Management of severe and/or intolerable adverse reactions may require temporary dose reduction and/or interruption of AFINITOR therapy. If dose reduction is required, the suggested dose is 5 mg daily *[see Warnings and Precautions (5.1)]*.

Hepatic impairment: For patients with moderate hepatic impairment (Child-Pugh class B), reduce the dose to 5 mg daily. AFINITOR has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this patient population *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.7)]*.

Strong CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). If patients require co-administration of a strong CYP3A4 inducer, consider increasing the AFINITOR dose from 10 mg daily up to 20 mg daily (based on pharmacokinetic data), using 5 mg increments. This dose of AFINITOR is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer *[see Drug Interactions (7.2)]*.

3 DOSAGE FORMS AND STRENGTHS

5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "5" on one side and "NVR" on the other.

10 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "UHE" on one side and "NVR" on the other.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Non-Infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. In the randomized study, non-infectious pneumonitis was reported in 14% of patients treated with AFINITOR. The incidence of Common Toxicity Criteria (CTC) grade 3 and 4 non-infectious pneumonitis was 4% and 0%, respectively *[see Adverse Reactions (6.1)]*. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR therapy without dose alteration. If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at 5 mg daily.

For cases where symptoms of non-infectious pneumonitis are severe, discontinue AFINITOR therapy and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with AFINITOR may be re-initiated at a reduced dose of 5 mg daily depending on the individual clinical circumstances.

5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to infections, especially infections with opportunistic pathogens *[see Adverse Reactions (6.1)]*. Localized and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis or candidiasis, have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to respiratory failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR, be vigilant for signs and symptoms of infection and institute appropriate treatment promptly. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

5.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR. In the randomized study, approximately 44% of AFINITOR-treated patients developed mouth ulcers, stomatitis, or oral mucositis, which were mostly CTC grade 1 and 2 *[see Adverse Reactions (6.1)]*. In such cases, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed *[see Drug Interactions (7.1)]*.

5.4 Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine, usually mild, have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter.

Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Hematological Parameters

Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.5 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong or moderate inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, voriconazole, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil or diltazem) or P-glycoprotein (PgP) should be avoided *[see Drug Interactions (7.1)]*.

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4 inducer (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) *[see Dosage and Administration (2.2) and Drug Interactions (7.2)]*.

5.6 Hepatic Impairment

The safety and pharmacokinetics of AFINITOR were evaluated in a study in eight patients with moderate hepatic impairment (Child-Pugh class B) and eight subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore a dose reduction is recommended.

AFINITOR has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population *[see Dosage and Administration (2.2) and Use in Specific Populations (8.7)]*.

5.7 Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.8 Use in Pregnancy

Pregnancy Category D

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Non-infectious pneumonitis *[see Warnings and Precautions (5.1)]*.
- Infections *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-295) for those receiving placebo.

The most common adverse reactions (incidence ≥30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions (incidence ≥3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Table 1 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 1 Adverse Reactions Reported in at least 10% of Patients and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Any Adverse Reaction	97	52	13	93	23	5

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Gastrointestinal Disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and Infestations[b]	37	7	3	18	1	0
General Disorders and Administration Site Conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and Nutrition Disorders						
Anorexia	25	1	0	14	<1	0
Nervous System Disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and Connective Tissue Disorders						
Pain in extremity	10	1	0	7	0	0
Median Duration of Treatment (d)		141			60	

CTCAE Version 3.0

[a] Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

[b] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of <10% include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%)

Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (<1%)

Nervous system disorders: Insomnia (9%), dizziness (7%), paresthesia (5%)

Eye disorders: Eyelid edema (4%), conjunctivitis (2%)

Vascular disorders: Hypertension (4%)

Renal and urinary disorders: Renal failure (3%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)

Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Hematologic disorders: Hemorrhage (3%)

Key treatment-emergent laboratory abnormalities are presented in Table 2.

Table 2 Key Laboratory Abnormalities Reported at a Higher rate in the AFINITOR Arm than the Placebo Arm

Laboratory Parameter	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology*						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical Chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

CTCAE Version 3.0

* Includes reports of anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia.

7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

7.1 Agents that may Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors: In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.3-and 3.5-fold, respectively.

Concomitant strong or moderate inhibitors of CYP3A4 and PgP inhibitors should not be used *[see Warnings and Precautions (5.5)]*.

7.2 Agents that may Decrease Everolimus Blood Concentrations

CYP3A4 Inducers: In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} by 64% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong inducers of CYP3A4 or PgP if alternative treatment cannot be administered *[see Dosage and Administration (2.2) and Warnings and Precautions (5.5)]*.

7.3 Agents whose Plasma Concentrations may be Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.8)]* .

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft) and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities occurred at approximately 4% the exposure (AUC_{0-24h}) in patients receiving the recommended dose of 10 mg daily. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose approximately 1.6 times the recommended human dose on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At approximately 10% of the recommended human dose based on body surface area, there were no adverse effects on delivery and lactation and there were no signs of maternal toxicity. However, there was reduced

body weight (up to 9% reduction from the control) and slight reduction in survival in offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

Doses that resulted in embryo-fetal toxicities in rats and rabbits were ≥0.1 mg/kg (0.6 mg/m^2) and 0.8 mg/kg (9.6 mg/m^2), respectively. The dose in the pre- and post-natal development study in rats that caused reduction in body weights and survival of offspring was 0.1 mg/kg (0.6 mg/m^2).

8.3 Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In the randomized study, 41% of AFINITOR-treated patients were ≥ 65 years in age, while 7% percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3)]*.

No dosage adjustment is required in elderly patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily *[see Dosage and Administration (2.2), Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

The impact of severe hepatic impairment (Child-Pugh class C) has not been assessed and use in this patient population is not recommended *[see Warnings and Precautions (5.6)]*.

10 OVERDOSAGE

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

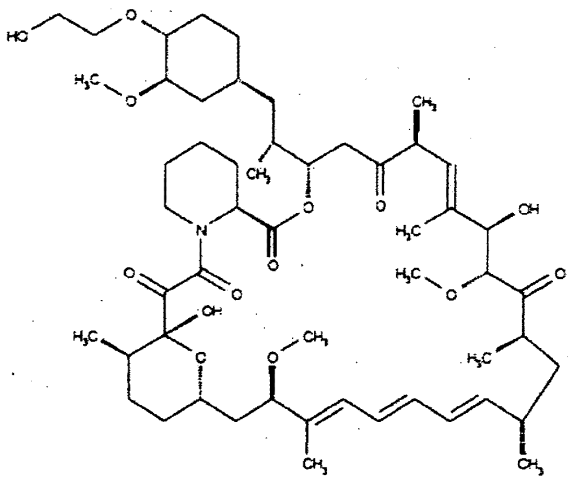
Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

11 DESCRIPTION

AFINITOR (everolimus), an inhibitor of mTOR, is an antineoplastic agent.

The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18- dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula is $C_{53}H_{83}NO_{14}$ and the molecular weight is 958.2. The structural formula is



AFINITOR is supplied as tablets for oral administration containing 5 mg and 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone and lactose anhydrous as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Everolimus is an inhibitor of mTOR (mammalian target of rapamycin), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation and inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP), downstream effectors of mTOR, involved in protein synthesis. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.

12.2 Pharmacodynamics

QT/QTc Prolongation Potential

In a randomized, placebo-controlled, crossover study, 59 healthy subjects were administered a single oral dose of AFINITOR (20 mg and 50 mg) and placebo. There is no indication of a QT/QTc prolonging effect of AFINITOR in single doses up to 50 mg.

Exposure Response Relationships

Markers of protein synthesis show that inhibition of mTOR is complete after a 10 mg daily dose.

12.3 Pharmacokinetics

Absorption

In patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses, C_{max} is dose-proportional between 5 mg and 10 mg. At doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within two weeks following once-daily dosing.

Food effect: Based on data in healthy subjects taking 1 mg everolimus tablets, a high-fat meal reduced C_{max} and AUC by 60% and 16%, respectively. No data are available with AFINITOR 5 mg and 10 mg tablets.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given AFINITOR 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself.

In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state C_{max} following an oral dose of 10 mg daily is more than 12-fold below the Ki-values of the *in vitro* inhibition. Therefore, an effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates is unlikely.

Excretion

No specific excretion studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabelled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

Patients with Renal Impairment

Approximately 5% of total radioactivity was excreted in the urine following a 3 mg dose of [^{14}C]-labeled everolimus. In a population pharmacokinetic analysis which included 170 patients with advanced cancer, no significant influence of creatinine clearance (25 – 178 mL/min) was detected on oral clearance (CL/F) of everolimus *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

The average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. A dose reduction for patients with Child-Pugh class B hepatic impairment is recommended. AFINITOR should not be used in patients with severe (Child-Pugh class C) hepatic impairment as the impact of severe hepatic impairment on everolimus exposure has not been assessed *[see Dosage and Administration (2.2), Warnings and Precautions (5.6) and Use in Specific Populations (8.7)]*.

Effects of Age and Gender

In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.

Ethnicity

Based on a cross-study comparison, Japanese patients (n = 6) had on average exposures that were higher than non-Japanese patients receiving the same dose.

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in Black patients than in Caucasians.

The significance of these differences on the safety and efficacy of everolimus in Japanese or Black patients has not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 4.3 and 0.2 times the estimated clinical exposure ($AUC_{0\text{-}24h}$) at the recommended human dose of 10 mg daily.

Everolimus was not genotoxic in a battery of *in vitro* assays (Ames mutation test in *Salmonella*, mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an *in vivo* mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m^2/day, approximately 255-fold the recommended human dose, based on the body surface area), administered as two doses, 24 hours apart.

Based on non-clinical findings, male fertility may be compromised by treatment with AFINITOR. In a 13-week male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm count, and plasma testosterone levels were diminished at 5 mg/kg, which resulted in infertility at 5 mg/kg. Effects on male fertility occurred at the $AUC_{0\text{-}24h}$ values below that of therapeutic exposure (approximately 10%-81% of the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 10 mg daily). After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60% (12/20 mated females were pregnant).

Oral doses of everolimus in female rats at ≥ 0.1 mg/kg (approximately 4% the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 10 mg daily) resulted in increases in pre-implantation loss, suggesting that the drug may reduce female fertility. Everolimus crossed the placenta and was toxic to the conceptus *[see Use in Specific Populations (8.1)]*.

14 CLINICAL STUDIES

An international, multicenter, randomized, double-blind trial comparing AFINITOR 10 mg daily and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon-α was also permitted. Randomization was stratified according to prognostic score[1] and prior anticancer therapy.

Progression-free survival (PFS), documented using RECIST (Response Evaluation Criteria in Solid Tumors) was assessed via a blinded, independent, central radiologic review. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label AFINITOR 10 mg daily.

In total, 416 patients were randomized 2:1 to receive AFINITOR (n=277) or placebo (n=139). Demographics were well balanced between the two arms (median age 61 years; 77% male, 88% Caucasian, 74% received prior sunitinib or sorafenib, and 26% received both sequentially).

AFINITOR was superior to placebo for progression-free survival (see Table 3 and Figure 1). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. The overall survival (OS) results were not mature and 32% of patients had died by the time of cut-off.

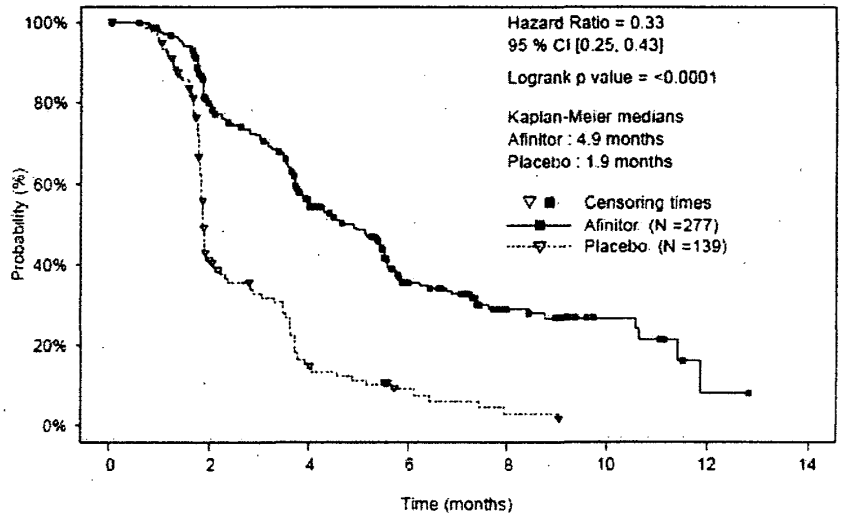
Table 3 Efficacy Results by Central Radiologic Review

	AFINITOR N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value[a]
Median Progression-free Survival (95% CI)	4.9 months (4.0 to 5.5)	1.9 months (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.0001
Objective Response Rate	2%	0%	n/a[b]	n/a[b]

[a] Log-rank test stratified by prognostic score.

[b] Not applicable.

Figure 1 Kaplan-Meier Progression-free Survival Curves



15 REFERENCES

1. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell cancer. J Clin Oncol (2004) 22:454-63.
2. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
3. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
4. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. (2006) 63:1172-1193.
5. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

5 mg tablets
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "5" on one side and "NVR" on the other; available in:
Blisters of 28 tablets ..... NDC 0078-0566-51
Each carton contains 4 blister cards of 7 tablets each

10 mg tablets
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "UHE" on one side and "NVR" on the other; available in:
Blisters of 28 tablets ..... NDC 0078-0567-51
Each carton contains 4 blister cards of 7 tablets each

Store AFINITOR (everolimus) tablets at 25° C (77°F); excursions permitted between 15°–30°C (59°–86°F). [See USP Controlled Room Temperature.] Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[2-5] AFINITOR tablets should not be crushed. Direct contact of crushed tablets with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed tablets.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (17.9)

17.1 Non-infectious Pneumonitis

Warn patients of the possibility of developing non-infectious pneumonitis. In clinical studies, some non-infectious pneumonitis cases have been severe and occasionally fatal. Advise patients to report promptly any new or worsening respiratory symptoms *[see Warnings and Precautions (5.1)]*.

17.2 Infections

Inform patients that they may be more susceptible to infections while being treated with AFINITOR. In clinical studies, some of these infections have been severe (e.g., leading to respiratory failure) and occasionally fatal. Patients should be aware of the signs and symptoms of infection and should report any such signs or symptoms promptly to their physician *[see Warnings and Precautions (5.2)]*.

17.3 Oral Ulceration

Inform patients of the possibility of developing mouth ulcers, stomatitis and oral mucositis. In such cases, mouthwashes and/or topical treatments are recommended, but these should not contain alcohol or peroxide *[see Warnings and Precautions (5.3)]*.

17.4 Laboratory Tests and Monitoring

Inform patients of the need to monitor blood chemistry and hematology prior to the start of AFINITOR therapy and periodically thereafter *[see Warnings and Precautions (5.4)]*.

17.5 Drug-drug Interactions

Avoid concurrent treatment with strong or moderate CYP3A4 and PgP inhibitors and strong CYP3A4 and PgP inducers. If AFINITOR must be co-administered with strong CYP3A4 inducers, consider a dose increase and carefully monitor the patient for clinical response. Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications and dietary supplements *[see Warnings and Precautions (5.5)]*..

17.6 Hepatic Impairment

Advise patients that AFINITOR is not recommended in patients with severe hepatic impairment (Child-Pugh class C). Prescribe a reduced dose of 5 mg AFINITOR per day for patients with moderate hepatic impairment (Child Pugh class B) *[see Dosage and Administration (2), Warnings and Precautions (5.6) and Clinical Pharmacology (12)]*.

17.7 Vaccinations

Advise patients to avoid the use of live vaccines and close contact with those who have received live vaccines *[see Warnings and Precautions (5.7)]*.

17.8 Pregnancy

Advise female patients of childbearing potential that AFINITOR may cause fetal harm and that an effective method of contraception should be used during therapy with AFINITOR and for 8 weeks after ending treatment.

17.9 FDA-approved Patient Labeling

PATIENT INFORMATION

AFINITOR®

(a-fin-it-or)

(everolimus)

Tablets

Read this patient information leaflet before you start taking AFINITOR and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about AFINITOR?

- **AFINITOR can cause you to have lung or breathing problems.** Tell your healthcare provider right away if you have new or worsening cough, shortness of breath, difficulty breathing, or wheezing. In some patients lung or breathing problems have been severe, and can even lead to death. You may need to stop AFINITOR for awhile or use a lower dose.
- **AFINITOR can make you more likely to have an infection** such as pneumonia or a bacterial or fungal infection. In some patients infections have been severe, and can even lead to death. You may need to be treated as soon as possible. Tell your healthcare provider right away if you have a temperature of 100.5° F or above, chills, or do not feel well.

What is AFINITOR?

AFINITOR is a prescription medicine used to treat people with advanced kidney cancer (renal cell carcinoma or RCC).

AFINITOR stops cancer cells from making new cancer cells and also cuts off the blood supply to the cancer. This may slow the growth and spread of kidney cancer.

AFINITOR has not been studied in children.

Who should not take AFINITOR?

Do not take AFINITOR if you are allergic to AFINITOR or to any of its ingredients. See the end of this leaflet for a complete list of ingredients in AFINITOR. Talk to your healthcare provider before taking this medicine if you are allergic to:

- sirolimus (Rapamune®, rapamycin)
- temsirolimus (Torisel®),

Ask your healthcare provider if you do not know.

What should I tell my healthcare provider before taking AFINITOR?

Before taking AFINITOR, tell your healthcare provider about all your medical conditions including if you:

- Have or have had liver problems.
- Have diabetes or high blood sugar.
- Have high cholesterol levels.
- Are scheduled for any immunization of a live vaccine or may be around people who have recently received an immunization with a live vaccine. If you are not sure about the type of immunization or vaccine, ask your healthcare provider.
- Are pregnant, or could become pregnant. AFINITOR may harm your pregnancy or fetus. You should use effective birth control while using AFINITOR and for 8 weeks after stopping treatment.
- Are breast-feeding or plan to breast-feed. It is not known if AFINITOR passes into your breast milk. You and your healthcare provider should decide if you will take AFINITOR or breast-feed. You should not do both.

How does AFINITOR impact your childbearing potential?

- AFINITOR may decrease male and female fertility.

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

AFINITOR can affect the way other medicines work, and other medicines can affect how AFINITOR works. Using AFINITOR with other medicines can cause serious side effects.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine. Especially tell your healthcare provider if you take:

- St. John's Wort (also known as *Hypericum perforatum*)
- Medicine for:
  - Fungal infections
  - Bacterial infections
  - Tuberculosis
  - Seizures
  - HIV-AIDS

- Heart conditions or high blood pressure
- Immunosuppression

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one of those taken for the conditions listed above. If you are taking any medicines for the conditions listed above, your healthcare provider might need to prescribe a different medicine. You should also tell your healthcare provider before you start taking any new medicine.

How should I take AFINITOR?

AFINITOR comes in 5 mg and 10 mg tablets.

- Take AFINITOR exactly as your healthcare provider tells you.
- Swallow AFINITOR tablets whole with a glass of water. Do not crush or chew the tablets. If you cannot swallow AFINITOR tablets whole, tell your healthcare provider.
- Take AFINITOR each day, at about the same time, with or without food.
- If you take too much AFINITOR contact your healthcare provider or go to the nearest hospital emergency department right away. Take the pack of AFINITOR with you.
- If you miss a dose of AFINITOR, you may still take it up to 6 hours after the time you normally take it. If it is more than 6 hours after you normally take your AFINITOR, skip the dose for that day. The next day, take AFINITOR at your usual time. Do not take 2 doses to make up for the one that you missed. If you are not sure about what to do, call your healthcare provider.
- You will have regular blood tests before you start and during your treatment with AFINITOR. These tests will show the number of blood cells in your body to see if AFINITOR is having an unwanted effect on these cells. Also, blood tests will monitor how your kidneys and liver are working and your blood sugar levels.

What should I avoid while taking AFINITOR?

- Do not drink grapefruit juice or eat grapefruit during your treatment with AFINITOR. It may make the amount of AFINITOR in your blood increase to a harmful level.

What are the possible side effects of AFINITOR?

AFINITOR can cause serious side effects. See the, "What is the most important information I should know about AFINITOR?" section at the beginning of this leaflet.

Common side effects:

- **Mouth ulcers.** AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. You might need treatment with a special mouthwash or mouth gel. Ask your healthcare provider what type of mouthwash or mouth gel to use.
- **Infections**
- **Feeling weak or tired**
- **Cough, shortness of breath, and lung or breathing problems**
- **Diarrhea**
- **Rash, dry skin, and itching**
- **Nausea and vomiting**
- **Fever**
- **Loss of appetite**
- **Swelling of arms, hands, feet, ankles, face or other parts of the body**
- **Abnormal taste**
- **Inflammation of lining of the digestive system**
- **Headache**
- **Nose bleeds**
- **Pain in arms and legs**

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of AFINITOR. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store AFINITOR?

- Keep AFINITOR at room temperature, between 59° to 86°F (15° to 30°C).
- Keep AFINITOR in the original package.
- Open blister package just before taking AFINITOR; use scissors to open blister.
- Keep the package and tablets dry.
- Keep AFINITOR out of light.
- Safely throw away AFINITOR that is out of date or no longer needed.

Keep this and all medicines out of the reach and sight of children.

General Information about AFINITOR

Medicines are sometimes prescribed for conditions that are not mentioned in this patient information leaflet. Do not use AFINITOR for a condition for which it was not prescribed.

Do not give AFINITOR to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about AFINITOR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information written for healthcare professionals.

For more information call 1-888-423-4648.

What are the ingredients in AFINITOR?

Active ingredient: everolimus.
Inactive ingredients: butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose anhydrous.

Manufactured by:

Novartis Pharma Stein AG

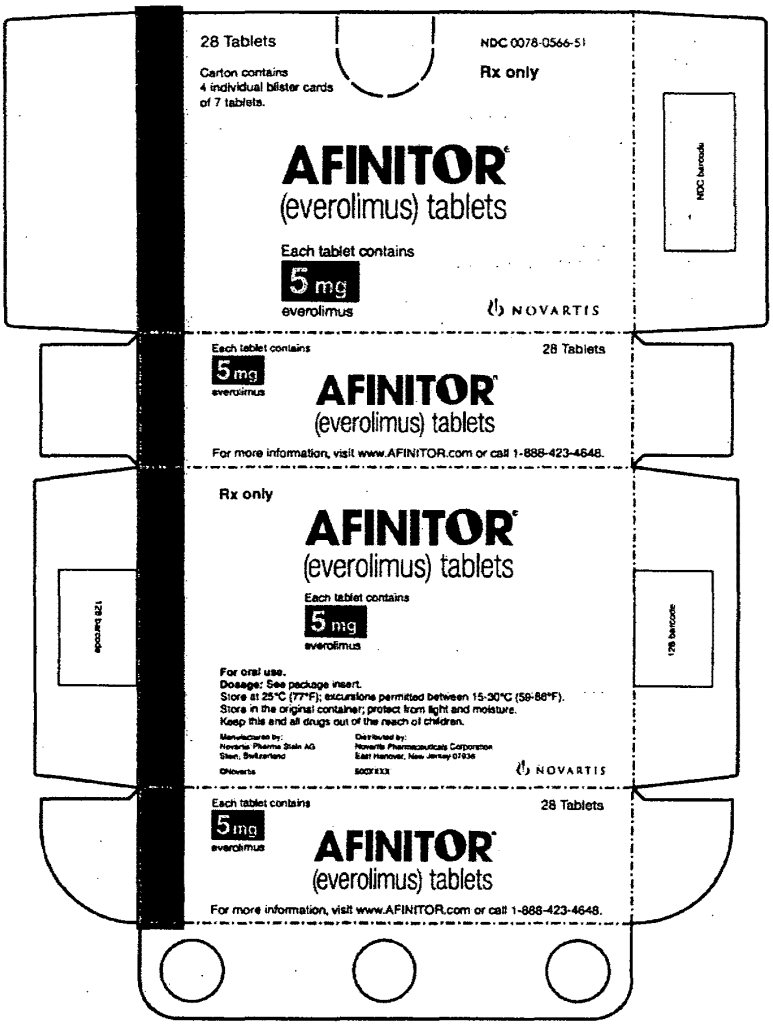
Stein, Switzerland

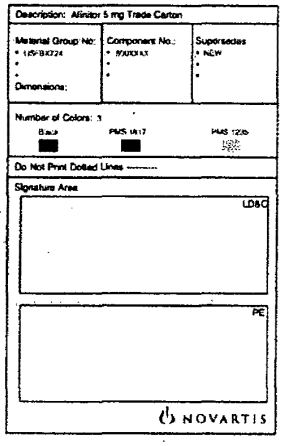
Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

MARCH 2009 PRINTED IN THE U.S.A. T2009-14 / T2009-15


28 Tablets
Carton contains
4 individual blister cards
of 7 tablets.
NDC 0078-0566-51
Rx only
AFINITOR
(everolimus) tablets
Each tablet contains
5 mg
everolimus
NOVARTIS
NDC barcode
Each tablet contains
5 mg
everolimus
28 Tablets
AFINITOR
(everolimus) tablets
For more information, visit www.AFINITOR.com or call 1-888-423-4648.
Rx only
AFINITOR
(everolimus) tablets
Each tablet contains
5 mg
everolimus
For oral use.
Dosage: See package insert.
Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).
Store in the original container; protect from light and moisture.
Keep this and all drugs out of the reach of children.
Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
NOVARTIS
128 barcode
Each tablet contains
5 mg
everolimus
28 Tablets
AFINITOR
(everolimus) tablets
For more information, visit www.AFINITOR.com or call 1-888-423-4648.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Material Group No:
Component No.:
Supersedes
NEW
Dimensions:
Number of Colors: 1
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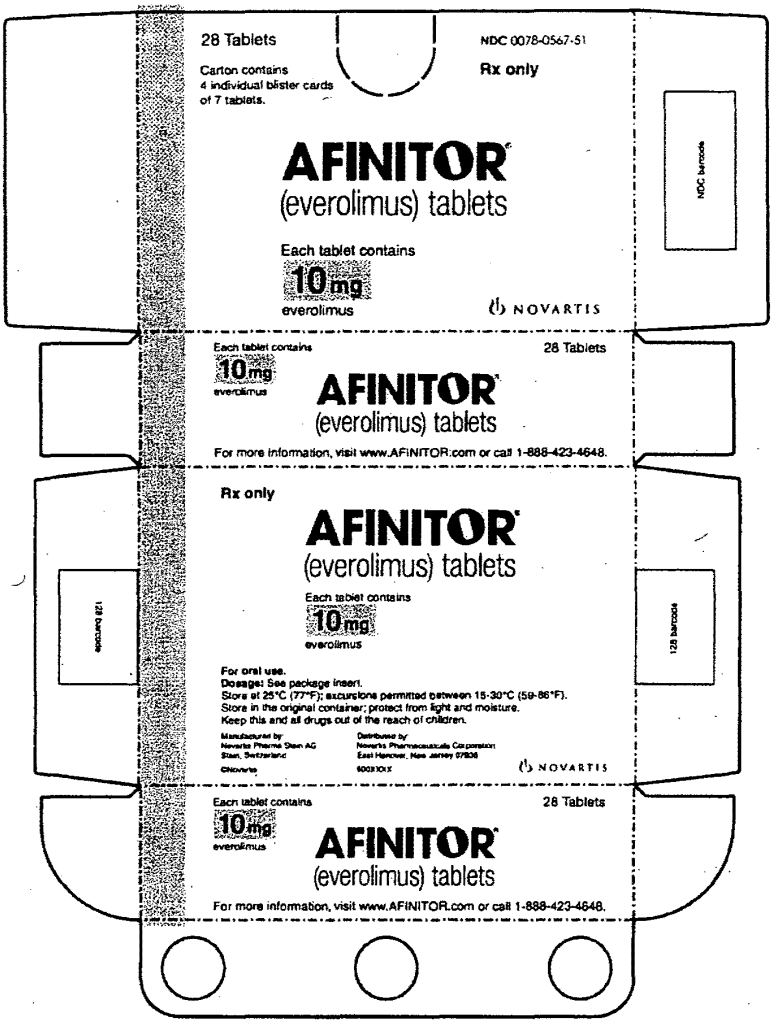
PMS 1235
Do Not Print Dotted Lines
Signature Area
LD&C
PE
NOVARTIS


28 Tablets
Carton contains
4 individual blister cards
of 7 tablets.
NDC 0078-0567-51
Rx only
AFINITOR
(everolimus) tablets
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For oral use.
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Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).
Store in the original container; protect from light and moisture.
Keep this and all drugs out of the reach of children.
Manufactured by
Novartis Pharma Stein AG
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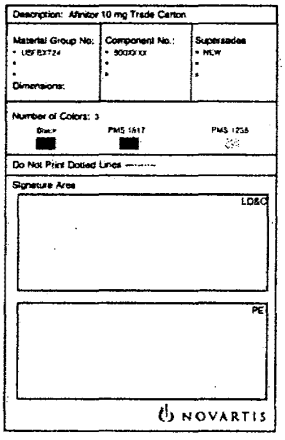
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Component No.:
Supersedes
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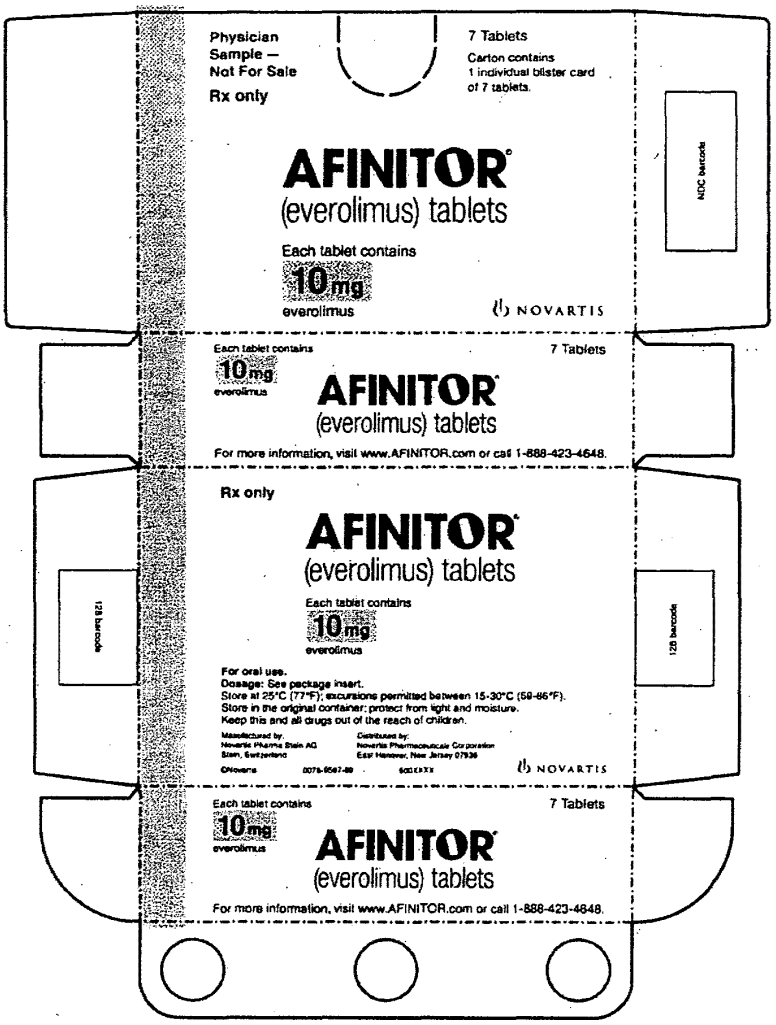
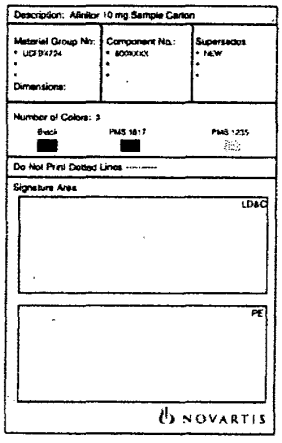
PMS 1817
PMS 1255
Do Not Print Dotted Lines
Signature Area
LD&C
PE
NOVARTIS


Physician
Sample —
Not For Sale
Rx only
7 Tablets
Carton contains
1 individual blister card
of 7 tablets.
AFINITOR
(everolimus) tablets
Each tablet contains
10 mg
everolimus
NOVARTIS
NDC barcode
Each tablet contains
10 mg
everolimus
7 Tablets
AFINITOR
(everolimus) tablets
For more information, visit www.AFINITOR.com or call 1-888-423-4648.
Rx only
AFINITOR
(everolimus) tablets
Each tablet contains
10 mg
everolimus
For oral use.
Dosage: See package insert.
Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).
Store in the original container; protect from light and moisture.
Keep this and all drugs out of the reach of children.
Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
NOVARTIS
12S barcode
12S barcode
Each tablet contains
10 mg
everolimus
7 Tablets
AFINITOR
(everolimus) tablets
For more information, visit www.AFINITOR.com or call 1-888-423-4648.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Material Group Nr.:
Component No.:
Supersedes
Dimensions:
Number of Colors: 3
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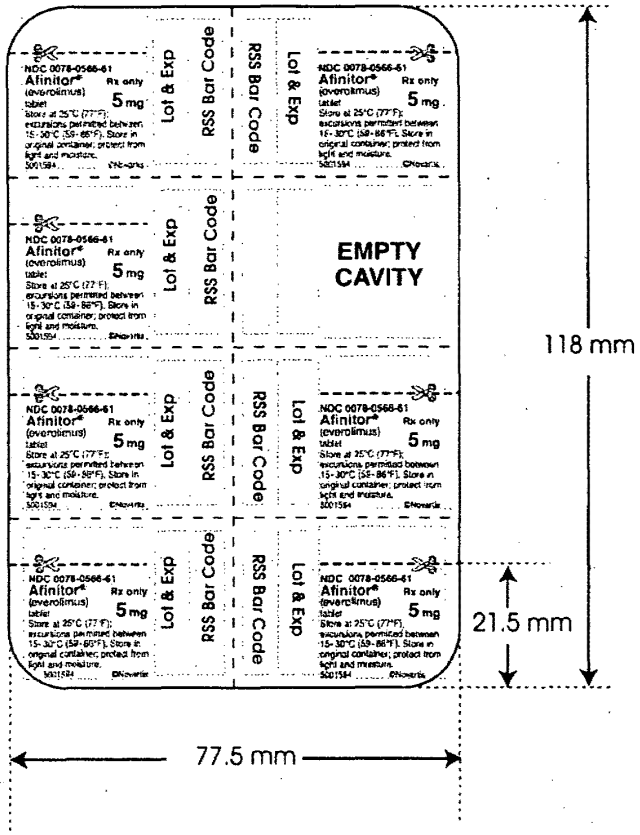
PMS 181 7
PMS 1235
Do Not Print Dotted Lines
Signature Area
LD&C
PE
NOVARTIS

12 mil DataBar (RSS) Limited

ZNV-NPD-887



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Number of Colors: 2 Black [redacted] PMS 1817 [redacted]		
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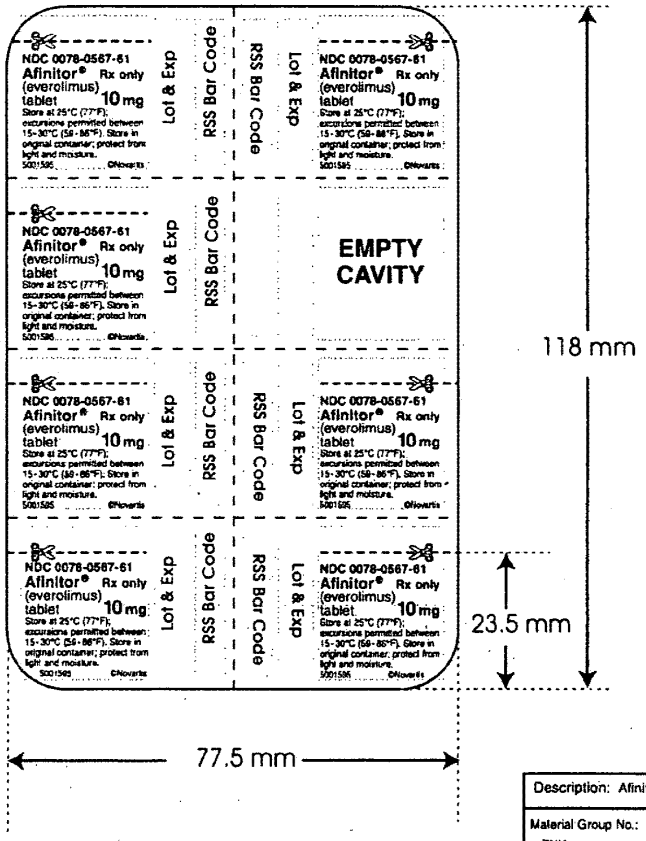
Signature Area LD&C		
PE		
NOVARTIS		

12 mil DataBar (RSS) Limited

ZNV-NPD-888



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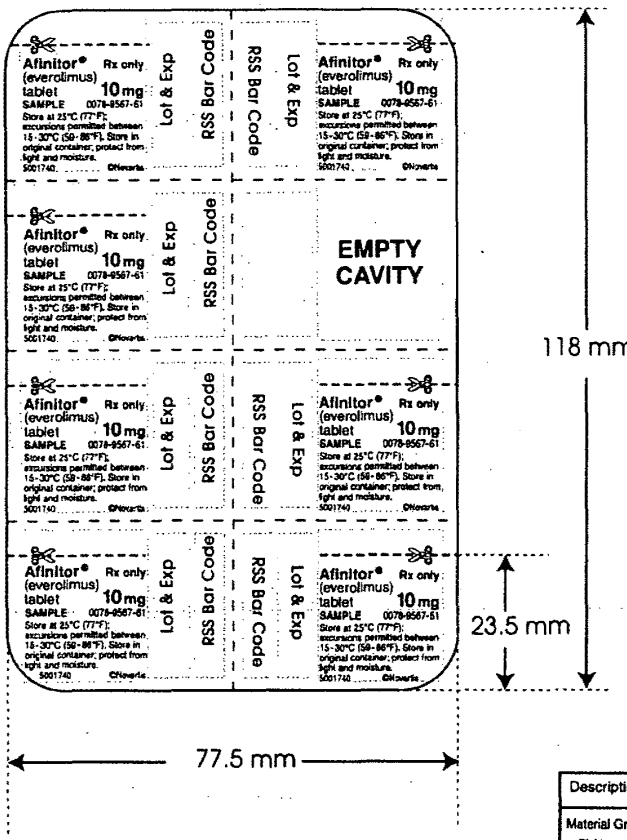
Do Not Print Dotted Lines ----------		
Signature Area LD&C PE NOVARTIS		

12 mil DataBar (RSS) Limited

ZNV-NPD-888



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Do Not Print Dotted Lines ----------		
Signature Area LD&C PE NOVARTIS		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
3/30/2009 01:00:32 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 2 2008

Ms. Kendra Basler
Regulatory Affairs Associate
Abbott Vascular
Cardiac Therapies
3200 Lakeside Drive
Santa Clara, CA 95054-2807

Re: P070015
XIENCE™ V Everolimus Eluting Coronary Stent System
PROMUS™ Everolimus Eluting Coronary Stent System
Filed: June 1, 2007
Amended: July 5, September 4, November 8, and December 13, 2007; February 20, April 2, May 12, May 13, June 9, June 23, and June 26, 2008
Procode: NIQ

Dear Ms. Basler:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the XIENCE™ V Everolimus Eluting Coronary Stent System, which will also be distributed as the PROMUS™ Everolimus Eluting Coronary Stent System. This device is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the periodic report (often referred to as annual report) requirements outlined in the enclosure, you have agreed to provide the following data in a separate postapproval study report:

1. You should collect and report to the Agency on an annual basis clinical outcomes through 5 years post-procedure on at least 80% of patients enrolled (excluding those discontinued due to death) from SPIRIT FIRST, SPIRIT II, SPIRIT III, and SPIRIT IV. When appropriate or as requested by FDA, you should submit PMA supplements requesting approval to update your Instructions for Use (IFU) to include these data.

2. You should collect clinical data on the implantation of the PMA-approved, commercially-distributed XIENCE V product in the U.S. The trial should be statistically powered to evaluate the annual rates of stent thrombosis, and the rate of cardiac death plus myocardial infarction (MI) through five years in patients treated with the XIENCE V stent according to its labeled indications. These data are needed to evaluate whether the rate of stent thrombosis plateaus or increases over time, and to evaluate the impact of stent thrombosis on rates of cardiac death and MI. These data are also needed to evaluate the potential for rare adverse events related to the drug substance and/or drug carrier that could not be detected in your initial clinical trials. You should also collect additional data on clinical outcomes (including target lesion revascularization rates at 12 months post-implantation) associated with use of the XIENCE V 4.0 mm diameter stent to confirm the outcomes observed in the 4.0 mm Arm of the SPIRIT III trial.

   You have proposed collecting these data from at least 5000 patients enrolled in the XIENCE V USA Postmarket Registry. FDA agrees that the registry protocol submitted in Supplement 97 of your Investigational Device Exemption (IDE), G050050, with the planned modifications to the statistical analysis plan, is acceptable. Please provide progress reports at 6, 12, 18, and 24 months and annually thereafter through 5 years with data from your U.S. registry. When appropriate or as requested by FDA, you should submit PMA supplements requesting approval to update your IFU to include these data. Please note that if subsequent data analyses identify areas of significant off-label use, you should submit an IDE to conduct an appropriate study to evaluate the off-label use.

3. You should conduct or participate in a study that will develop clinical data to identify the optimal duration of dual antiplatelet therapy following percutaneous intervention with the XIENCE V drug-eluting stent.

   The issue of the optimal duration of dual antiplatelet therapy following PCI with drug-eluting stents (DES) remains a key question that has not been addressed by any clinical trials conducted to date on the Cordis Cypher DES, the Boston Scientific Taxus Express[2] DES, the Endeavor DES, or the XIENCE V DES. At the December 7 – 8, 2006 meeting of FDA's Circulatory System Devices Advisory Panel meeting on DES thrombosis, the Panel recommended that the labeling for all marketed DES include the then-current ACC/AHA/SCAI guidelines for dual anti-platelet therapy, which specified that patients should receive aspirin indefinitely and clopidogrel for a minimum of 3 or 6 months for the Cypher or Taxus stents, respectively, after implantation, with this duration extended to 12 months in patients who are at low risk for bleeding complications.

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However, it is important to recognize that the current recommendation for an extended duration of clopidogrel use reflects a consensus opinion among experts within cardiovascular professional societies based on limited data, rather than on rigorous randomized clinical trials. Further, it is not clear that 12 months is the optimal maximum duration of a dual anti-platelet therapy. In fact, the ACC/AHA/SCAI guidelines were recently revised to specify that patients with low bleeding risks should receive clopidogrel for at least 12 months post-procedure. While extending the duration of clopidogrel use may decrease the risk of very late stent thrombosis events, this strategy may also result in an increased risk for major bleeding complications and involves lifestyle modifications, such as deferral of surgical and dental procedures that may affect a patient's health and overall quality of life. Finally, it is known that stent thrombosis can occur in some individuals despite the continued use of dual antiplatelet therapy. With these considerations in mind, it is imperative that the risks and benefits of continued clopidogrel use be evaluated to determine with greater precision the optimal duration of dual anti-platelet therapy to ensure that these patients receive the best care possible.

Based on the important public health impact of this information, as stated above, you should collect clinical data to identify the optimal duration of dual anti-platelet therapy following PCI with the XIENCE V stent. Such an evaluation should encompass a consecutively enrolled patient population or utilize an approach to enroll patients representative of the actual use of your commercialized product. You may wish to limit your investigation to the XIENCE V stent, or your study may involve pooling with other approved drug-eluting stents. You may also choose to collect these data in a manner that would satisfy, wholly or in part, condition #2 above. When appropriate or as requested by FDA, you should submit PMA supplements requesting approval to update your IFU to include these data. You should submit your proposed plan to address this issue within six months of the date of this letter.

As FDA views the investigation of the optimal duration of dual anti-platelet therapy as a DES class effect, we are requesting that manufacturers of other approved DES collect the same information.

4. You should comply with the commitments made in Amendment 11 related to the implementation of updated final product testing methodologies.

Expiration dating for this device has been established and approved at 12 months.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made

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to the Dockets Management Branch. (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with any postapproval requirement constitutes a ground for withdrawal of approval of a PMA. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Dr. Heather Agler at 240-276-4229.

Sincerely yours,

Donna-Bea Tillman, Ph.D., M.P.A.
Director
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Last Modified: 10-18-06

CONDITIONS OF APPROVAL

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e) or (f). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations that require a PMA supplement cannot be briefly summarized; therefore, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report (see below). FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

Alternate submissions permitted under 21 CFR 814.39(f) for manufacturing process changes include the use of a 30-day Notice. The manufacturer may distribute the device 30 days after the date on which the FDA receives the 30-day Notice, unless the FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

1. Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

2. Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

   a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

   b. reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

1. A mix-up of the device or its labeling with another article.

2. Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and:

   a. has not been addressed by the device's labeling; or

   b. has been addressed by the device's labeling but is occurring with unexpected severity or frequency.

3. Any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION.

The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Additional information on MDR is available at http://www.fda.gov/cdrh/devadvice/351.html

8

Appendix E

US005665772A

United States Patent [19]

Cottens et al.

[11] Patent Number: 5,665,772

[45] Date of Patent: Sep. 9, 1997

[54] **O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS**

[75] Inventors: **Sylvain Cottens**, Witterswil; **Richard Sedrani**, Basel, both of Switzerland

[73] Assignee: **Sandoz Ltd.**, Basel, Switzerland

[21] Appl. No.: **416,673**

[22] PCT Filed: **Sep. 24, 1993**

[86] PCT No.: **PCT/EP93/02604**

§ 371 Date: **Apr. 7, 1995**

§ 102(e) Date: **Apr. 7, 1995**

[87] PCT Pub. No.: **WO94/09010**

PCT Pub. Date: **Apr. 28, 1994**

[30] **Foreign Application Priority Data**

Oct. 9, 1992 [GB] United Kingdom 9221220

[51] Int. Cl.[6] **A61K 31/395**; C07D 498/16

[52] U.S. Cl. **514/514**; 540/456

[58] Field of Search 540/456; 514/514

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,120,842	6/1992	Failli et al.	540/542
5,151,413	9/1992	Caufield et al.	514/63
5,258,389	11/1993	Goulet et al.	514/291

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[57] **ABSTRACT**

Novel derivatives of rapamycin, particularly 9-deoxorapamycins, 26-dihydro-rapamycins, and 40-O-substituted and 28,40-O,O-di-substituted rapamycins, are found to have pharmaceutical utility, particularly as an immunosuppressants.

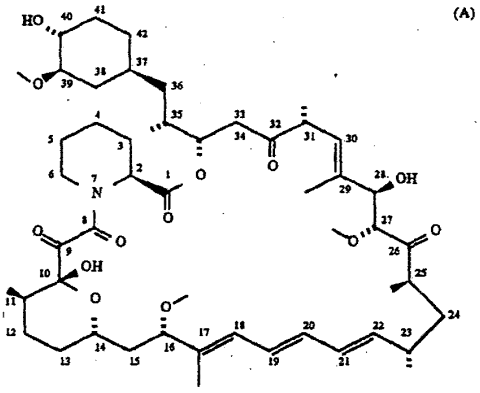
10 Claims, No Drawings

O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS

This application is a 371 of PCT/EP93/02604, filed Sep. 24, 1993.

This invention comprises novel alkylated derivatives of rapamycin having pharmaceutical utility, especially as immunosuppressants.

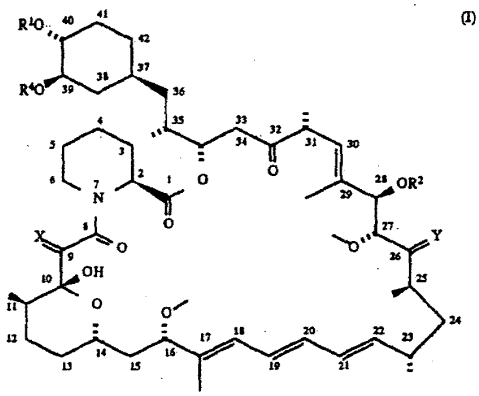
Rapamycin is a known macrolide antibiotic produced by *Streptomyces hygroscopicus*, having the structure depicted in Formula A:



(A)

See, e.g., McAlpine, J. B., et al., J. Antibiotics (1991) 44: 688; Schreiber, S. L., et al., J. Am. Chem. Soc. (1991) 113: 7433; U.S. Pat. No. 3,929,992. Rapamycin is an extremely potent immunosuppressant and has also been shown to have antitumor and antifungal activity. Its utility as a pharmaceutical, however, is restricted by its very low and variable bioavailability as well as its high toxicity. Moreover, rapamycin is highly insoluble, making it difficult to formulate stable galenic compositions.

It has now surprisingly been discovered that certain novel derivatives of rapamycin (the Novel Compounds) have an improved pharmacologic profile over rapamycin, exhibit greater stability and bioavailability, and allow for greater ease in producing galenic formulations. The Novel Compounds are alkylated derivatives of rapamycin having the structure of Formula I:



(I)

wherein

X is (H,H) or O;

Y is (H,OH) or O;

R^1 and R^2 are independently selected from H, alkyl, thioalkyl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkylarylalkyl, dihydroxyalkylarylalkyl, alkoxyalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylaminoalkyl, acylaminoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, carbalkoxyalkyl, and $(R^3)_3Si$ where each R^3 is independently selected from H, methyl, ethyl, isopropyl, t-butyl, and phenyl; wherein "alk-" or "alkyl" refers to C_{1-6} alkyl, branched or linear preferably C_{1-3} alkyl, in which the carbon chain may be optionally interrupted by an ether (—O—) linkage; and

R^4 is methyl, or R^4 and R^1 together form C_{2-5} alkylene; provided that R^1 and R^2 are not both H; and provided that where R^1 is $(R^3)_3Si$ or carbalkoxyalkyl, X and Y are not both O.

Preferred Novel Compounds include the following:

1. 40-O-Benzyl-rapamycin
2. 40-O-(4'-Hydroxymethyl)benzyl-rapamycin
3. 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin
4. 40-O-Allyl-rapamycin
5. 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin
6. (2'E,4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin
7. 40-O-(2-Hydroxy)ethoxycarbonylmethyl-rapamycin
8. 40-O-(2-Hydroxy)ethyl-rapamycin
9. 40-O-(3-Hydroxy)propyl-rapamycin
10. 40-O-(6-Hydroxy)hexyl-rapamycin
11. 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin
12. 40-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin
13. 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin
14. 40-O-(2-Acetoxy)ethyl-rapamycin
15. 40-O-(2-Nicotinoyloxy)ethyl-rapamycin
16. 40-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin
17. 40-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin
18. 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin
19. 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin
20. (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin
21. 28-O-Methyl-rapamycin
22. 40-O-(2-Aminoethyl)-rapamycin
23. 40-O-(2-Acetaminoethyl)-rapamycin
24. 40-O-(2-Nicotinamidoethyl)-rapamycin
25. 40-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido) ethyl)-rapamycin
26. 40-O-(2-Ethoxycarbonylaminoethyl)-rapamycin
27. 40-O-(2-Tolylsulfonamidoethyl)-rapamycin
28. 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin

The Novel Compounds for immunosuppressive use are preferably the 40-O-substituted rapamycins where X and Y are both O, R^2 is H, R^4 is methyl, and R^1 is other than H; most preferably where R^1 is selected from hydroxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl, and aminoalkyl; especially 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy) propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-O-(2-acetaminoethyl)-rapamycin).

Preferably O-substitution at C40 or O,O-disubstitution at C28 and C40 is performed according to the following general process: Rapamycin (or dihydro or deoxorapamycin) is reacted with an organic radical attached to a leaving group (e.g., RX where R is the organic radical,

e.g., an alkyl, allyl, or benzyl moiety, which is desired as the O-substituent, and X is the leaving group, e.g., $CCl_3C(NH)O$ or CF_3SO_3) under suitable reaction conditions, preferably acidic or neutral conditions, e.g., in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their respective pyridinium or substituted pyridinium salts when X is $CCl_3(NH)O$ or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when X is CF_3SO_3. O-substituents at C28 only are accomplished in the same manner, but with prior protection at C40. Further modifications are possible. For example, where the substituent is allyl, the isolated, monosubstituted double bond of the allyl moiety is highly amenable to further modification.

The 9-deoxorapamycin compounds are preferably produced by reducing a rapamycin using hydrogen sulfide, by reacting rapamycin with diphenyldiselenide and tributylphosphine or by other suitable reduction reaction.

The 26-dihydro-rapamycins are preferably produced by reducing rapamycins or 9-deoxorapamycins from keto to hydroxy at C26 by a mild reduction reaction, such as a borohydride reduction reaction.

The Novel Compounds are particularly useful for the following conditions:

a) Treatment and prevention of organ or tissue transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants. They are also indicated for the prevention of graft-versus-host disease, such as following bone marrow transplantation.

b) Treatment and prevention of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an etiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific autoimmune diseases for which the compounds of the invention may be employed include, autoimmune hematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy) and juvenile dermatomyositis.

c) Treatment and prevention of asthma.

d) Treatment of multi-drug resistance (MDR). The Novel Compounds suppress P-glycoproteins (Pgp), which are the membrane transport molecules associated with MDR. MDR is particularly problematic in cancer patients and AIDS patients who will not respond to conventional chemotherapy because the medication is pumped out of the cells by Pgp. The Novel Compounds are therefore useful for enhancing the efficacy of other chemotherapeutic agents in the treatment and control of multidrug resistant conditions such as multidrug resistant cancer or multidrug resistant AIDS.

e) Treatment of proliferative disorders, e.g. tumors, hyperproliferative skin disorder and the like.

f) Treatment of fungal infections.

g) Treatment and prevention of inflammation, especially in potentiating the action of steroids.

h) Treatment and prevention of infection, especially infection by pathogens having Mip or Mip-like factors.

i) Treatment of overdoses of FK-506, rapamycin, immunosuppressive Novel Compounds, and other macrophilin binding immunosuppressants.

The invention thus provides the Novel Compounds described herein, for use as novel intermediates or as pharmaceuticals, methods of treating or preventing the above-described disorders by administering an effective amount of Novel Compound to a patient in need thereof, use of a Novel Compound in the manufacture of a medicament for treatment or prevention of the above-described disorders, and pharmaceutical compositions comprising a Novel Compound in combination or association with a pharmaceutically acceptable diluent or carrier.

Most of the Novel Compounds described herein are highly immunosuppressive, especially those Novel Compounds which are O-substituted at C40, and these Novel Compounds are particularly useful in indications a and b, but not in indication *i*. Those of the Novel Compounds which are less immunosuppressive, especially those which are O-substituted at C28 only, are particularly useful in indications h and i, but are less preferred in indications a or b.

The Novel Compounds are utilized by administration of a pharmaceutically effective dose in pharmaceutically acceptable form to a subject in need of treatment. Appropriate dosages of the Novel Compounds will of course vary, e.g. depending on the condition to be treated (for example the disease type or the nature of resistance), the effect desired and the mode of administration.

In general however satisfactory results are obtained on administration orally at dosages on the order of from 0.05 to 5 or up to 10 mg/kg/day, e.g. on the order of from 0.1 to 2 or up to 7.5 mg/kg/day administered once or, in divided doses 2 to 4× per day, or on administration parenterally, e.g. intravenously, for example by i.v. drip or infusion, at dosages on the order of from 0.01 to 2.5 up to 5 mg/kg/day, e.g. on the order of from 0.05 or 0.1 up to 1.0 mg/kg/day. Suitable daily dosages for patients are thus on the order of 500 mg p.o., e.g. on the order of from 5 to 100 mg p.o., or on the order of from 0.5 to 125 up to 250 mg i.v., e.g. on the order of from 2.5 to 50 mg i.v.

Alternatively and even preferably, dosaging is arranged in patient specific manner to provide pre-determined trough blood levels, e.g. as determined by RIA technique. Thus patient dosaging may be adjusted so as to achieve regular on-going trough blood levels as measured by RIA on the order of from 50 or 150 up to 500 or 1000 ng/ml, i.e. analogously to methods of dosaging currently employed for Ciclosporin immunosuppressive therapy.

The Novel Compounds may be administered as the sole active ingredient or together with other drugs. For example, in immunosuppressive applications such as prevention and treatment of graft vs. host disease, transplant rejection, or autoimmune disease, the Novel Compounds may be used in combination with Ciclosporin, FK-506, or their immunosuppressive derivatives; corticosteroids; azathioprene; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to CD3, CD4, CD25, CD28, or CD45; and 7 or other immunomodulatory compounds. For anti-inflammatory applications, the Novel Compounds can be used together with anti-inflammatory agents, e.g., corticos-

teroids. For anti-infective applications, the Novel Compounds can be used in combination with other anti-infective agents, e.g., anti-viral drugs or antibiotics.

The Novel Compounds are administered by any conventional route, in particular enterally, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise, e.g. from 1 to 50 mg of a compound of the invention, usually 1 to 10 mg. Pharmaceutical compositions comprising the novel compounds may be prepared analogously to pharmaceutical compositions comprising rapamycin, e.g., as described in EPA 0 041 795, which would be evident to one skilled in the art.

The pharmacological activity of the Novel Compounds are demonstrated in, e.g., the following tests:

1. Mixed lymphocyte reaction (MLR)

The Mixed Lymphocyte Reaction was originally developed in connection with allografts, to assess the tissue compatibility between potential organ donors and recipients, and is one of the best established models of immune reaction in vitro. A murine model MLR, e.g., as described by T. Meo in "Immunological Methods", L. Lefkovits and B. Peris, Eds., Academic Press, N.Y. pp. 227–239 (1979), is used to demonstrate the immunosuppressive effect of the Novel Compounds. Spleen cells (0.5×10^6) from Balb/c mice (female, 8–10 weeks) are co-incubated for 5 days with 0.5×10^6 irradiated (2000 rads) or mitomycin C treated spleen cells from CBA mice (female, 8–10 weeks). The irradiated allogeneic cells induce a proliferative response in the Balb/c spleen cells which can be measured by labeled precursor incorporation into the DNA. Since the stimulator cells are irradiated (or mitomycin C treated) they do not respond to the Balb/c cells with proliferation but do retain their antigenicity. The antiproliferative effect of the Novel Compounds on the Balb/c cells is measured at various dilutions and the concentration resulting in 50% inhibition of cell proliferation (IC_{50}) is calculated. The inhibitory capacity of the test sample may be compared to rapamycin and expressed as a relative IC_{50} (i.e. IC_{50} test sample/IC_{50} rapamycin).

2. IL-6 mediated proliferation

The capacity of the Novel Compounds to interfere with growth factor associated signalling pathways is assessed using an interleukin-6 (IL-6)-dependent mouse hybridoma cell line. The assay is performed in 96-well microtiter plates. 5000 cells/well are cultivated in serum-free medium (as described by M. H. Schreier and R. Tees in Immunological Methods, I. Lefkovits and B. Pernis, eds., Academic Press 1981, Vol. II, pp. 263–275), supplemented with 1 ng recombinant IL-6/ml. Following a 66 hour incubation in the absence or presence of a test sample, cells are pulsed with 1 μCi (3-H)-thymidine/well for another 6 hours, harvested and counted by liquid scintillation. (3-H)-thymidine incorporation into DNA correlates with the increase in cell number and is thus a measure of cell proliferation. A dilution series of the test sample allows the calculation of the concentration resulting in 50% inhibition of cell proliferation (IC_{50}). The inhibitory capacity of the test sample may be compared to rapamycin and expressed as a relative IC_{50} (i.e. IC_{50} test sample/IC_{50} rapamycin).

3. Macrophilin binding assay

Rapamycin and the structurally related immunosuppressant, FK-506, are both known to bind in vivo to macrophilin-12 (also known as FK-506 binding protein or FKBP-12), and this binding is thought to be related to the immunosuppressive activity of these compounds. The Novel Compounds also bind strongly to macrophilin-12, as is demonstrated in a competitive binding assay.

In this assay, FK-506 coupled to BSA is used to coat microtiter wells. Biotinylated recombinant human macrophilin-12 (biot-MAP) is allowed to bind in the presence or absence of a test sample to the immobilized FK-506. After washing (to remove non-specifically bound macrophilin), bound biot-MAP is assessed by incubation with a streptavidin-alkaline phosphatase conjugate, followed by washing and subsequent addition of p-nitrophenyl phosphate as a substrate. The read-out is the OD at 405 nm. Binding of a test sample to biot-MAP results in a decrease in the amount of biot-MAP bound to the FK-506 and thus in a decrease in the OD405. A dilution series of the test sample allows determination of the concentration resulting in 50% inhibition of the biot-MAP binding to the immobilized FK-506 (IC_{50}). The inhibitory capacity of a test sample is compared to the IC_{50} of free FK-506 as a standard and expressed as a relative IC_{50} (i.e., IC_{50}-test sample/IC_{50}-free FK-506).

4. Localized Graft-Versus-Host (GvH) Reaction

In vivo efficacy of the Novel Compounds is proved in a suitable animal model, as described, e.g., in Ford et al, TRANSPLANTATION 10 (1970) 258. Spleen cells (1×10^7) from 6 week old female Wistar/Furth (WF) rats are injected subcutaneously on day 0 into the left hind-paw of female $(F344\times WF)F_1$ rats weighing about 100 g. Animals are treated for 4 consecutive days and the popliteal lymph nodes are removed and weighed on day 7. The difference in weight between the two lymph nodes is taken as the parameter for evaluating the reaction.

5. Kidney Allograft Reaction in Rat

One kidney from a female fisher 344 rat is transplanted onto the renal vessel of a unilaterally (left side) nephrectomized WF recipient rat using an end-to-end anastomosis. Ureteric anastomosis is also end-to-end. Treatment commences on the day of transplantation and is continued for 14 days. A contralateral nephrectomy is done seven days after transplantation, leaving the recipient relying on the performance of the donor kidney. Survival of the graft recipient is taken as the parameter for a functional graft.

6. Experimentally Induced Allergic Encephalomyelitis (EAE) in Rats

Efficacy of the Novel Compounds in EAE is measured, e.g., by the procedure described in Levine & Wenk, AMER J PATH 47 (1965) 61; McFarlin et al, J IMMUNOL 113 (1974) 712; Borel, TRANSPLANT. & CLIN. IMMUNOL 13 (1981) 3. EAE is a widely accepted model for multiple sclerosis. Male Wistar rats are injected in the hind paws with a mixture of bovine spinal cord and complete Freund's adjuvant. Symptoms of the disease (paralysis of the tail and both hind legs) usually develop within 16 days. The number of diseased animals as well as the time of onset of the disease are recorded.

7. Freund's Adjuvant Arthritis

Efficacy against experimentally induced arthritis is shown using the procedure described, e.g., in Winter & Nuss, ARTHRITIS & RHEUMATISM 9 (1966) 394; Billingham & Davies, HANDBOOK OF EXPERIMENTAL PHARMACOL (Vane & Ferreira Eds, Springer-Verlag, Berlin) 50/II (1979) 108–144. OFA and Wistar rats (male or female, 150 g body weight) are injected i.e. at the base of the tail or in the hind paw with 0.1 ml of mineral oil containing 0.6 mg of lyophilized heat-killed Mycobacterium smegmatis. In the developing arthritis model, treatment is started immediately after the injection of the adjuvant (days 1–18); in the

established arthritis model treatment is started on day 14, when the secondary inflammation is well developed (days 14–20). At the end of the experiment, the swelling of the joints is measured by means of a micro-caliper. ED_{50} is the oral dose in mg/kg which reduces the swelling (primary or secondary) to half of that of the controls.

8. Antitumor and MDR activity

The antitumor activity of the Novel Compounds and their ability to enhance the performance of antitumor agents by alleviating multidrug resistance is demonstrated, e.g., by administration of an anticancer agent, e.g., colchicine or etoposide, to multidrug resistant cells and drug sensitive cells in vitro or to animals having multidrug resistant or drug sensitive tumors or infections, with and without co-administration of the Novel Compounds to be tested, and by administration of the Novel Compound alone.

Such in vitro testing is performed employing any appropriate drug resistant cell line and control (parental) cell line, generated, e.g. as described by Ling et al., J. Cell. Physiol. 83, 103–116 (1974) and Bech-Hansen et al. J. Cell. Physiol. 88, 23–32 (1976). Particular clones chosen are the multidrug resistant (e.g. colchicine resistant) line CHR (subclone C5S3.2) and the parental, sensitive line AUX B1 (subclone AB1 S11).

In vivo anti-tumor and anti-MDR activity is shown, e.g., in mice injected with multidrug resistant and drug sensitive cancer cells. Ehrlich ascites carcinoma (EA) sub-lines resistant to drug substance DR, VC, AM, ET, TE or CC are developed by sequential transfer of EA cells to subsequent generations of BALB/c host mice in accordance with the methods described by Slater et al., J. Clin. Invest, 70, 1131 (1982).

Equivalent results may be obtained employing the Novel Compounds test models of comparable design, e.g. in vitro, or employing test animals infected with drug-resistant and drug sensitive viral strains, antibiotic (e.g. penicillin) resistant and sensitive bacterial strains, anti-mycotic resistant and sensitive fungal strains as well as drug resistant protozoal strains, e.g. Plasmodial strains, for example naturally occurring sub-strains of *Plasmodium falciparum* exhibiting acquired chemotherapeutic, anti-malarial drug resistance.

9. FKBP binding

Certain of the Novel Compounds are not immunosuppressive, particularly those which are O-substituted at C28 only, such as 28-O-methyl-rapamycin. This can be shown in standard in vitro assays in comparison to FK506 and rapamycin. FK506, for example, is known to be a potent inhibitor of IL-2 transcription, as can be shown in an IL-2 reporter gene assay. Rapamycin, although not active in the IL-2 reporter gene assay, strongly inhibits IL-6 dependent T-cell proliferation. Both compounds are very potent inhibitors of the mixed lymphocyte reaction. Nonimmunosuppressivity can also be shown in the in vivo models 1–7 above. Even those Novel Compounds which are not immunosuppressive, however, bind to macrophilin, which confers certain utilities in which nonimmunosuppressivity is an advantage.

Those of the Novel Compounds which bind strongly to macrophilin and are not themselves immunosuppressive can be used in the treatment of overdoses of macrophilin-binding immunosuppressants, such as FK506, rapamycin, and the immunosuppressive Novel Compounds.

10. Steroid potentiation

The macrophilin binding activity of the Novel Compounds also makes them useful in enhancing or potentiating the action of corticosteroids. Combined treatment with the compounds of the invention and a corticosteroid, such as dexamethasone, results in greatly enhanced steroidal activity. This can be shown, e.g., in the murine mammary tumor virus-chloramphenicol acetyltransferase (MMTV-CAT) reporter gene assay, e.g., as described in Ning, et al., *J. Biol. Chem.* (1993) 268: 6073. This synergistic effect allows reduced doses of corticosteroids, thereby reducing the risk of side effects in some cases.

11. Mip and Mip-like factor inhibition

Additionally, the Novel Compounds bind to and block a variety of Mip (macrophage infectivity potentiator) and Mip-like factors, which are structurally similar to macrophilin. Mip and Mip-like factors are virulence factors produced by a wide variety of pathogens, including those of the genera Chlamidia, e.g., *Chlamidia trachomatis;* Neisseria, e.g., *Neisseria meningitidis;* and Legionella, e.g., *Legionella pneumophilia;* and also by the obligately parasitic members of the order Rickettsiales. These factors play a critical role in the establishment of intracellular infection. The efficacy of the Novel Compounds in reducing the infectivity of pathogens which produce Mip or Mip-like factors can be shown by comparing infectivity of the pathogens in cells culture in the presence and absence of the macrolides, e.g., using the methods described in Lundemose, et al., *Mol. Microbiol.* (1993) 7: 777. The nonimmunosuppressive compounds of the invention are preferred for use in this indication for the reason that they are not immunosuppressive, thus they do not compromise the body's natural immune defenses against the pathogens.

The Novel Compounds are also useful in assays to detect the presence or amount of macrophilin-binding compounds, e.g., in competitive assays for diagnostic or screening purposes. Thus, in another embodiment, the invention provides for use of the Novel Compounds as a screening tool to determine the presence of macrophilin-binding compounds in a test solution, e.g., blood, blood serum, or test broth to be screened. Preferably, a Novel Compound is immobilized in microtiter wells and then allowed to bind in the presence and absence of a test solution to labelled macrophilin-12 (FKBP-12). Alternatively, the FKBP-12 immobilized in microtiter wells and allowed to bind in the presence and absence of a test solution to a Novel Compound which has been labelled, e.g., fluoro-, enzymatically- or radio-labelled, e.g., a Novel Compound which has been O-substituted at C40 and/or C28 with a labelling group. The plates are washed and the amount of bound labelled compound is measured. The amount of macrophilin-binding substance in the test solution is roughly inversely proportional to the amount of bound labelled compound. For quantitative analysis, a standard binding curve is made using known concentrations of macrophilin bind compound.

EXAMPLES:

In the following examples, characteristic spectroscopic data is given to facilitate identification. Peaks which do not differ significantly from rapamycin are not included. Biological data is expressed as a relative IC_{50}, compared to rapamycin in the case of the mixed lymphocyte reaction (MLR) and IL-6 dependent proliferation (IL-6 dep. prol.) assays, and to FK-506 in the macrophilin binding assay (MBA). A higher IC_{50} correlates with lower binding affinity.

Example 1: 40-O-Benzyl-rapamycin

To a stirred solution of 183 mg (0.200 mmol) of rapamycin in 2.1 mL of 2:1 cyclo-hexane-methylene chloride is added 75 µL (0.402 mmol) of benzyl-trichloroacetimidate, followed by 2.6 µL (29 µmol 15 mol %) of trifluoromethanesulfonic acid whereupon the mixture turned immediately yellow. After 3 h the mixture is diluted with ethyl acetate and

quenched with 10% aqueous sodium bicarbonate. The layers are separated and the aqueous layer is extracted twice with ethyl acetate. The combined organic solution is washed with 10% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (50:50 hexane-ethyl acetate) to afford 40-O-benzyl-rapamycin as a white amorphous solid: ^{1}H NMR ($CDCl_3$) δ0.73 (1H, dd), 1.65 (3H, s), 1.73 (3H, s), 3.12 (4H, s and m), 3.33 (3H, s), 3.49 (3H, s), 4.15 (1H, bd), 4.65 (1H, d), 4.71 (1H, d), 7.22–7.38 (5H, m); MS (FAB) m/z 1026 ($[M+Na]^+$), 972 ($[M-OCH_3)]^+$), 954 ($[M-(OCH_3+H_2O)]^+$).

MBA (rel. IC50)	1.8
IL-6 dep. prol. (rel. IC50)	10
MLR (rel. IC50)	110

Example 2: 40-O-(4'-Hydroxymethyl)benzyl-rapamycin

a) 40-O-[4'-(t-Butyldimethylsilyl)oxymethyl]benzyl-rapamycin

To a stirred, cooled (–78° C.) solution of 345 μL (2.0 mmol) of triflic anhydride in 5 mL of methylene chloride is added a solution of 504 mg (2.0 mmol) of 4-(t-butyldimethylsilyl)oxymethyl-benzyl alcohol and 820 mg (4.0 mmol) of 2,6-di-t-butyl-4-methyl-pyridine in 5 mL of methylene chloride. The resulting mixture is warmed to –20° C. and stirring is continued at this temperature for 0.5 h. The mixture is then cooled back to –78° C. and a solution of 914 mg (1.0 mmol) of rapamycin in 5 mL of methylene chloride is added. This mixture is allowed to warm to room temperature overnight and is then quenched with 10% aqueous sodium bicarbonate. The layers are separated and the aqueous layer is extracted with ethyl acetate. The combined organic solution is washed with saturated brine, dried over sodium sulfate, filtered under reduced pressure and concentrated. The residue is purified by column chromatography on silica gel (50:50 hexane-ethyl acetate) to afford 40-O-[4'-(t-butyldimethylsilyl)oxymethyl]benzyl-rapamycin a white foam: MS (FAB) m/z 1170 ($[M+Na]^+$), 1098 ($[M-(OCH_3+H_2O)]^+$).

b) 40-O-(4'-Hydroxymethyl)benzyl-rapamycin

To a stirred, cooled (0° C.) solution of 98 mg (0.093 mmol) of the compound obtained in example 2 in 2 mL of acetonitrile is added 0.2 mL of HF-pyridine. The resulting mixture is stirred for 2 h and quenched with aqueous sodium bicarbonate, then extracted with ethyl acetate. The organic solution is washed with brine, dried over sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (20:80 hexane-ethyl acetate) to afford the title compound as a white foam: ^{1}H NMR ($CDCl_3$) δ0.73 (1H, dd), 1.65 (3H, s), 1.74 (3H, s), 3.22 (1H, m), 4.67 (4H, m), 7.35 (4H, m); MS (FAB) m/z 1056 ($[M+Na]^+$), 1002 ($[M-OCH_3]^+$), 984 ($[M-(OCH_3+H_2O)]^+$), 966 ($[M-(OCH_3+2H_2O)]^+$), 934 ($[M-(OCH_3+CH_3OH+2H_2O)]^+$).

MBA (rel. IC50)	2.7
IL-6 dep. prol. (rel. IC50)	3.9
MLR (rel. IC50)	3

Example 3: 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin

a) 40-O-[4'-(2,2-Dimethyl-1,3-dioxolan-4-yl)]benzyl-rapamycin

In 10 mL of 1:1 cyclohexane-methylene chloride is dissolved 452 mg (1.24 mmol) of 4-(2,2-dimethyl-1,3-dixolan-4-yl)benzyl trichloroacetimidate, followed by 0.14 mL (0.64 mmol) of 2,6-di-t-butylpyridine 56 μL (0.64 mmol) of trifluoromethanesulfonic acid. To this mixture is added a solution of 587 mg (0.64 mmol) of rapamycin in 2 mL of methylene chloride. The reaction is stirred overnight at room temperature and quenched with aqueous sodium bicarbonate. The layers are separated and the aqueous layer is extracted twice with ethyl acetate. The combined organic solution is washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (50:50 hexane-ethyl acetate) to give 40-O-[4'-(2,2-Dimethyl-1,3-dioxolan-4-yl)]benzyl-rapamycin as a white, amorphous solid: ^{1}H NMR ($CDCl_3$) δ0.73 (1H, dd), 1.48 (3H, s), 1.55 (3H, s), 1.65 (3H, s), 1.74 (3H, s), 3.67 (3H, m), 4.28 (1H, dd), 4.62 (1H, d), 4.69 (1H, d), 5.06 (1H, dd), 7.33 (4H, m), MS (FAB) m/z 1126 ($[M+Na]^+$), 1072 ($[M-OCH_3]^+$), 1054 ($[M-OCH_3+H_2O)]^+$), 1014 ($[M-(OCH_3+CH_3COCH_3)]^+$), 996 ($[M-(OCH_3+H_2O+CH_3COCH_3)]^+$), 978 ($[M-(OCH_3+2H_2O+CH_3COCH_3)]^+$).

b) 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin

To a solution of 90.7 mg (0.08 mmol) of 40-O-[4'-(2,2-Dimethyl-1,3-dioxolan-4-yl)]benzyl-rapamycin in 4 mL of methanol is added 1 mL of 1N aqueous HCl. After 2 h the mixture is quenched with aqueous sodium bicarbonate and extracted twice with ethyl acetate. The organic solution is washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue is purified by column chromatography on silica gel (ethyl acetate) and the title compound is obtained as a white foam: ^{1}H NMR ($CDCl_3$) δ0.73 (1H, dd), 1.65 (3H, s), 1.74 (3H, s), 3.70 (4H, m), 4.63 (1H, d), 4.69 (1H, d), 4.80 (1H, dd), 7.33 (4H, m); MS (FAB) m/z 1086 ($[M+Na]^+$), 1032 ($[M-OCH_3]^+$), 1014 ($[M-OCH_3+H_2O)]^+$), 996 ($[M-(OCH_3+2H_2O)]^+$).

MBA (rel. IC50)	0.92
IL-6 dep. prol. (rel. IC50)	10.5
MLR (rel. IC50)	22

Example 4: 40-O-Allyl-rapamycin

To a stirred, cooled (–78° C.) solution of 0.33 mL (2.01 mmol) of triflic anhydride in 10 mL of methylene chloride is slowly added a solution of 0.14 mL (2.06 mmol) of allyl alcohol and 0.42 g (2.04 mmol) of 2,6-di-t-butyl-4-methyl-pyridine in 5 mL of methylene chloride. The resulting greenish solution is stirred for 1.5 h and a solution of 915 mg (1.00 mmol) of rapamycin and 0.42 g (2.04 mmol) of 2,6-di-t-butyl-4-methyl-pyridine in 5 mL of methylene chloride is added. Stirring is continued for 0.5 h at –78° C. and then the mixture is warmed to room temperature. After one more hour the mixture is quenched with aqueous sodium bicarbonate and the layers are separated. The aqueous layer is extracted twice with ethyl acetate. The combined organic solution is washed with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting green oil is purified by column chromatography on silica gel (60:40 hexane-ethyl acetate) to afford the title compound as a colorless, amorphous solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.74 (3H, s), 3.05 (1H, m), 4.13 (2H, bd), 5.14 (2H, m), 5.27 (2H, m), 5.92 (2H, m). MS (FAB) m/z 976 ($[M+Na]^+$), 922 ($[M-OCH_3]^+$), 904 ($[M-OCH_3+H_2O)]^+$), 886 ($[M-(OCH_3+2H_2O)]^+$), 872 ($[M-(2CH_3OH+OH)]^+$), 854 ($[M-(OCH_3OH+2H_2O)]^+$).

MBA (rel. IC50)	1
IL-6 dep. prol. (rel. IC50)	8
MLR (rel. IC50)	260

Example 5: 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin

To a stirred, cooled (−78° C.) solution of 0.64 g (4.00 mmol) of E-(4S)-4,5-O,O-isopropylidene-pent-2-en-1,4,5-triol and 1.26 g (6.00 mmol) of 2,6-di-t-butyl-4-methyl-pyridine in 20 mL of methylene chloride is added 0.82 mL (5.00 mmol) of triflic anhydride. The resulting mixture is stirred at this temperature for 2 h and a solution of 1.82 g (2.00 mmol) of rapamycin and 1.26 g (6.00 mmol) of 2,6-di-t-butyl-4-methyl-pyridine in 5 mL of methylene chloride is added. The mixture is allowed to gradually warm to room temperature overnight and is then quenched with aqueous sodium bicarbonate. The layers are separated and the aqueous layer is extracted three times with ethyl acetate. The organic solution is washed with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (40:60 hexane-ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.38 (3H, s), 1.42 (3H, s), 1.65 (3H, s), 1.73 (3H, s), 3.06 (1H, m), 3.58 (2H, m), 4.08 (1H, dd), 4.15 (2H, m), 4.52 (1H, bdd), 5.72 (1H, m), 5.88 (1H, m); MS (FAB) m/z 1076 ([M+Na]$^+$), 1022 ([M-OCH_3]$^+$), 1004 ([M-OCH_3+H_2O)]$^+$), 964 ([M-(OCH_3+CH_3COCH_3)]$^+$), 946 ([M-(OCH_3+H_2O+CH_3COCH_3)]$^+$), 946 ([M-(OCH_3+2H_2O+CH_3COCH_3)]$^+$).

MBA (rel. IC50)	0.64
IL-6 dep. prol. (rel. IC50)	11
MLR (rel. IC50)	8

Example 6: (2'E, 4'S)-40-O-(4,5'-Dihydroxypent-2'-en-1'-yl)-rapamycin

The conditions described in example 3, step b) applied to the compound obtained in the previous example, followed by purification through column chromatography on silica gel (95:5 ethyl acetate-methanol) afford the title compound as a white foam: ^{1}H NMR ($CDCl_3$) δ0.68 (1H, dd), 3.04 (1H, m), 4.18 (5H, m), 5.75 (1H, dd), 5.88 (1H, m), MS (FAB) m/z 1036 ([M+Na]$^+$), 1013 (M$^+$), 995 ([M-H_2O]$^+$), 982 ([M-OCH_3]$^+$), 964 ([M-OCH_3+H_2O)]$^+$), 946 ([M-(OCH_3+2H_2O)]$^+$), 832 ([M-(2CH_3OH+OH)]$^+$), 914 ([M-(OCH_3CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	1.7
IL-6 dep. prol. (rel. IC50)	12
MLR (rel. IC50)	3.5

Example 7: 40-O-(2-Hydroxy)ethoxycarbonylmethyl-rapamycin

a) 40-O-[2-(t-Butyldimethylsilyl)oxy]ethoxycarbonylmethyl-rapamycin

To a stirred solution of 2.74 g (3.00 mmol) of rapamycin and 30 mg (0.06 mmol of dirhodium tetraacetate dihydrate in 30 mL of methylene chloride is added a solution of 0.38 mL (3.60 mmol) of 2-(t-butyldimethylsilyl)oxyethyl diazoacetate in 10 ml of methylene chloride over 5 h. After the addition is complete stirring is continued for one more hour, then the reaction is quenched with 1N aq. HCl. The layers are separated and the aqueous layer is extracted with ethyl acetate. The combined organic solution is washed with aq. sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (40:60 hexane-ethyl acetate) yielding 40-O-[2-(t-butyldimethylsilyl)oxy]ethoxycarbonylmethyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.06 (6H, s), 0.68 (1H, dd), 0.88 (9H, s), 1.64 (3H, s), 1.73 (3H, s), 3.12 (5H, s and m), 3.81 (2H, dd), 4.19 (2H, dd), 4.32 (2H, s); MS (FAB) m/z 1152 ([M+Na]$^+$), 1080 ([M-(OCH_3+H_2O)]$^+$).

b) 40-O-(2-Hydroxy)ethoxycarbonylmethyl-rapamycin

To a stirred, cooled (0° C.) solution of 81 g (0.07 mmol) of 40-O-[2-(t-butyldimethylsilyl)oxy]ethoxycarbonylmethyl-rapamycin in 1.5 mL of acetonitrile is added 0.15 mL of HF-pyridine. After 2 h the reaction is quenched with aq. sodium bicarbonate. The mixture is extracted with ethyl acetate. The organic solution is washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by PTLC (ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.70 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.13 (5H, s and m), 3.85 (3H, m), 4.25 (5H, m); MS (FAB) m/z 1038 ([M+Na]$^+$), 984 ([M-(OCH_3]$^+$), 966 ([M-(OCH_3+H_2O)]$^+$), 948 ([M-(OCH_3+2H_2O)]$^+$).

MBA (rel. IC50)	4
IL-6 dep. prol. (rel. IC50)	9.7
MLR (rel. IC50)	2.1

Example 8: 40-O-(2-Hydroxy)ethyl-rapamycin

a) 40-O-[2-(t-Butyldimethylsilyl)oxy]ethyl-rapamycin

A solution of 9.14 g (10 mmol) of rapamycin and 4.70 mL (40 mmol) of 2,6-lutidine in 30 mL of toluene is warmed to 60° C. and a solution of 6.17 g (20 mmol) of 2-(t-butyldimethylsilyl)oxyethyl triflate and 2.35 mL (20 mmol) of 2,6-lutidine in 20 mL of toluene is added. This mixture is stirred for 1.5 h. Then two batches of a solution of 3.08 g (10 mmol) of triflate and 1.2 mL (10 mmol) of 2,6-lutidine in 10 mL of toluene are added in a 1.5 h interval. After addition of the last batch, stirring is continued at 60° C. for 2 h and the resulting brown suspension is filtered. The filtrate is diluted with ethyl acetate and washed with aq. sodium bicarbonate and brine. The organic solution is dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (40:60 hexane-ethyl acetate) to afford 40-O-[2-(t-butyldimethylsilyl)oxy]ethyl-rapamycin as a white solid: ^{1}H NMR ($CDCl_3$) δ0.06 (6H, s), 0.72 (1H, dd), 0.90 (9H, s), 1.65 (3H, s), 1.75 (3H, s), 3.02 (1H, m); 3.63 (3H, m), 3.72 (3H, m); MS (FAB) m/z 1094 ([M+Na]$^+$), 1022 ([M-(OCH_3+H_2O)]$^+$).

b) 40-O-(2-Hydroxy)ethyl-rapamycin

To a stirred, cooled (0° C.) solution of 4.5 g (4.2 mmol) of 40-O-[2-(t-butyldimethylsilyl)oxy]ethyl-rapamycin in 20 mL of methanol is added 2 mL of 1N HCl. This solution is stirred for 2 h and neutralized with aq. sodium bicarbonate. The mixture is extracted with three portions of ethyl acetate. The organic solution is washed with aq. sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purification by column chromatography on silica gel (ethyl acetate) gave the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.13 (5H, s and m), 3.52–3.91 (8H, m); MS (FAB) m/z 980 ([M+Na]$^+$), 926 ([M-(OCH_3]$^+$), 908 ([M-(OCH_3+H_2O)]$^+$), 890 ([M-(OCH_3+2H_2O)]$^+$), 876 ([M-(2CH_3OH+OH)]$^+$), 858 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	2.2
IL-6 dep. prol. (rel. IC50)	2.8
MLR (rel. IC50)	3.4

Example 9: 40-O-(3-Hydroxy)propyl-rapamycin

a) 40-O-[3-(t-Butyldimethylsilyl)oxy]propyl-rapamycin

The same procedure as described in example 8, step a) using 3-(t-butyldimethylsilyl)oxyprop-1-yl triflate affords 40-O-[3-(t-butyldimethylsilyl)oxy]propyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.05 (6H, s), 0.72 (1H, dd), 0.90 (9H, s), 1.65 (3H, s), 1.74 (3H, s), 1.77 (2H, m), 3.03 (1H, m), 3.52–3.73 (7H, m); MS (FAB) m/z 1108 ([M+Na]$^+$), 1036 ([M-(OCH_3+H_2O)]$^+$).

b) 40-O-(3-Hydroxy)propyl-rapamycin

Treatment of the compound obtained in step a) in the conditions described in example 8, step b) yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 1.80 (2H, m), 3.05 (1H, m), 3.55–3.91 (8H, m); MS (FAB) m/z 994 ([M+Na]$^+$), 940 ([M-(OCH_3]$^+$), 922 ([M-(OCH_3+H_2O)]$^+$), 904 ([M-(OCH_3+2H_2O)]$^+$), 872 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	1.6
IL-6 dep. prol. (rel. IC50)	2.7
MLR (rel. IC50)	11

Example 10: 40-O-(6-Hydroxy)hexyl-rapamycin

a) 40-O-[6-(t-Butyldimethylsilyl)oxy]hexyl-rapamycin

The same procedure as described in example 8, step a) using 6-(t-butyldimethylsilyl)oxyhex-1-yl triflate affords 40-O-[6-(t-Butyldimethylsilyl)oxy]hexyl-rapamycin: MS (FAB) m/z 1150 ([M+Na]$^+$).

b) 40-O-(6-Hydroxy)hexyl-rapamycin

Treatment of the compound obtained in step a) in the conditions described in example 8, step b) yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.38 (2H, m), 1.57 (4H, m), 1.65 (3H, s), 1.74 (3H, s), 3.02 (1H, m), 3.49–3.72 (8H, m); MS (FAB) m/z 1036 ([M+Na]$^+$), 982 ([M-(OCH_3]$^+$), 964 ([M-(OCH_3+H_2O)]$^+$), 946 ([M-(OCH_3+2H_2O)]$^+$), 914 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	0.8
IL-6 dep. prol. (rel. IC50)	8.5
MLR (rel. IC50)	18

Example 11: 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin

a) 40-O-[2-t-Butyldimethylsilyl)oxyethoxy]ethyl-rapamycin

The same procedure as described in example 8, step a) using 2-[2-(t-butyldimethylsilyl)oxy-ethoxy]ethyl triflate affords 40-O-[2-(t-butyldimethylsilyl)oxyethoxy]ethyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.06 (6H, s), 0.71 (1H, dd), 0.88 (9H, s), 1.65 (3H, s), 1.74 (3H, s), 3.07 (1H, m), 3.51–3.79 (11H, m); MS (FAB) m/z 1138 ([M+Na]$^+$), 1115 (M$^+$), 1097 ([M-H_2O]$^+$), 1084 ([M-(OCH_3]$^+$), 1066 ([M-(OCH_3+H_2O)]$^+$), 1048 ([M-(OCH_3+2H_2O)]$^+$), 1034 ([M-(2CH_3OH+OH)]$^+$), 1016 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

b) 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin

Treatment of the compound obtained in step a) in the conditions described in example 8, step b) yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.74 (3H, s), 3.05 (1H, m), 3.51–3.77 (11H, m); MS (FAB) m/z 1024 ([M+Na]$^+$), 1001 (M$^+$), 983 ([M-H_2O]$^+$), 970 ([M-(OCH_3]$^+$), 952 ([M-(OCH_3+H_2O)]$^+$), 934 ([M-(OCH_3+2H_2O)]$^+$), 920 ([M-(2CH_3OH+OH)]$^+$), 902 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	1.2
IL-6 dep. prol. (rel. IC50)	3.2
MLR (rel. IC50)	2

Example 12: 40-O-[(3S)-2,2-Dimethyldioxolan-3-yl] methyl-rapamycin

The same procedure as described in example 8, step a) using the triflate of glycerol acetonide affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.36 (3H, s), 1.42 (3H, s), 1.65 (3H, s), 1.75 (3H, s), 3.06 (1H, m), 3.55 (2H, m), 3.69 (3H, m), 4.06 (1H, dd), 4.26 (1H, m); MS (FAB) m/z 1050 ([M+Na]$^+$), 996 ([M-(OCH_3]$^+$), 978 ([M-(OCH_3+H_2O)]$^+$), 960 ([M-(OCH_3+2H_2O)]$^+$).

MBA (rel. IC50)	0.9
IL-6 dep. prol. (rel. IC50)	8
MLR (rel. IC50)	290

Example 13: 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin

Treatment of the compound obtained in the previous example in the conditions described in example 3 yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.07 (1H, m), 3.68 (8H, m); MS (FAB) m/z 1010 ([M+Na]$^+$), 956 ([M-(OCH_3]$^+$), 938 ([M-(OCH_3+H_2O)]$^+$), 920 ([M-(OCH_3+2H_2O)]$^+$), 888 ([M-(OCH_3+CH_3OH 2H_2O)]$^+$).

MBA (rel. IC50)	0.67
IL-6 dep. prol. (rel. IC50)	9
MLR (rel. IC50)	10

Example 14: 40-O-(2-Acetoxy)ethyl-rapamycin

To a stirred, cooled (0° C.) solution of 53 mg (0.055 mmol) of 40-O-hydroxyethyl-rapamycin in 2 mL of methylene chloride is added 0.2 mL of pyridine followed by 0.02 mL (0.281 mmol) of acetyl chloride. The mixture is stirred for 3 h and diluted with ethyl acetate, then washed with aq. sodium bicarbonate, cold 1N HCl and again with aq. sodium bicarbonate. The organic solution is dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (30:70 hexane-ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 2.08 (3H, s), 3.07 (1H, m), 3.78 (2H, dd), 4.20 (2H, dd); MS (FAB) m/z 1022 ([M+Na]$^+$), 999 (M$^+$), 982 ([M-(OH]$^+$), 968 ([M-(OCH_3]$^+$), 950 ([M-(OCH_3+H_2+H_2O)]$^+$), 932 ([M-(OCH_3+2H_2O)]$^+$), 918 ([M-(2CH_3OH+OH)]$^+$), 900 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	2
IL-6 dep. prol. (rel. IC50)	7.6
MLR (rel. IC50)	3.6

Example 15: 40-O-(2-Nicotinoyloxy)ethyl-rapamycin

The same procedure as described in the previous example using nicotinoyl chloride hydrochloride affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.07 (1H, m), 3.94 (2H, dd), 4.49 (2H, t), 7.39 (1H, dd), 8.31 (1H, ddd), 8.78 (1H, ddd), 9.24 (1H, dd); MS (FAB) m/z 1085 ([M+Na]$^+$), 1063 ([M+H]$^+$), 1045

([M-OH]$^+$), 1031 ([M-(OCH$_3$]$^+$), 1013 ([M-(OCH$_3$+H$_2$O)]$^+$).

MBA (rel. IC50)	1.1
IL-6 dep. prol. (rel. IC50)	6.9
MLR (rel. IC50)	5

Example 16: 40-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin

a) 40-O-(2-Bromoacetoxy)ethyl-rapamycin

The same procedure as described in example 14 using bromoacetyl chloride affords 40-O-(2-bromoacetoxy)ethyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.76 (3H, s), 3.03 (1H, m), 3.82 (2H, m), 3.87 (2H, s), 4.31 (2H, m); MS (FAB) m/z 1100, 1102 ([M+Na]$^+$), 1077 (M$^+$), 1061 ([M-H$_2$O]$^+$), 1046, 1048 ([M-(OCH$_3$]$^+$), 1028, 1030 ([M-(OCH$_3$+H$_2$O)]$^+$), 1012 ([M-(OCH$_3$+2H$_2$O)]$^+$), 996 ([M-(2CH$_3$OH+OH)]$^+$), 980 ([M-(OCH$_3$+CH$_3$OH+2H$_2$O)]$^+$).

b) 40-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin

To a stirred, cooled (−45° C.) solution of 54 mg (0.05 mmol) of 40-O-(2-bromoacetoxy)ethyl-rapamycin in 0.5 mL of DMF is added a solution of 0.022 mL (0.25 mmol) of morpholine in 0.2 mL of DMF and the resulting mixture is stirred at that temperature for 1 h, then treated with aq. sodium bicarbonate. This mixture is extracted three times with ethyl acetate. The organic solution is washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (95:5 ethyl acetate-methanol) yielding the title compound as an amorphous white solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.76 (3H, s), 2.60 (3H, m), 3.07 (1H, m), 3.24 (2H, s), 3.78 (8H, m), 4.27 (2H, t); MS (FAB) m/z 1107 ([M+Na]$^+$), 1085 ([M+H]$^+$), 1067 ([M-OH]$^+$), 1053 ([M-(OCH$_3$]$^+$), 1035 ([M-(OCH$_3$+H$_2$O)]$^+$).

MBA (rel. IC50)	1.3
IL-6 dep. prol. (rel. IC50)	4
MLR (rel. IC50)	3.5

Example 17: 40-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin

The same procedure as described in example 16, step b) using imidazole affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.78 (3H, s), 3.06 (3H, m), 3.80 (2H, m), 4.32 (2H, m), 4.73 (2H, s), 6.97 (1H, dd), 7.09 (1H, dd), 7.52 (1H, dd); MS (FAB) m/z 1066 ([M+Na]$^+$), 1048 ([M+OH]$^+$), 1034 ([M-(OCH$_3$]$^+$), 1016 ([M-(OCH$_3$+H$_2$O)]$^+$).

MBA (rel. IC50)	1
IL-6 dep. prol. (rel. IC50)	7.6
MLR (rel. IC50)	3.4

Example 18: 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy] ethyl-rapamycin

The same procedure as described in example 16, step b) using N-methylpiperazine affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.77 (3H, s), 2.78 (4H, s and m), 3.02 (4H, bs), 3.08 (1H, m), 3.32 (2H, s), 3.80 (2H, dd), 4.27 (2H, t); MS (FAB) m/z 1098 ([M+Na]$^+$), 1066 ([M-(OCH$_3$]$^+$).

MBA (rel. IC50)	2.6
IL-6 dep. prol. (rel. IC50)	10.3
MLR (rel. IC50)	5

Example 19: 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin

To a stirred, cooled (−20° C.) solution of 48 mg (0.05 mmol) of 40-O-hydroxyethyl-rapamycin and 0.023 mL (0.20 mmol) of 2,6-lutidine in 0.5 mL of methylene chloride is added 0.008 mL (0.05 mmol) of triflic anhydride. The mixture is stirred at this temperature for 2 h, then allowed to warm to room temperature and stirred for one more hour. The reaction is quenched with aq. sodium bicarbonate and the resulting mixture is extracted with three portions of ethyl acetate. The organic solution is washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (30:70 hexane-ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ1.66 (3H, s), 1.75 (3H, s), 3.14 (3H, s), 3.35 (3H, s), 3.76 (4H, s); MS (FAB) m/z 948 ([M+Na]$^+$), 925 (M$^+$), 908 ([M-OH]$^+$), 894 ([M-(OCH$_3$]$^+$), 876 ([M-(OCH$_3$+H$_2$O)]$^+$), 858 ([M-(OCH$_3$+2H$_2$O)]$^+$), 844 ([M-(2CH$_3$OH+OH)]$^+$), 826 ([M-(OCH$_3$+CH$_3$OH+2H$_2$O)]$^+$).

MBA (rel. IC50)	1.6
IL-6 dep. prol. (rel. IC50)	22.9
MLR (rel. IC50)	16

Example 20: (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin

a) (26R)-26-Dihydro-40-O-[2-(t-Butyldimethylsilyloxy)] ethyl-rapamycin

In 4.5 mL of 2:1 acetonitrile-acetic acid is dissolved 315 mg (1.2 mmol) of tetramethylammonium-triacetoxyborohydride. The resulting solution is stirred for 1 at room temperature and cooled to −35° C., then 161 mg (0.15 mmol) of 40-O-[2-(t-butyldimethylsilyloxy)]ethyl-rapamycin is added. The resulting mixture is stirred at the same temperature overnight and is quenched by the addition of aq. sodium bicarbonate. The mixture is extracted with three portions of ethyl acetate. The organic solution is washed with aq. sodium bicarbonate, two portions of 30% aq. Rochelle's salt and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (40:60 hexane-ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.06 (6H, s), 0.73 (1H, dd), 0.90 (9H, s), 1.64 (3H, s), 1.67 (3H, s), 3.02 (1H, m), 3.15 (1H, m), 3.64 (3H, m), 3.71 (2H, dd), 3.91 (1H, s); MS (FAB) m/z 1096 ([M+Na]$^+$), 1041 ([M-HOCH$_3$]$^+$), 1024 ([M-(OCH$_3$+H$_2$O)]$^+$), 1006 ([M-(OCH$_3$+2H$_2$O)]$^+$), 974 ([M-(OCH$_3$+CH$_3$OH+2H$_2$O)]$^+$).

MBA (rel. IC50)	3.9
IL-6 dep. prol. (rel. IC50)	53
MLR (rel. IC50)	18

Example 21: 28-O-Methyl-rapamycin

To a stirred solution of 103 mg (0.1 mmol) of 40-O-TBS-rapamycin (obtained by silylation of rapamycin with 1 eq. of TBS triflate in methylene chloride in the presence of 2 eq. of 2,6-lutidine at 0° C.) in 0.5 mL of methylene chloride is added 85.8 mg (0.40 mmol) of proton sponge followed by 44

mg (0.30 mmol) of trimethyloxonium tetrafluoroborate. The resulting brown heterogeneous mixture is stirred overnight, quenched with aq. sodium bicarbonate and extracted with ethyl acetate. The organic solution is washed with 1N HCl, aq. sodium bicarbonate and brine, then dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (60:40 hexane-ethyl acetate) to afford 40-O-t-butyldimethylsilyl-28-O-methyl-rapamycin. The latter compound is desilylated in the conditions described in example 10, step b) to afford, after PTLC (ethyl acetate), the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.70 (1H, dd), 1.68 (6H, 2s), 2.95 (1H, m), 3.13 (3H, s), 3.14 (3H, s), 3.28 (3H, s), 3.41 (3H, s); MS (FAB) m/z 950 ($[M+Na]^+$), 927 (M^+), 909 ($[M-H_2O]^+$), 896 ($[M-OCH_3]^+$), 878 ($[M-(OCH_3+H_2O)]^+$), 864 ($[M-(OCH_3+CH_3OH)]^+$), 846 ($[M-(2CH_3OH+OH)]^+$), 832 ($[M-(OCH_3+2CH_3OH)]^+$), 814 ($[M-(3CH_3OH+OH)]^+$).

MBA (rel. IC50)	1.58
IL-6 dep. prol. (rel. IC50)	1240
MLR (rel. IC50)	1300

Example 22: 40-O-(2-aminoethyl)-rapamycin

a) 40-O-(2-bromoethyl)-rapamycin

A solution of 914 mg rapamycin in 5 mL toluene containing 0.64 ml of 2,6-lutidine and 1.28 g of 2-bromoethyl triflate is heated at 65° C. for 18 h. The reaction mixture is then cooled to room temperature, poured on 20 ml of a saturated bicarbonate solution and extracted with 3×20 mL ethyl acetate. The organic phases are dried over sodium carbonate and the solvent removed at reduced pressure on the rotary evaporator. The residue is chromatographed on 100 g silica gel, eluting with hexane/ethyl acetate 3/2 to afford 40-O-(2-bromoethyl)-rapamycin as an amorphous solid: MS (FAB) m/z 1044 and 1042 (100%; M+Na); 972 and 970 (55%, M-(MeOH+H2O)).

H-NMR (CDCl3) d: 0.72 (1H, q, J=12 Hz); 3.13 (3H, s); 3.33 (3H, s); 3.45 (3H,s); 3.9 (4H, m); 4.78 (1H, s)

b) 40-O-(2-azidoethyl)-rapamycin

A solution of 2.4 g of 40-O-(2-bromoethyl)-rapamycin in 40 mL DMF is treated with 0.19 g sodium azide at room temperature. After 2 h, the mixture is poured on 100 mL of saturated sodium bicarbonate and extracted with 3×100 mL ethyl acetate. The organic phases are combined, dried over sodium sulfate and the solvent removed under reduced pressure. The crude product is purified by chromatography on silica gel eluting with hexane/ethyl to afford 40-O-(2-azidoethyl)-rapamycin: MS (FAB): 1005 (100%, M+Na); 951 (24%, M-MeOH); 933 (57%, M-(MeOH+H2O)

c) 40-O-(2-aminoethyl)-rapamycin

To a solution of 230 mg 40-O-(azidoethyl)-rapamycin in 3 mL of THF/water 5/1 at room temperature are added 307 mg of triphenylphosphine. The reaction mixture is becomes yellow. After 7 h, the reaction mixture is loaded on x g silica gel and chromatographed with ethyl acetate/methanol/acetic acid 50/50/0.5 to afford the title product in the form of its acetate: MS (FAB) m/z 979 (45%, M+Na); 957 (100% MH); 925 (63%, M-MeOH); 907 (25%, M-(MeOH+H2O)

MBA (rel. IC50): 0.7

IL-6 dep. prol. (rel. IC50): 10

Example 23: 40-O-(2-acetaminoethyl)-rapamycin

To a solution of 101 mg of the acetate of 40-O-(2-aminoethyl)-rapamycin in 2 mL THF are added 0.02 mL pyridine and 0.07 mL acetyl chloride. The reaction mixture is kept at room temperature for 18 h and then poured on 7 mL saturated sodium bicarbonate. The aqueous phase is extracted 3× with 5 mL ethyl acetate, the organic phases are combined and dried over sodium sulfate. The solvent is evaporated and the residue chromatographed on 10 g silica gel eluting first with ethyl acetate followed by ethyl acetate/methanol/acetic acid 50/50/0.5 to afford the title product: MS (FAB) m/z 1021 (20%, M+Na); 967 (28%, M-MeOH); 949 (100%, M-(MeOH+H2O)

H-NMR (CDCl3) d: 0.71 (1H, q, J=12 Hz); 1.98 (3H, s); 3.13 (3H, s); 3.34 (3H, s); 3.44 (3H, s); 4.75 (1H, s)

MBA (rel. IC50): 1.1

IL-6 dep. prol. (rel. IC50): 2.3

Example 24: 40-O-(2-nicotinamidoethyl)-rapamycin

101 mg of 40-O-(2-aminoethyl)-rapamycin acetate are dissolved in 5 ml ethyl acetate and extracted 2× with saturated sodium bicarbonate. The organic phase is dried over sodium sulfate and the solvent evaporated. The residue is dissolved in 2 mL THF and treated with 22 mg DCC and 15 mg nicotinic acid. After 15 h at room temperature the reaction mixture is evaporated and the residue chromatographed on silica gel, eluting with ethyl acetate followed by ethyl acetate/methanol 9/1, to afford the title product: MS (FAB) m/z 1084 (80%, M+Na); 1062 (40%, MH); 1038 (100%, M-MeOH); 1012 (50%, M-(MeOH+H2O)

H-NMR (CDCl3) d: 0.72 (1H, q, J=12 Hz); 3.13 (3H, s); 3.33 (3H, s); 3.37 (3H, s); 7.39 (1H, dd); J=6 Hz, J=8 Hz), 8.19 (1H, d, J=8 Hz); 8.75 (1H, d, J=6 Hz); 9.04 (1H, broad s)

MBA (rel. IC50): 1.2

IL-6 dep. prol. (rel. IC50): 2.8

Example 25: 40-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin

To a solution of 30 mg N-methyl-imidazol-2-carboxylic acid in 1 mL DMF are added 58 mg DCC and 58 mg HOBT. After 2 h, 150 mg 40-O-(2-aminoethyl)-rapamycin are added and the reaction mixture is stirred for 18 at room temperature. The suspension is then filtered, the filtrate diluted with 5 mL ethyl acetate and washed with 2×2 mL of a saturated aqueous bicarbonate solution. The organic phase is dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue is chromatographed over 10 silica gel, eluting with hexane/ethyl acetate ¼ and then ethyl acetate to afford the title product:

MS (FAB) m/z 1087 (36%, M+Na); 1065 (57%, MH); 1033 (100%, M-MeOH); 1015 (46%, M-(MeOH+H2O)

H-NMR (CDCl3) d: 0.72 (1H, q, J=12 Hz); 3.13 (3H, s); 3.33 (3H, s); 3.46 (3H, s); 4.03 (3H, s); 6.93 (1H, broad s); 6.98 (1H, broad s); 7.78 (1H, m);

MBA (rel. IC50): 1.1

IL-6 dep. prol. (rel. IC50): 7

Example 26: 40-O-(2-ethoxycarbonylaminoethyl)-rapamycin

A solution of 200 mg 40-O-(2-azidoethyl)-rapamycin in 3 mL THF/water 5/1 is treated with 267 mg triphenylphosphine for 7 h at room temperature. Then 0.4 mL pyridine are added followed by 194 μL ethyl chloroformiate. After 2 h, the reaction mixture is poured on 5 mL ethyl acetate and washed successively with 10 mL saturated sodium bicarbonate, 5 mL water and 5 ml 10% citric acid. The organic phase is dried over sodium sulfate and the solvent evaporated. The residue is chromatographed over 20 g silica gel, eluting with ethyl acetate followed by ethyl acetate/methanol 9/1, to afford the title product.: MS (FAB) m/z 1051 (35%, M+Na); 997 (30%, M-MeOH); 979 (100%, M-(MeOH+H2O)

H-NMR (CDCl3) d: 0.71 (1H, q, J=12 Hz); 1.24 (3H, t, J=8 Hz), 3.13 (3H, s); 3.34 (3H, s); 3.43 (3H, s); 4.10 (2H, q, J=8 Hz); (1H, m)

MBA (rel. IC50): 1.1
IL-6 dep. prol. (rel. IC50): 1.7

Example 27: 40-O-(2-tolylsulfonamidoethyl)-rapamycin

A solution of 200 mg 40-O-(2-aminoethyl)-rapamycin in 3 mL THF is treated with 0.4 mL pyridine and 390 mg tosyl chloride and the reaction mixture is stirred for 12 h at room temperature. The solution is then poured onto 5 ml of a saturated bicarbonate solution and the aqueous phase is extracted with 2×5 mL ethyl acetate. The combined organic phases are washed with 5 mL of 10% citric acid and 5 mL water. After drying on sodium sulfate the solvent is evaporated and the residue chromatographed on 20 g silica gel, eluting with hexane/ethyl acetate 1/1 to afford the title product as a white foam: MS (FAB) m/z 1133 (100%, M+Na); 1078 (25%, M-MeOH); 1061 (85%, M-(MeOH+H2O))

H-NMR (CDCL3) d: 0.68 (1H, q, J=12 Hz); 2,43 (3H, s); 3,13 (3H, s); 3,35 (3H, s); 3,41 (3H, s); 4.76 (1H, s); 5.85 (1H, t, J=6 Hz); 7.30 (2H, d, J=8 Hz); 7.75 (2H, d, J=8 Hz).

MBA (rel. IC50): 15.9
IL-6 dep. prol. (rel. IC50): 14

Example 28: 40-O-[2-(4',5'-dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin

98 mg of 40-O-(2-azidoethyl)-rapamycin and 32 mg diethylacetylene dicarboxylate are suspended in 0.5 ml toluene and heated at 65° C. for 5 h. The reaction mixture is then cooled at room temperature, loaded on 10 g silica gel and eluted with hexane/ethyl acetate 1/1 to afford the title product: MS (FAB) m/z 1175 (20%, M+Na); 1121 (15%, M-MeOH); 1103 (60%, M-(MeOH+H2O))

H-NMR (CDCl3) d: 0.62 (1H, q, J=12 Hz); 1.40 (3H, t, J=8 Hz); 1.42 (3H, t, J=8 Hz); 3.13 (3H, s); 3.25 (3H, s); 3.33 (3H, s)

MBA (rel. IC50): 2.7
IL-6 dep. prol. (rel. IC50): 12

The previous examples may also be made using as starting material instead of rapamycin, 9-deoxo-rapamycin, 26-dihydro rapamycin, or 9-deoxo-, 26-dihydro-rapamycin. Alternatively, and preferably, as described e.g., in example 20, the rapamycin compounds of the above examples may be hydrogenated or reduced, using suitable protecting groups where necessary. The following novel methods for reducing the keto at C9, or hydrogenating the keto at C26 are provided:

Example 29: Removal of keto at C9

A stream of hydrogen sulfide is passed at room temperature through a stirred solution of 3.2 g (3.5 mmol) of rapamycin in 50 ml pyridine and 2.5 ml DMF. The solution turns from colorless to yellow. After two hours, the introduction of hydrogen sulfide is stopped and stirring is continued for five days, during which time the solution turns gradually orange. TLC and HPLC analysis verifies complete consumption of the starting material and the presence of a single new compound. The solution is purged with nitrogen for one hour and concentrated under reduced pressure. The residue is taken up in ethyl acetate, washed with cold 1N HCl solution (3×), saturated sodium bicarbonate solution and saturated brine. The organic layer is dried over anhydrous sodium sulfate and filtered and concentrated under reduced pressure. The residue is taken up in ether and precipitated sulfur is filtered off. Concentration of the ethereal solution followed by column chromatography on silica gel (10:4:1 CH_2Cl_2/i-Pr_2O/MeOH) yields 9-deoxorapamycin as a colorless foam. The identity of the product is confirmed by nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), and/or infrared spectrosopy (IR). 9-deoxorapamycin is found to exhibit the following characteristic physical data: ^{1}H NMR ($CDCL_3$) δ1.61 (3H,d,J=1 Hz, C17-CH_3), 1.76 (3H,d,J=1.2 Hz, C29-CH_3), 2.42 (1H,d,J=14.5 Hz, H-9), 2.74 (1H,d,J=14.5 Hz, H-9), 3.13 (3H,s,C16-OCH_3) 3.5 (3H,s,C27-OCH_3), 3.40 (3H,s,C39-OCH_3), 5.40 (1H,d,J=10 Hz, H-30), 5.57 (1H, dd,J_1=8.6 Hz, J_2=15 Hz, H-22), 5.96 (1H,d,J=9 Hz, H-18), 6.09 (1H,d,J=1.7 Hz, 10-OH), 6.15 (1H,dd,J_1=10 Hz, J_2=15 Hz, H-21), 6.37 (1H,dd,J_1=1.5 Hz, J_2=5 Hz, H-19), 6.38 (1H,J=9.5 Hz, H-20). ^{13}C NMR ($CDCl_3$) δ38.5 (C-9), 98.0 (C-10), 170.7 (C-1), 173.0 (C-8), 208.8 (C-32), 216.9 (C-26).

MS(FAB) m/z 922 8[M+Na^+]), 899 (M^+), 881 ([M-H_2O]$^+$), 868 ([M-OCH_3]$^+$), 850 ([M-(H_2O+OCH_3)]$^+$).

IR (major peaks)(cm^{-1}) 987, 1086, 1193, 1453, 1616, 1717, 1739, 3443.

MBA (rel. IC_{50}): 1
MLR (rel. IC_{50}): 14
IL-6 dep. prol. (rel. IC_{50}): 9

Example 30: Dihydrogenation of keto at C26

To a stirred solution of 421 mg (1.6 mmol) of tetramethylammonium triacetoxyborohydride in 2 ml of acetonitrile is added 2 ml of acetic acid. The resulting mixture is stirred for 30 minutes at room temperature and cooled to −35° C. At this temperature a solution of 180 mg (0.2 mmol) of 9-deoxo-rapamycin in 1 ml of acetonitrile is added and the resulting mixture is allowed to stir for 24 hours. The mixture is quenched with a saturated solution potassium tartrate solution and allowed to warm to room temperature. Stirring is continued until both layers are clear and ethyl acetate is added. The layers are separated and the aqueous layer is extracted twice with ethyl acetate. The resulting organic solution is washed once with a 10% sodium bicarbonate solution and twice with saturated brine, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (90:10 AcOEt-hexane). As the starting material in this case was 9-deoxorapamycin, the final compound is 9-deoxorapamycin, 26-dihydrorapamycin is produced as a colorless foam, having the following characteristic spectroscopic data: ^{1}H NMR ($CDCl_3$) (major isomer) E0.9 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 0.93 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.00 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.07 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.17 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.61 (3H,d,J=1 Hz, C17-CH_3), 1.73 (3H,d,J=1.2 Hz, C29-CH_3), 2.43 (1H,dd,J=4.1 and 16.0 Hz, H-33), 2.46 (1H,dd,J=13.8 Hz, H-9), 2.58 (1H,m,H-25), 2.77 (1H,dd,J=13.8 Hz, H-9), 2.82 (1H,dd,J=8.3 and 16.0 Hz, H-33), 3.17 (1H,dd,J=4.1 and 9.2 Hz, H-27), 3.61 (2H,m, H-14 and H28), 5.19 (1H,ddd,J=4.1, 4.6 and 8.3 Hz, H-34), 5.49 (1H, broad d,J=5.0 Hz, H-2), 5.56 (1H,d,J=9.1 Hz, H-30), 5.75 (1H,dd, J=6.9 and 14.7 Hz, H-22), 5.76 (1H,s,10-OH), 5.99 (1H, broad d,J=9.2 Hz, H-18), 6.10 (1H,m,H-21), 6.36 (2H,m,H-19 and H-20);

MS (FAB) m/z 924 ([M+Na]), 852 ([M-(H_2O+CH_3O)]$^+$).

MBA (rel. IC_{50}): 47
MLR (rel. IC_{50}): 134
IL-6 dep. prol. (rel. IC_{50}): 78

26-dihydrorapamycin is prepared in the same manner, using rapamycin in place of 9-deoxorapamycin. This product has the following characteristic spectroscopic data: ^{13}C-NMR ($CDCl_3$) (major isomer) d=208.3 (C-32); 194.0 (C-9); 169.3 (C-1); 166.6 (C-8); 140.9 (C-22); 136.5 (C-29); 136.2 (C-17); 133.5 (C-20); 129.1 (C-21); 128.7 (C-18); 126.2 (C-30); 125.3 (C-19); 98.6 (C-10); 84.4 (C-39); 83.9 (C-16; 81.6 (C-27); 75.4 (C-34); 74.3 (C-28); 73.9 (C-40); 72.9 (C-26); 67.4 (C-14); 59.1 (27-O$\underline{CH_3}$); 56.6 (39-O$\underline{CH_3}$); 55.9 (16-O$\underline{CH_3}$); 51.3 (C-2); 46.8 (C-31); 44.3 (C-6); 40.4

(C-33); 40.4 (C-25); 39.5 (C-24); 38.8 (C-15); 38.0 (C-36); 34.3 (C-23); 34.2 (C-38); 33.5 (C-11); 33.3 (C-37); 33.2 (C-35); 31.5 (C-42); 31.3 (C-41); 30.9 (C-13); 27.1 (C-12); 27.0 (C-3); 25.2 (C-5); 21.4 (23-$\underline{C}H_3$); 20.7 (C-4); 17.3 (11-$\underline{C}H_3$); 16.1 (31-$\underline{C}H3$); 15.9 (35-$\underline{C}H_3$); 14.4 (25-$\underline{C}H_3$); 14.2 (29-$\underline{C}H_3$); 10.3 (17-$\underline{C}H_3$).

MS (FAB) m/z: 884 (M-OCH_3, 35%); 866 (M-[OCH_3+H_2O]. 100%; 848 (M-[OCH_3+2 H_2O], 40%).

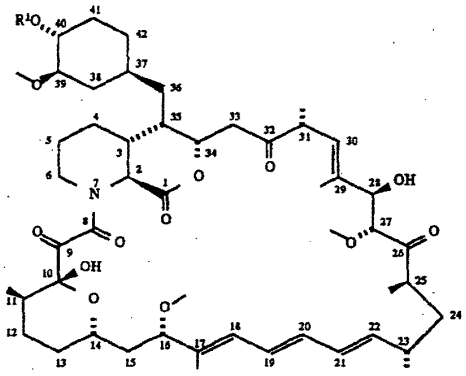
MBA (rel. IC_{50}): 1.7

MLR (rel. IC_{50}): 1

IL-6 dep. prol. (rel. IC_{50}): 7.5

We claim:

1. A compound of the formula



wherein R^1 is hydroxy(C_{1-6})alkyl or hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

2. A compound according to claim 1 in which R^1 is hydroxy(C_{1-3})alkyl or hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

3. A compound according to claim 1 in which R^1 is hydroxy(C_{1-3})alkyl.

4. A compound according to claim 1 in which R^1 is hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

5. The compound according to claim 1 which is 40-O-(3-hydroxypropyl)-rapamycin.

6. The compound according to claim 1 which is 40-O-[2-(2-hydroxyethoxy)ethyl]-rapamycin.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier therefor.

8. A method of inducing an immunosuppressant effect in a subject in need of immunosuppression, which comprises administering to said subject an immunosuppressant effective amount of a compound according to claim 1.

9. A method of preventing allograft rejection in a subject in need of such treatment, which comprises administering to said subject a compound according to claim 1 in an amount effective to prevent allograph rejection.

10. The compound according to claim 1 which is 40-O-(3-hydroxyethyl)-rapamycin.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,665,772
DATED : September 9, 1997
INVENTOR(S) : Sylvain Cottens and Richard Sedrani

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 10, lines 1-2, delete "40-O-(3-hydroxyethyl)-rapamycin" and replace it with — 40-O-(2-hydroxyethyl)-rapamycin —.

Signed and Sealed this
Thirtieth Day of June, 1998

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Appendix F

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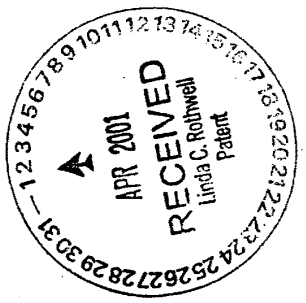

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The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

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ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,665,772	183	850	----	08/416,673	09/09/97	04/07/95	04	NO	PAID

4/100-7932/PCT DEF

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PATENT NUMBER	FEE CODE	FEE AMT	SUR CHARGE	APPLICATION NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT	ATTY DKT NUM
5,665,772	1552	$2,300.00	$0.00	08/416,673	09/09/97	04/07/95	08	NO	PAID	100-7932/PCT

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Appendix G

Case No. 100-7932/PCT

Application/Serial No. 08/416,673

Mailing Date: March 30, 1998

Due Date: _____

The Patent & Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below:

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- ☐ Appeal Brief - Fee $ _____
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- ☐ Petition for extension of time - Fee $ _____
- ☐ Reply Brief
- ☐ Request for Oral Hearing - Fee $ _____
- ☒ Request for Certification of Correction - Fee $ 100.00
- ☐

☒ Amendment Under 37 CFR 1.312 (3-14-97)

☒ Certificate of Correction

OFFICE JC5 APR - 3 1998 PATENT & TRADEMARK OFFICE

APR 9 1998

LINDA [illegible] PATENT

OEF

83049/97

CASE 100-7932/PCT

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Phyllis Kelly	Phyllis Kelly	March 30, 1998
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

COTTENS ET AL.

U. S. Patent No. 5,665,772 Certificate of Correction Branch

APPLICATION NO: 08/416,673

FILED: APRIL 7, 1995

FOR: O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS

Assistant Commissioner for Patents
Washington, D.C. 20231

REQUEST FOR CERTIFICATE OF CORRECTION

Sir:

An error has been noted in the above-identified United States Patent, and a Certificate of Correction is hereby requested.

In particular, the error resides in claim 10 of the issued patent. This claim was presented as new claim "20" of applicants' "Amendment Under 37 CFR 1.312" mailed March 14, 1997 (copy appended). At page 3 of said Amendment, applicants indicated that said claim 20 was intended to replace claim 4 of the application as filed, which applicants indicated may have been erroneously cancelled by the Office during prosecution.

However, through applicants' inadvertent error, said claim 20 was incorrectly drawn to the compound "40-0-(3-hydroxyethyl)-rapamycin," rather than reciting the compound of claim 4 of the application as filed.

Accordingly, a Certificate of Correction is enclosed correcting the error in claim 10, lines 1-2 of the subject U.S. Patent No. 5,665,772 by deleting "40-0-(3-hydroxyethyl)-rapamycin" and replacing it with "40-O-(2-hydroxyethyl)-rapamycin". Applicants respectfully request issuance of said Certificate.

If the Office should deem the present request to be made pursuant to 37 CFR §1.323 ("Certificate of Correction of Applicant's Mistake"), and not 37 CFR §1.322(a) ("Certificate of Correction of Office Mistake"), then the Office is authorized to charge the fee of $100 set forth in 37 CFR § 1.20(a) and any other fees necessitated by this paper, to Patentee's Deposit Account No. 19-0134. This page is enclosed in duplicate for fee purposes.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for Applicants
Reg. No. 31,104

Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6924

DEF:mjl
Date: March 30, 1998

Enclosures: "Amendment Under 37 CFR 1.312" (March 14, 1997)
Certificate of Correction (in duplicate)
This page in duplicate
Postcard

Case No. 100-7932/PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Sylvain Cottens, et al.	:	Art Unit: 1202
Serial No. 08/416,673	:	Examiner: R. Bond
Filed: April 7, 1995	:	Batch No.: H50
For: O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS	:	

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on March 14, 1997
(Date of Deposit)
Thomas O. McGovern
Name of applicant, assignee, or Registered Representative
Signature
March 14, 1997
Date of Signature

AMENDMENT UNDER 37 CFR 1.312

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Under the provision of 37 CFR 1.312, please amend the above identified application as follows:

IN THE CLAIMS

Please cancel claim 4, 9, and 10.

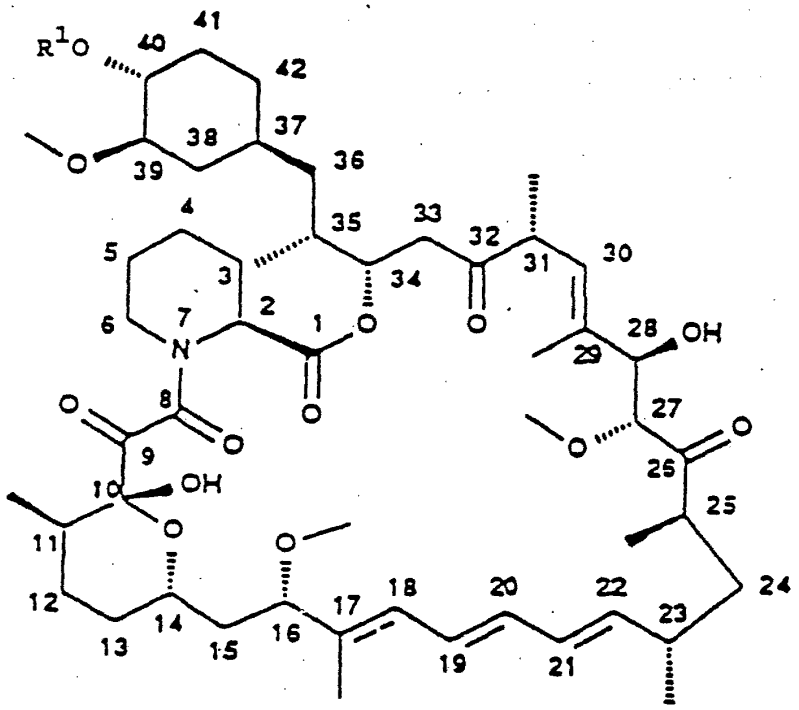
In line 1 of claims 11 to 15, after the word "claim", delete the number "10", and insert in its place in each instance the number -- 19 --.

In line 1 of claims 11, 12, and 13, after the word "which", delete the term "R_1", and insert in its place in each instance the term -- R^1 --.

Claim 16, line 2; claim 17, line 4; and claim 18, line 3, after the word "claim", delete the number "10", and insert in its place in each instance the number -- 19 --.

Please add the following new claims 19 and 20.

19. A compound of the formula



wherein R^1 is hydroxy(C_{1-6})alkyl or hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

20. The compound according to claim 19 which is 40-O-(3-hydroxyethyl)-rapamycin.

REMARKS

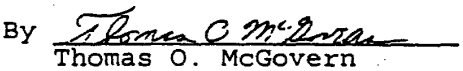
Claims 9 to 18 have been allowed and claims 11 to 20 are now in the application. No additional fee is required.

The instant application was allowed on December 16, 1996; and the issue fee is being submitted concurrently with this amendment.

It is respectfully requested that the above amendments of the claims be entered. The entering of these amendments will not require a new search nor will it require substantial additional work on the part of the Patent and Trademark Office. This Amendment is believed to be proper under the provisions of Rule 312, because it corrects minors errors in the structures and definitions of the claims. Claim 10 has been replaced with new claim 19 to remove the space in the double bond between carbons 17 and 18 in claim 10 and conform the bond to that of the generic compound of formula I on page 2 of the application. Substituent R^1 has been amended in claims 11 to 13 and in new claim 19 to properly identify it. The definition of substituent R^1 has also been amended to limit the alkylene groups of the hydroxyalkoxyalkyl moiety to the preferred C_{1-3} alkylene set out on page 3, line 10 of the application. Applicant have added new claim 20 to the application to replace claim 4, which may have been inadvertently deleted from the application instead of claim 9, which was canceled by the Amendment of October 15, 1996.

The proposed amendment do not broaden the scope of the claims or introduce new matter. They were not presented earlier because it was only during a review of the allowed application that it was noted that the amendments were needed. It is therefore respectfully requested that the proposed amendment be entered under the provisions of 35 CFR 1.312.

Respectfully submitted,

By 
Thomas O. McGovern
Registration No. 25,741
(201) 503-8480

TOM:lmc

NOVARTIS CORPORATION
59 Route 10
E. Hanover, N.J. 07936

March , 1997

Enclosures: COM Stamp; Postcard

Case No. 100-7932/PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Sylvain Cottens, et al. : Art Unit: 1202

Serial No. 08/416,673 : Examiner: R. Bond

Filed: April 7, 1995 : Batch No.: H50

For: O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS :

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on March 14, 1997
(Date of Deposit)
Thomas O. McGovern
Name of applicant, assignee, or Registered Representative
Thomas O'McGovern
Signature
March 14, 1997
Date of Signature

AMENDMENT UNDER 37 CFR 1.312

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Under the provision of 37 CFR 1.312, please amend the above identified application as follows:

IN THE CLAIMS

Please cancel claim 4, 9, and 10.

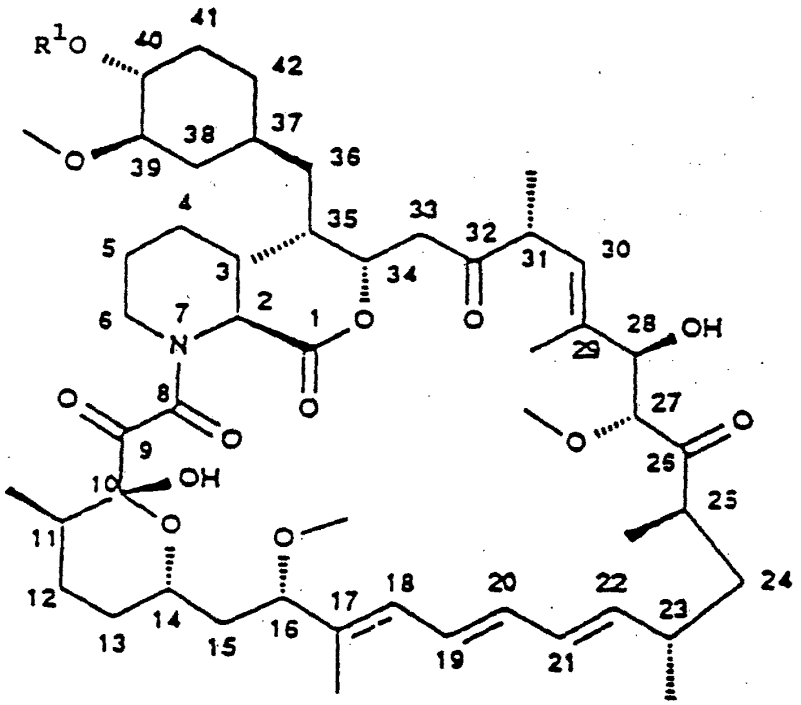
In line 1 of claims 11 to 15, after the word "claim", delete the number "10", and insert in its place in each instance the number -- 19 --.

In line 1 of claims 11, 12, and 13, after the word "which", delete the term "R_1", and insert in its place in each instance the term -- R^1 --.

Claim 16, line 2; claim 17, line 4; and claim 18, line 3, after the word "claim", delete the number "10", and insert in its place in each instance the number -- 19 --.

Please add the following new claims 19 and 20.

19. A compound of the formula



wherein R^1 is hydroxy(C_{1-6})alkyl or hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

20. The compound according to claim 19 which is 40-O-(3-hydroxyethyl)-rapamycin.

REMARKS

Claims 9 to 18 have been allowed and claims 11 to 20 are now in the application. No additional fee is required.

The instant application was allowed on December 16, 1996; and the issue fee is being submitted concurrently with this amendment.

It is respectfully requested that the above amendments of the claims be entered. The entering of these amendments will not require a new search nor will it require substantial additional work on the part of the Patent and Trademark Office. This Amendment is believed to be proper under the provisions of Rule 312, because it corrects minors errors in the structures and definitions of the claims. Claim 10 has been replaced with new claim 19 to remove the space in the double bond between carbons 17 and 18 in claim 10 and conform the bond to that of the generic compound of formula I on page 2 of the application. Substituent R^1 has been amended in claims 11 to 13 and in new claim 19 to properly identify it. The definition of substituent R^1 has also been amended to limit the alkylene groups of the hydroxyalkoxyalkyl moiety to the preferred C_{1-3} alkylene set out on page 3, line 10 of the application. Applicant have added new claim 20 to the application to replace claim 4, which may have been inadvertently deleted from the application instead of claim 9, which was canceled by the Amendment of October 15, 1996.

The proposed amendment do not broaden the scope of the claims or introduce new matter. They were not presented earlier because it was only during a review of the allowed application that it was noted that the amendments were needed. It is therefore respectfully requested that the proposed amendment be entered under the provisions of 35 CFR 1.312.

Respectfully submitted,

By Thomas O McGovern
Thomas O. McGovern
Registration No. 25,741
(201) 503-8480

TOM:lmc

NOVARTIS CORPORATION
59 Route 10
E. Hanover, N.J. 07936

March , 1997

Enclosures: COM Stamp; Postcard

Appendix H

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,665,772
DATED : September 9, 1997
INVENTOR(S) : Sylvain Cottens and Richard Sedrani

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 10, lines 1-2, delete "40-O-(3-hydroxyethyl)-rapamycin" and replace it with — 40-O-(2-hydroxyethyl)-rapamycin —.

Signed and Sealed this

Thirtieth Day of June, 1998

Attest:

Attesting Officer

BRUCE LEHMAN

Commissioner of Patents and Trademarks

Appendix I

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS
ONCOLOGY

December 18, 2002

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Division Document Control Room #3067
1451 Rockville Pike
Rockville, Maryland 20852-1448

IND No. 66,279

RAD001 (Oncology)

- **Response to FDA Request for Information**

Serial No. 002

Dear Dr. Pazdur:

Reference is made to our Investigational New Drug Application (IND) for RAD001 (also RAD001C, SDZ RAD, SDZ RAD 666, SDZ 222-666, evirolimus) submitted to the division on November 22, 2002 and to a telephone call from Dr. Haripada Sarker on December 18, 2002. Dr. Sarker requested that Novartis provide the following statement of clarification to allow cross referencing of IND 52,003 for this compound originally filed by Sandoz Pharmaceuticals Corporation (now Novartis Pharmaceuticals Corporation) within the FDA Division of Special Pathogens and Immunologic Drug Products (HFD-590):

> **As of January 1, 1997, the former Ciba Pharmaceuticals Division and Sandoz Pharmaceuticals Corporation became Novartis Pharmaceutical Corporation.**

If you have any questions or comments regarding this submission, please contact me at (862) 778-8165.

Sincerely,

Kevin M. Carl, Pharm.D.
Drug Regulatory Affairs

KMC/da
Submitted in triplicate

Desk copies: Ann Staten and Haripada Sarker (HFD-150) via fax at 301/594-0498

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: September 30, 2002
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
NOVARTIS PHARMACEUTICALS CORPORATION

2. DATE OF SUBMISSION
December 18, 2002

3. ADDRESS *(Number, Street, City, State and Zip Code)*
One Health Plaza
East Hanover, New Jersey 07936-1080

4. TELEPHONE NUMBER *(Include Area Code)*
(862) 778-8165
Kevin M. Carl, PharmD, Post-Doctoral Fellow

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
RAD001

6. IND NUMBER *(If previously assigned)*
66,279

7. INDICATION(S) *(Covered by this submission)*
Solid Tumor Cancers

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☒ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER
(Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (*21 CFR Part 314*), DRUG MASTER FILES (*21 CFR Part 314.420*), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

IND 52,003 DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD 590)

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
002

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☒ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVED, TERMINATED OR DISCONTINUED ☐ OTHER *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE 312.23 SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(c) ☐ CHARGE TO PATIENT NOTIFICATION PROTOCOL

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

FORM FDA 1571 (10/99) PREVIOUS EDITION IS OBSOLETE. PAGE 1 OF 2

12. **CONTENTS OF APPLICATION**

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

☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*

☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*

☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*

☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*

☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*

☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*

- ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
- ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572

☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*

- ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*

☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*

☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*

☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐YES ☒NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐YES ☐NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Nicholas Shand, MD
Senior Clinical Research Physician
Clinical Research

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Dionigi Maladorno, MD
Medical Safety Expert
Clinical Safety and Epidemiology

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Kevin M. Carl, PharmD, Post-Doctoral Fellow **Drug Regulatory Affairs**		
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
One Health Plaza **East Hanover, New Jersey 07936-1080**	**(862) 778-8165**	12/18/2002

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments egarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
5516 Nicholson Lane
Kensington, MD 20895

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

Please DO NOT RETURN this application to this address.

********** -COMM. JOURNAL- ********** DATE DEC-18-2002 ***** TIME 14:33 **********

MODE = MEMORY TRANSMISSION START=DEC-18 14:31 END=DEC-18 14:33

FILE NO.=488

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	913015940498	002/002	00:01:05

-DRA ONCOLOGY BU -

********** - ***** - 973 781 5217- **********

Kevin Carl, PharmD
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

Tel (973) 781 8165
Fax (973) 781 5217

NOVARTIS

Fax

Attention	Ann Staten Project Manager Division of Oncology Drug Products (HFD-150) Food and Drug Administration
Fax Number	(301) 594-0498
Number of pages	2 (including coversheet)
Date	December 18, 2002
Concerning	URGENT: RAD001 IND No. 66,279 – FDA Request for Information

Dear Ann,

Dr. Sarker requested that Novartis provide the accompanying statement of clarification to allow cross referencing of IND 52,003 for this compound originally filed by Sandoz Pharmaceuticals Corporation (now Novartis Pharmaceuticals Corporation) within the FDA Division of Special Pathogens and Immunologic Drug Products (HFD-590).

Sincerely,
Kevin

RAD001 IND# 66,279 Dec 19, 2002

Archives
cc: chron

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Kevin Carl, Novartis	**From:**	Ann Staten, Project Manager
Fax:	973-781-5217	**Fax:**	301-827-4590
Phone:	973-781-8165	**Phone:**	301-594-0490
Pages:	1	**Date:**	December 19, 2002
Re:	IND 66,279 RAD001		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Mr. Carl,

Please refer to your Investigational New Drug Application (IND) submitted November 22, 2002 pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for RAD001.

We have completed the review of your IND and conclude it is reasonably safe to proceed with your proposed study based upon your December 19, 2002 agreement to correct the deficiency, which was forwarded to you by e-mail transmission on December 18, 2002.

Please let me know if you have any questions.

Sincerely,

Ann

APPENDIX J

SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

SANDOZ

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL 201 503 7500
FAX 201 503 6325

November 15, 1996

Food and Drug Administration
Center for Drug Evaluation
and Research
Central Document Room
12229 Wilkins Avenue
Rockville Maryland 20857

INVESTIGATIONAL NEW DRUG APPLICATION

Serial No. 000

Gentleman:

In accordance with 21 CFR §312.23, Sandoz Pharmaceuticals Corporation is submitting an Investigational New Drug Application (FDA Form 1571) and supporting documents for the following investigational compound:

SDZ RAD Capsules

Indication: Prophylaxis of organ rejection

Please note that we have included in IND Section X, Additional Information, a Point-By-Point Response to the FDA communication of October 11, 1996 which provided general comments and recommendations for product development. The Pre-IND Briefing Book for SDZ RAD was submitted to the FDA Division of Anti-Viral Drug Products/HFD-530 on August 26, 1996.

This IND and all subsequent amendments are confidential and their contents are not to be disclosed without the express written consent of Sandoz Pharmaceuticals Corporation.

If there are comments or question, please call me at (201) 503-7646.

Sincerely,

Ronald G. Van Valen
Associate Director
Drug Registration and Regulatory Affairs

Attachments: Volumes 1-14
submitted in quadruplicate
cc: S. Cobb/HFD-530 (letter only)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: November 30, 1995.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Sandoz Pharmaceuticals Corporation

2. DATE OF SUBMISSION
November 15, 1996

3. ADDRESS *(Number, Street, City, State and Zip Code)*
59 Route 10
East Hanover, New Jersey 07936-1080

4. TELEPHONE NUMBER *(Include Area Code)*
(201) 503-7646
Ronald G. Van Valen

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
SDZ RAD

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Adjunct Immunosuppressant Organ Transplantation

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☒ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 312)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.
Type I DMF 5846 - Sandoz Pharma Ltd.

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
000

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☒ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.34(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

STATEMENT OF CONFIDENTIALITY

SANDOZ PHARMACEUTICALS CORPORATION has expended substantial sums of money in developing the information and data contained in this original Investigational New Drug Application for SDZ RAD and considers such information and data to be its valuable commercial property.

Further, SANDOZ PHARMACEUTICALS CORPORATION considers the information contained in the following pages to be trade secrets, therefore, protected by 21 U.S.C. 331 (j).

SECTION II TABLE OF CONTENTS SDZ RAD		
	VOL.	PAGE NO.
SECTION I - 1571 FORM		
A. DESCRIPTION OF CRO, IF ANY, TO WHOM OBLIGATIONS HAVE BEEN TRANSFERRED	N/A	N/A
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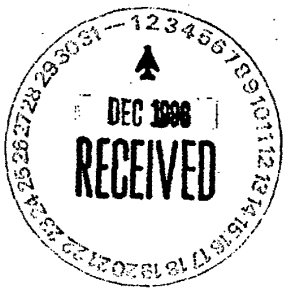
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 52,003

Date NOV 25



Sandoz Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936-1080

ATTN: Michael S. Perry, DVM, Ph.D.

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 52,003

Sponsor: Sandoz Pharmaceuticals Corporation

Name of Drug: SDZ RAD

Date of Submission: November 15, 1996

Date of Receipt: November 19, 1996

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

FORM FDA 3228a (9/89) PREVIOUS EDITION IS OBSOLETE.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-530)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact: CAROLE BROADNAX @(301) 827-2335

Sincerely yours,

Chief, Project Management Staff
Division of Anti-Viral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-530 - yellow
HFD-530/CSO - green

IND ACKNOWLEDGEMENT

FORM FDA 3228k (11/95)

APPENDIX K

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

November 22, 2002

Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
12229 Wilkins Avenue
Rockville, MD 20852

INVESTIGATIONAL NEW DRUG APPLICATION

Serial No. 000

Dear Sir or Madam:

In accordance with 21 CFR § 312.23, Novartis Pharmaceuticals Corporation is submitting an Investigational New Drug Application (IND) and supporting documents for the following investigational compound:

RAD001

RAD001 (also RAD001C, SDZ RAD, SDZ RAD 666, SDZ 222-666, evirolimus) has an extensive prior regulatory history within the FDA Division of Special Pathogens and Immunologic Drug Products (HFD-590) under IND 52,003. Consequently, portions of this IND cross-reference contents of IND 52,003 within HFD-590. Additionally, NDA filing for RAD001 within HFD-590 is planned for December 2002 under NDA number 21-560 and the trade name Certican™.

RAD001 is a macrolide, a new derivative of rapamycin, hydroxyethylated to increase polarity and facilitate its formulation for oral administration. RAD001 is being developed as an antiproliferative drug with applications as an immunosuppressant and anticancer agent. In the transplantation setting, numerous studies have been conducted with RAD001 with over a thousand patients having received the drug for over a year as part of a multidrug immunosuppressant regimen. RAD001 acts by selectively inhibiting mTOR (mammalian target of rapamycin), an intracellular protein kinase implicated in the control of cellular proliferation be it of activated T-lymphocytes or neoplastic cells.

Reference is made to a telephone conversation with Ms. Ann Staten, Project Manager (HFD-150), on September 6, 2002 discussing our intent to file this IND within the Division of Oncology Drug Products. During this conversation, we discussed the possibility of submission of IND safety reports for all oncology related events only to the Oncology Division and Ms. Staten asked that we revisit this proposal formally within the IND cover letter at the time of filing in order to obtain FDA guidance. Is this proposal acceptable?

Novartis Pharmaceuticals Corporation considers the information contained within this IND and all subsequent amendments to confidential, and their contents are not to be disclosed without

express written consent.

If you have any questions or comments regarding this submission, please contact me at (862) 778-8165.

Sincerely,

Kevin M. Carl, PharmD
Drug Regulatory Affairs

/da
Submitted in triplicate

Attachments: Form FDA 1571
Volumes 1-26

Coverletter: Ann Staten (HFD-150) via fax at 301/827-4590

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

STATEMENT OF CONFIDENTIALITY

NOVARTIS PHARMACEUTICALS CORPORATION has expended substantial sums of money in developing the information and data contained in this Investigational New Drug application for RAD and considers such information and date to be its valuable commercial property

Further, NOVARTIS PHARMACEUTICALS CORPORATION considers the information contained in the following pages to be trade secrets, therefore, protected by 21 U.S.C. 331 (j).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: September 30, 2002
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
NOVARTIS PHARMACEUTICALS CORPORATION

2. DATE OF SUBMISSION
November 22, 2002

3. ADDRESS *(Number, Street, City, State and Zip Code)*
One Health Plaza
East Hanover, New Jersey 07936-1080

4. TELEPHONE NUMBER *(Include Area Code)*
(862) 778-8165
Kevin M. Carl, PharmD, Post-Doctoral Fellow

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
RAD001

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Solid Tumor Cancers

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☒ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER
(Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

IND 52.003 DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD 590)

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
000

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☒ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVED, TERMINATED OR DISCONTINUED ☐ OTHER
(Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

FORM FDA 1571 (10/99) PREVIOUS EDITION IS OBSOLETE. **PAGE 1 OF 2**

12. **CONTENTS OF APPLICATION**

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

☒1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*

☒2. Table of Contents *[21 CFR 312.23(a)(2)]*

☒3. Introductory statement *[21 CFR 312.23(a)(3)]*

☒4. General Investigational plan *[21 CFR 312.23(a)(3)]*

☒5. Investigator's brochure *[21 CFR 312.23(a)(5)]*

☒6. Protocol(s) *[21 CFR 312.23(a)(6)]*

- ☒a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
- ☒b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☒c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☒d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572

☒7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*

- ☒Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*

☒8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*

☒9. Previous human experience *[21 CFR 312.23(a)(9)]*

☐10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐YES ☒NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐YES ☐NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Nicholas Shand, MD
Senior Clinical Research Physician
Clinical Research

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Dionigi Maladorno, MD
Medical Safety Expert
Clinical Safety and Epidemiology

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Kevin M. Carl, PharmD, Post-Doctoral Fellow **Drug Regulatory Affairs**		
18. ADDRESS *(Number, Street, City, State and Zip Code)* **One Health Plaza** **East Hanover, New Jersey 07936-1080**	19. TELEPHONE NUMBER *(Include Area Code)* **(862) 778-8165**	20. DATE 11/22/02

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments egarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
5516 Nicholson Lane
Kensington, MD 20895

"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 application to this address.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

RAD 001

Investigational New Drug Application

Author(s):	Judith Fast
Document type:	IND Table of Contents
Document status:	Final
Submission date:	22-November-2002
Number of pages:	19

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[2] Huang S, Houghton PJ. Inhibitors of mammalian target of rapamycin as novel antitumor agents: From bench to clinic. Curr Opin Invest Drugs 2002;3(2):295-304.	2	8-131
[3] Hashemolhosseini S, Nagamine Y, Morley SJ, Desrivieres S, Mercep L, Ferrari S. Rapamycin inhibition of the G1 to S transition is mediated by effects on cyclin D1 mRNA and protein stability. J Biol Chem 1998;273:14424-14429.	2	8-141
[4] Mahajan PB. Modulation of transcription of rRNA genes by rapamycin. Int J Immunopharmacol 1994;16:711-721	2	8-147
[5] Leicht M, Simm A, Bertsch G, Hoppe J. Okadaic acid induces cellular hypertrophy in AKR-2B fibroblasts: involvement of the p70S6 kinase in the onset of protein and rRNA synthesis. Cell Growth Differ 1996;7:1199-1209.	2	8-157
[6] Ziegler WH, Parekh DB, Le-Good JA, Whelan RD, Kelly JJ, Frech M, Hemmings BA, Parker PJ. Rapamycin-sensitive phosphorylation of PKC on a carboxy-terminal site by an atypical PKC complex. Curr Biol 1999;9:522-529.	2	8-168
[7] Le-Bihan S, Marsaud V, Mercier-Bodard C, Baulieu EE, Mader S, White JH, Renoir JM. Calcium/calmodulin kinase inhibitors and immunosuppressant macrolides rapamycin and FK506 inhibit progestin- and glucocorticosteroid receptor-mediated transcription in human breast cancer T47D cells. Mol Endocrinol 1998;12: 986-1001.	2	8-176
[8] Bonatti S, Simili M, Galli A, Bagnato P, Pigullo S, Schiestl RH, Abbondandolo A. Inhibition of the Mr 70,000 S6 kinase pathway by rapamycin results in chromosome malsegregation in yeast and mammalian cells. Chromosoma 1998;107:498-506.	2	8-192
[9] Francesc V, Chambard JC, Pouysségur J. p70 S6 Kinase-mediated protein synthesis is a critical step for vascular endothelial cell proliferation. J Biol Chem 1999;274:26776-26782.	2	8-201
[10] Yu Y, Sato JD. MAP kinases, phosphatidylinositol 3-kinase, and p70 S6 kinase mediate the mitogenic response of human endothelial cells to vascular endothelial growth factor. J Cell Physiol 1999;178:235-246.	2	8-208

	Vol	Page No.
[11] Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, Bruns CJ, Zuelke C, Farkas S, Anthuber M, Jauch KW, Geissler EK. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med 2002;8:128-135.	2	8-220
[12] Vivanco I, Sawyers CL. The phosphatidylinositol 3-kinase-Akt pathway in human cancer. Nature Cancer 2002;2:489-501.	2	8-228
[13] Inoki K, Li Y, Zhu T, Wu J, Guan K-L. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. Nat Cell Biol 2002; published online: 12 August 2002; DOI: 10.1038/ncb839.	2	8-241
[14] Nave BT, Ouwens M, Withers DJ, Alessi DR, Shepherd PR. Mammalian target of rapamycin is a direct target for protein kinase B: identification of a convergence point for opposing effects of insulin and amino-acid deficiency on protein translation. Biochem J 1999;344:427-431.	2	8-251
[15] Neshat MS, Mellinghoff IK, Tran C, Stiles B, Thomas G, Petersen R, Frost P, Gibbons JJ, Wu H, Sawyers CL. Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. Proc Natl Acad Sci 2001;98:10314-10319.	2	8-256
[16] Podsypanina K, Lee RT, Politis C, Hennessy I, Crane A, Puc J, Neshat M, Wang H, Yang L, Gibbons J, Frost P, Dreisbach V, Blenis J, Gaciong Z, Fisher P, Sawyers C, Hedrick-Ellenson L, Parsons R. An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in Pten+/- mice. Proc Natl Acad Sci 2001;98:10320-10325	2	8-262
[17] Meyer T, Becker M, Centeleghe M, Köppler J, Liebetanz J, Manfrina D, Martin N, Muller L, Fabbro D, Lane H, O'Reilly T. Enzymatic profile of RAD001: In vitro inhibition of protein kinases. Novartis Release Ready Report 2001;RD-2001-01088	2	8-268
[18] Hattenberger M, Muller M, Vaxelaire J, Sedrani R, Lane H, O'Reilly T. RAD001 potentiates the activity of conventional anticancer cytotoxics in vitro. Novartis Release Ready Report 2000;RD-2000-02546.	2	8-282
[19] Hattenberger M, Boulay A, Lane HA, Maira M, O'Reilly T. In vitro antiproliferative activity of RAD001 against a broad panel of tumor cell lines. Novartis Release Ready Study Report 2002;RD-2002-03223.	2	8-295
[20] Beuvink I, Zilbermann F, Zumstein-Mecker S, Sedrani R, Thomas G, O'Reilly T, Lane H. Downregulation of mTOR targets in tumor cell lines in vitro (comparison with CCI-779). Novartis Release Ready Report 2000;RD-2000-02544.	2	8-313
[21] Hungerford V, Thomas G, Schuler W. RAD inhibits the growth factor-stimulated activation of p70 S6 kinase. Novartis Release Ready Report 2000;RD-2000-02151.	2	8-331

	Vol	Page No.
[22] Boulay A, Zumstein-Mecker S, Stephan C, Solf R, Ruetz S, O'Reilly T, Lane HA. RAD001 potentiates the loss of A549 cell viability induced by gemcitabine treatment in vitro. Novartis Release Ready Study Report 2002;RD-2002-03250.	2	8-341
[23] Boulay A, Hattenberger M, Zumstein-Mecker S, Solf R, Ruetz S, O'Reilly T, Lane H. Effect of scheduling on the in vitro antiproliferative activity of RAD001/gemcitabine combinations in A549 cells. Novartis Release Ready Report 2001;RD-2001-01087.	26	8-9732
[24] Wood JM, Theuer A. RAD001: effects on endothelial and fibroblast cell proliferation. Novartis Release Ready Report 2001;RD-2001-00852.	2	8-357
[25] Boulay A, Hattenberger M, O'Reilly T, Maira M, Lane HA. Comparison of the antiproliferative activity of RAD001 with activation of the PTEN/PI3 kinase/Akt/mTOR pathway in tumor cell lines. Novartis Release Ready Study Report 2002;RD-2002-03252.	2	8-369
[26] Muller M, Vaxelaire J, Hattenberger M, Sedrani R, Lane H, O'Reilly T. RAD001 is an effective antitumor agent in experimental KB-31 xenograft tumor models of epidermoid cancer. Novartis Release Ready Report 2000;RD-2000-02549.	2	8-388
[27] Zumstein-Mecker S, Beuvink I, Zilbermann F, Muller M, Vaxelaire, Sedrani R, Thomas G, O'Reilly T, Lane H. Downregulation of mTOR targets in tumors and skin derived from KB-31 human epidermoid carcinoma xenograft studies. Novartis Release Ready Report 2000;RD-2000-02541.	2	8-404
[28] Marti A,Stolz B, Haller R, Tobler S, O'Reilly T, Lane H. Effect of the rapamycin derivative RAD001 in the syngeneic CA20948 rat pancreatic tumor model. Novartis Release Ready Report 2002;RD-2002-03707	26	8-9744
[29] Zumstein-Mecker S, Beuvink I, Zilbermann F, Stephan C, Haller R, Tobler S, Thomas G, Stolz B, O'Reilly T, Lane H. Prolonged inactivation of $p70^{s6k}$ in tumors and skin derived from CA20948 pancreatic tumor-bearing rats. Novartis Release Ready Report 2001;RD-2001-00450.	2	8-422
[30] Zumstein-Mecker S, Beuvink I, Zilbermann F, Sedrani R, Hattenberger M, Thomas G, O'Reilly T, Lane H. Inhibition of the mTOR target p70s6k in rat peripheral lymphocytes. Novartis Release Ready Report 2000;RD-2000-02545.	2	8-437
[31] Zumstein-Mecker S, Boulay A, Beuvink I, Zilbermann F, Haller R, Tobler S, Thomas G, Stolz B, O'Reilly T, Lane H. Prolonged inactivation of $p70^{s6k}$ in peripheral blood mononucleocytes derived from CA20948 pancreatic tumor-bearing rats and non-tumor-bearing rats. Novartis Release Ready Report 2002;RD-2002-03817.	3	8-451
[32] Gingras AC, Raught B, Sonenberg N. Regulation of translation initiation by FRAP/mTOR. Genes Dev 2001;15:807-826.	3	8-471

	Vol	Page No.
[33] Zumstein-Mecker S, Stephan C, Boulay A, Lane HA. Detection of p70S6 activity in human peripheral mononucleocytes (PBMCs) using the 40S ribosomal protein kinase assay. Novartis Release Ready Study Report 2002;RD-2002-02974.	3	8-491
[34] Vaxelaire J, Muller M, Hattenberger, Lane H, O'Reilly T. RAD001 is an effective antitumor agent in experimental A549 xenograft tumor model of lung cancer. Novartis Release Ready Report 2001;RD-2001-00848.	3	8-507
[35] Wenger F, O'Reilly T, Martinuzzi-Duboc L, Tinetto W, Lane H, Brandt R, Cozens R. RAD001 is an effective antitumor agent in experimental NCI H-596 lung xenograft tumor model of lung cancer. Novartis Release Ready Report; 2001;RD-2001-00860.	3	8-523
[36] Hattenberger M, Weckbecker G, Muller M, Vaxelaire J, Sedrani R, Lane H, O'Reilly T. Evaluation of the antitumor activity of RAD001 in experimental xenograft tumor models of pancreatic cancer. Novartis Release Ready Report 2000;RD-2000-02548.	3	8-538
[37] Vaxelaire J, Muller M, Hattenberger M, Sedrani R, Lane H, O'Reilly T. RAD001 is active in vivo against xenograft tumors of HCT116 human colon carcinoma, a cell line resistant to RAD001 in vitro. Novartis Release Ready Report 2000;RD-2000-02550.	3	8-565
[38] Muller M, Vaxelaire J, Hattenberger M, Maira SM, Lane H, O'Reilly T. RAD001 is an effective antitumor agent in the experimental NCI H-520 xenograft tumor model of lung cancer. Novartis Release Ready Study Report 2002;RD-2002-00002.	3	8-594
[39] Fiebig HH, Dengler WA, Roth T. Human tumor xenografts: predictivity, characterization and discovery of new anticancer agents. In: Fiebig HH, Burger AM, editors. Relevance of tumor models for anticancer drug development. Contrib Oncol Basel: Karger, 1999;54:29-50.	3	8-612
[40] Fiebig HH, Cozens R, O'Reilly T. Activity of RAD001 against low passage human tumor xenografts. Novartis Release Ready Report 2000;RD-2000-02552.	3	8-634
[41] Arceci RJ, Stieglitz K, Bierer BE. Immunosuppressants FK506 and rapamycin function as reversal agents of the multidrug resistance phenotype. Blood 1992;80:1528-1536.	3	8-654
[42] Muller M, Vaxelaire J, Hattenberger M, Lane H, O'Reilly T. RAD001 is an effective antitumor agent against experimental epidermoid multi-drug resistant KB-8511 tumors. Novartis Release Ready Study Report 2002;RD-2002-03237.	3	8-663
[43] Akiyam S, Fojo A, Hanover JA, Pastan I, Gottesman MM. Isolation and genetic characterization of human KB cell lines resistant to multiple drugs. Somatic Cell Molec Genetics 1985;11:117-126.	3	8-682

	Vol	Page No.
[44] Fojo A, Akiyama S, Gottesman MM, Pastan I. Reduced drug accumulation in multiply drug-resistant human KB carcinoma cell lines. Cancer Res 1997;45:3002-3007.	3	8-692
[45] Wenger F, O'Reilly T, Martinuzzi-Duboc L, Tinetto W, Lane H, Brandt R, Cozens R. Evaluation of RAD001 in combination with conventional anticancer agents against experimental NCI H-596 lung xenograft tumor models of cancer. Novartis Release Ready Report 2001;RD-2001-00861.	3	8-698
[46] Muller M, Hattenberger M, Vaxelaire J, Lane H, O'Reilly T. Evaluation of RAD001 in combination with conventional anticancer agents against experimental KB-31 epidermoid xenograft tumors. Novartis Release Ready Report 2001;RD-2001-00849.	3	8-727
[47] Vaxelaire J, Hattenberger M, Muller M, Lane HA, O'Reilly T. Effect of administration schedule on the antitumor activity of RAD001 in combination with Taxol®. Novartis Release Ready Study Report 2002;RD-2002-03251.		**To be submitted in 12/2002**
[48] Muller M , Vaxelaire J, Hattenberger M, Lane HA, O'Reilly T. Administration schedule has little effect on the antitumor activity of RAD001 in combination with cisplatinum. Novartis Release Ready Study Report 2002;RD-2002-03253.		**To be submitted in 12/2002**
[49] Hattenberger M, Muller M, Vaxelaire J, Lane HA, O'Reilly T. Administration schedule has little effect on the antitumor activity of RAD001 in combination with low dose gemcitabine against NCI H-596 lung tumor xenografts. Novartis Release Ready Study Report 2002;RD-2002-02354.		**To be submitted in 12/2002**
[50] Wood JM, Schnell CR. RAD001: effects on angiogenesis-induced by growth factor-impregnated, subcutaneous implants in mice. Novartis Release Ready Report 2001; RD-2001-00853.	3	8-768
[51] Wood JM, Schnell CR. RAD001: effects in orthotopic B16/BL6 melanoma model in C57BL/6 mice. Novartis Release Ready Report 2001; RD-2001-00854.	3	8-783
[52] Saunders RN, Metcalfe MS, Nicholson ML. Rapamycin in transplantation: A review of the evidence. Kidney Int. 2000; 59:3-16.	3	8-809
[53] Schuler W, Sedrani R, Cottens S, Haberlin B, Schulz M, Schuurman HJ, Zenke G, Zerwes HG, Schreier MH. A new rapamycin derivative: pharmacological properties in vitro and in vivo. Transplantation 1997;64: 36-42.	3	8-823
[54] Kovarik JM, Kaplan B, Tedesco Silva H, Kahan BD, Dantal J, Vitko S, Boger R, Rordorf C. Exposure-response relationships for everolimus in de novo kidney transplantation: defining a therapeutic range. Transplantation 2000;73:920-925.	3	8-830

	Vol	Page No.
[55] O'Reilly T, Schmutz P, Hattenberger M, Vaxelaire J, Muller M, Lane H, Huesser C. Reduction of the immunosuppressive properties of RAD001 by intermittent administration. Novartis Release Ready Study Report 2002; RD-2002-01534.	26	8-9759
[56] Vaxelaire J, Muller M, Hattenberger M, O'Reilly, T. Studies on the tolerability of athymic BALB/c *nu/nu* (nude) mice to RAD001. Novartis Release Ready Report 2000;RD-2000-02547.	3	8-836
[57] Muller M, Hattenberger M, Vaxelaire J, O'Reilly, T. Tolerability of athymic BALB/c *nu/nu* (nude) mice to RAD001 in combination with conventional cytotoxic anti-cancer agents. Novartis Release Ready Report 2001;RD-2001-00401.	3	8-845
[58] Vaxelaire J, Muller M, Hattenberger M, Lane H, O'Reilly, T. Tolerability of athymic BALB/c nu/nu (nude) mice to RAD001 in combination with carboplatin. Novartis Release Ready Report 2001;RD-2001-00844.	3	8-864
[59] Muller M, Hattenberger M, Vaxelaire J, Lane H, O'Reilly, T. Effect of schedule on the tolerability of athymic BALB/c nu/nu (nude) mice to RAD001 in combination with gemcitabine. Novartis Release Ready Report 2001;RD-2001-00850.	3	8-879
[60] Capdeville R, Buchdunger E, Zimmermann J, Matter A. Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. Nat Rev Drug Discov. 2002;1:493-502	3	8-893
[61] Muller M, O'Reilly T, Vaxelaire J, Hattenberger M, Maira SM. Tolerability of concomittant STI571 (Gilvec®) and RAD001 in athymic Harlan mice. Novartis Release Ready Study Report 2002;RD-2002-03186.	26	8-9777
• Cited DMPK & Toxicilogy Reports and Literature		
[1] Kretz O. Pharmacokinetics and excretion after single intravenous and peroral administration (0.9 mg/kg) of 3H-labeled RAD001 to mice. Novartis Pharma AG, 28-Aug-2000. Document DMPK(CH)R98-707	4	8-903
[2] Figueiredo J, Kretz O. RAD001: Pharmacokinetics in mice after intravenous bolus administration (0.9 mg/kg) with RAD001. Novartis Pharma AG, 16-Mar-2000. Document DMPK(CH)R00-874	4	8-920
[3] Lemaire M, Dannecker R. SDZ RAD: Absorption, distribution, metabolism and excretion in rats after single intravenous (1 mg/kg, 10 mg/kg) and oral (1.5 mg/kg, 15 mg/kg) administration of [^{3}H]SDZ RAD. Sandoz Pharma Ltd., 25-Jan-1996. Document 303-013 (159604.010)		**x-reference to IND 52,003 11/15/96
[4] Schuetz H. SDZ RAD: Distribution and excretion of total radioactivity in rats after peroral administration of 1.5 mg/kg ^{14}C-labelled SDZ RAD. Novartis Pharma AG, 10-Mar-1998. Document 303-092 (DMPK(CH)1997/515)	4	8-936

		Vol	Page No.
[5]	Schweitzer A. RAD001: Whole-body autoradioluminography in albino and pigmented rats after po and iv doses of [^{3}H]RAD001. Novartis Pharma AG, 19-Nov-1998. Document 303-097 (DMPK(CH)R98-194)	4	8-954
[6]	Schweitzer A. RAD001: Embryofetal transfer in pregnant rats on day 13 and day 17 of gestation after po administration of [^{3}H]RAD001. Novartis Pharma AG, 20-Nov-1998. Document 303-098 (DMPK(CH)R98-732)	4	8-969
[7]	Lemaire M. RAD001: Dose-dependent brain penetration in rat. Novartis Pharma AG, 4-Oct-2000. Document DMPK(CH)R00-2214	4	8-983
[8]	Lemaire M. SDZ RAD (SDZ 222-666): Absorption, disposition and excretion in Cynomolgus monkeys after single intravenous (1 mg/kg) and oral (5 mg/kg) administration of [^{3}H]SDZ RAD. Sandoz Pharma Ltd., 23-Sep-1996. Document 303-049 (162258.01)		**x-reference to IND 52,003 11/15/96
[9]	Kaufmann H, Kawai R. RAD001: In vitro blood distribution, plasma protein binding and stability of RAD001 in mouse plasma. Novartis Pharma AG, 28-Aug-2000. Document DMPK(CH)R00-1253	4	8-996
[10]	Duerr L, Lemaire M. SDZ RAD: Blood distribution and plasma protein binding. Sandoz Pharma Ltd., 18-Jul-1996. Document 303-044		**
[11]	Zimmermann H. RAD001: Protein binding of RAD001 in serum from healthy volunteers and from patients with moderate hepatic insufficiency. Novartis Pharma AG, 22-Feb-2001. Document DMPK(CH)R00-2228	4	8-1008
[12]	Crowe A, Bruelisauer A, Delaborde S, Dannecker R, Lemaire M. SDZ RAD: Intestinal absorption and presystemic metabolism of SDZ RAD. Novartis Pharma AG, 17-Dec-1997. Document 303-086 (DMPK(CH)1997/417)	4	8-1022
[13]	Bruelisauer A. SDZ RAD: Liquid chromatography-reverse isotope dilution method (LC-RID) for the determination of [^{3}H]SDZ RAD in biological media. Sandoz Pharma Ltd., 21-Sep-1995. Document 303-015 (159606)		**
[14]	Feltin M, Hensel S. SDZ RAD: Determination of SDZ RAD in whole blood by HPLC with uv detection. Method description and validation. Sandoz Pharma Ltd., 21-Aug-1996. Document 303-045	4	8-1048
[15]	Legay F. SDZ RAD: Development and validation of an ELISA. Sandoz Pharma Ltd., 21-Sep-1995. Document 303-017 (160139)		**
[16]	Jean C, Laplanche R. SDZ RAD: Method of determination of SDZ RAD in blood by liquid chromatography/atmospheric pressure chemical ionization/mass spectrometry (HPLC/APCI/MS). Method description and validation. Sandoz Pharma Ltd., 26-Nov-1996. Document 303-066	4	8-1083

	Vol	Page No.
[17] Jean C, Stefani M. SDZ RAD: Quantitative determination of rapamycin and SDZ RAD in blood samples after single and multiple administration in human and monkey. Novartis Pharma AG, 9-Dec-1997. Document 303-085 (DMPK(CH)1997/287)	4	8-1190
[18] Vickers A, Dannecker R. SDZ RAD 666: In vitro biotransformation. Sandoz Pharma Ltd., 28-Mar-1996. Document 303-037	4	8-1206
[19] Dannecker R, Hauck C. SDZ RAD: Human in vitro biotransformation. LC-MS investigation of metabolites. Novartis Pharma AG, 18-Dec-1997. Document DMPK(CH)1997/467	4	8-1228
[20] Fischer V, Tynes R. RAD: Metabolism in human liver: potential for drug-drug interactions. Novartis Pharm. Corp., 28-Jan-1998. Document 303-090 (DMPK(US)1998/005)	4	8-1241
[21] Zimmerlin A, Kraus G, Heitz F. RAD001: Inhibition of RAD001 in vitro metabolism by ketoconazole, itraconazole and fluconazole. Novartis Pharma AG, 31-May-2000. Document DMPK(CH)R99-2448	5	8-1279
[22] Wiegand H, Meno-Tetang G. In vitro blood distribution and plasma protein binding of RAD001 in rat plasma. Addendum 2 to report: In vitro blood distribution, plasma protein binding and stability of RAD001 in mouse plasma. Novartis Pharma AG. 08-Oct-2001. Document DMPK(CH) R00-1253-2.	5	8-1291
[23] Dannecker R, Kretz O. Galactogenic transfer, kinetics and metabolism in milk and blood after single peroral administration (0.9 mg/kg) of ^{3}H-labeled RAD001 to lactating rats. Novartis Pharma AG. 18-June-2001. Document DMPK(CH) R98-708.	5	8-1303
[24] Fraser S. Effect of RAD N BHT on action potential parameters in sheep isolated cardiac Purkinje fibers. Quintiles Scotland Limited, Edinburgh, UK. Report No. ITU00201 (Sponsor's reference No. 982042), 09-Dec-1998.	5	8-1329
[25] Kameda H. General pharmacology of SDZ-RAD. Preclinical Safety, Toxicology/ Pathology, Novartis Pharma K.K., Tsukuba-shi, Japan. Report No. RAD 02-c, 29-Aug-1997.	5	8-1363
[26] McAllister KH. RAD001: Primary observation test of RAD001. Novartis Pharma AG, Basel, Switzerland, PKF-93-02177, 24-Oct-2000.	5	8-1381
[27] Yamada Y. Antigenicity study of SDZ RAD. Nihon Bioresearch Inc., Hashima Laboratory, Hashima, Japan. Report No. 802416, 18-Aug-1997.	5	8-1392
[28] Buescher H, Buchheit K, PKF222-666 (RAD): Effect of RAD on lung function in the guinea pig.(Safety Pharmacology) Preclinical Safety, Novartis Pharma AG, Basel, Switzerland, RD-2000-01492, 11-Aug-2000.	5	8-1446

	Vol	Page No.
[29] Kimura M, Mitani H. RAD: Cardiovascular effect of RAD in anesthetized pigs. Novartis Pharma KK, Tsukuba-shi, Japan, RD-2000-1460, 25-Jul-2000.	5	8-1452
[30] Pfister T. SDZ RAD 666: Acute oral toxicity study in mice. Research & Consulting Company Ltd., Itingen, Switzerland. RCC Project No. 393131 (203-023), 16-Jan-1996.		**x-reference to IND 52,003 11/15/96
[31] Pfister T. SDZ RAD 666: Acute oral toxicity study in rats. Research & Consulting Company Ltd., Itingen, Switzerland. RCC Project No. 393118 (203-024), 12-Jan-1996.		**
[32] Pfister T. SDZ RAD 666: Acute intravenous toxicity study in mice. Research & Consulting Company Ltd., Itingen, Switzerland. RCC Project No. 393142 (203-051), 12-Jan-1996.		**
[33] Pfister T. SDZ RAD 666: Acute intravenous toxicity study in rats. Research & Consulting Company Ltd., Itingen, Switzerland. RCC Project No. 393120 (203-047), 16-Jan-1996.		**
[34] Noakes JP. SDZ RAD: Range finding toxicity study by oral gavage administration to CD-1 mice for 13 weeks. Huntingdon Life Sciences Ltd, Eye, England. Report No. 96/SPM107/1177 (203-082), 06-Nov-1997.		**
[35] Mahl A. SDZ RAD 666: A 2-week oral (gavage) dose-range-finding study in rats. Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Report No. 196DFR (203-038), 28-Mar-1996.		**
[36] Schmid H, Allard G, Keller B, Weber K, Amstrom J. SDZ RAD: A comparative 2-week oral (gavage) toxicity study in the rat with a microemulsion and a solid dispersion. Research & Consulting Company Ltd., Itingen, Switzerland. RCC Project No. 617951 (203-078). 14-Aug-1997.		x-reference to IND 52,003 01/26/98
[37] Chase KR. SDZ RAD: Toxicity study by oral gavage administration to HanIBM Wistar rats for 4 weeks followed by a 2 week reversibility period. Huntingdon Life Sciences Ltd, Eye, England. Report No. 95/SPM**/0888 (203-042), 14-Jun-1996. Chase KR. Additional pathology investigations to a toxicity study by oral gavage administration to HanIBM Wistar rats for 4 weeks followed by a 2 week reversibility period. Huntingdon Life Sciences Ltd, Alconbury, England. Report No. NVR052/002947 (BS-101), 02-Aug-2000.		**
[38] Chase KR. SDZ RAD: A repeat toxicity study by oral gavage administration to HanIBM Wistar rats for 4 weeks followed by a 2 week reversibility period. Huntingdon Life Sciences Ltd, Eye, England. Report No. 96/SPM090/0404 (203-050), 08-Aug-1996. Chase KR. Electron microscopy report. Huntingdon Life Sciences Ltd, Huntingdon, England. Report No. SPM 090/960876, 21-Aug-1996.		**

	Vol	Page No.
[39] Nicholls IM. SDZ RAD: Toxicity study by oral gavage administration to Hanlbm Wistar rats for 26 weeks followed by a 4-week reversibility period. Huntingdon Life Sciences Ltd, Eye, England. Report No. 96/SPM083/1130 (203-069), 11-Apr-1997		**x-reference to IND 52,003 01/26/98**
[40] Makin A. SDZ RAD: Dose range finding study (intravenous infusion administration) in rats. Huntingdon Life Sciences Ltd., Huntingdon, England. Report No. SAZ 500/951169 (203-060), 05-Sep-1996.		****x-reference to IND 52,003 11/15/96**
[41] Makin A. SDZ RAD: Comparative intravenous infusion study in rats. Huntingdon Life Sciences Ltd, Huntingdon, England. Report No. SAZ 522/960021 (203-053), 20-Aug-1996.		******
[42] Cooper S. SDZ RAD: Toxicity study by intravenous (bolus) administration to Hanlbm Wistar rats for 2 weeks. Huntingdon Life Sciences Ltd, Eye, England. Study SPM115/970022 (203-071), 04-Aug-1997.		**x-reference to IND 52,003 01/26/98**
[43] Spähni M. RAD001: A 2-week oral (gavage) dose-range finding study in minipigs. Novartis Pharma AG, Basel, Switzerland. Report No. 212DFP (BS-610), 15-May-2000.	**5**	**8-1463**
[44] Mahl A. SDZ RAD: 4-week oral (gavage) toxicity study in minipigs. Novartis Pharma AG, Basel, Switzerland. Report No. 971033 (BS-659), 10-Aug-2000.	**6**	**8-1565**
[45] Brinck P. SDZ RAD: Two-week intravenous infusion toxicity study in minipigs. Scantox, Lille Skensved, Denmark. Report No.19404 (203-075), 13-Aug-1997.		**x-reference to IND 52,003 01/26/98**
[46] Makin A. SDZ RAD: Dose escalating study (oral administration) in cynomolgus monkeys. Huntingdon Life Science Ltd., Huntingdon, England. Report No. SAZ 471/943030 (203-055), 13-Aug-1996.		******
[47] Makin A. SDZ RAD: 14-day dose range finding study (oral route) in cynomolgus monkeys. Huntingdon Life Sciences Ltd., Huntingdon, England. Report No. SAZ 494/951127 (203-059), 03-Sep-1996. Makin A. Supplementary report: ECG analysis. Huntingdon Life Sciences Ltd., Huntingdon, England. Report No. NVR 036/984906a (BS-032), 23-Dec-1998.		******
[48] Noakes JP. SDZ RAD: Toxicity study by oral gavage administration to cynomolgus monkeys for 4 weeks followed by a 2-week reversibility period. Huntingdon Life Sciences Ltd., Eye, England. Report No. 95/SPM049/1008 (203-054), 19-Aug-1996		******
[49] Zühlke U. SDZ RAD: 28-day oral gavage toxicity study in juvenile cynomolgus monkeys with a 2-week reversibility period. Covance Laboratories GmbH, Münster, Germany. Report No. 1463-019 (203-070), 03-Jul-1997.		**x-reference to IND 52,003 01/26/98**

	Vol	Page No.
[50] Noakes JP. SDZ RAD: Toxicity study by oral gavage administration to cynomolgus monkeys for 26 weeks. Huntingdon Life Sciences Ltd, Eye, England. Report No. 96/SPM078/1067 (203-072), 05-Aug-1997. Noakes JP. Addendum to final report: Virology. Addendum No. SPM078/980023 (BS-033), 25-Feb-1998.		**x-reference to IND 52,003 01/26/98**
[51] Zühlke U. SDZ RAD: 52-week oral (gavage) toxicity study in the cynomolgus monkey. Covance Laboratories GmbH, Münster, Germany. Report No. 1463-045, Sponsor's Ref. No. 972001 (BS-375), 02-Nov-1999.	7-8	**8-1863**
[52] Makin A. SDZ RAD 666: Dose finding study in Cynomolgus monkeys by intravenous infusion for 2 weeks. Huntingdon Research Centre, Huntingdon, England. Report No. SAZ 484/950394 (203-012), 21-Aug-1995.		****x-reference to IND 52,003 11/15/96**
[53] Makin A. SDZ RAD: 4-week toxicity study in Cynomolgus monkeys by intravenous infusion followed by a 2-week reversibility period. Huntingdon Life Sciences Ltd, Huntingdon, England. Study SAZ 523/960379 (203-079), 26-Sep-1997.	9	**8-2443**
[54] Makin A. SDZ RAD: 4-week toxicity study in Cynomolgus monkeys by intravenous infusion followed by a 2-week reversibility period. Huntingdon Life Sciences Ltd, Huntingdon, England. Report No. SAZ 539/962684 (203-083), 13-Oct-1997.	10	**8-2802**
[55] Längle U. RAD001 (SDZ RAD-666): An oral dose-escalating study in dogs. Novartis Pharma AG, Basel, Switzerland. Report No. 41DED (BS-674), 30-Aug-2000.	10	**8-3106**
[56] Noakes JP. SDZ RAD: Comparative toxicity study in Hanlbm Wistar rats with batches differing in by-product content. Huntingdon Life Sciences Ltd, Eye, England. Report No. 96/SPM091/0532 (203-076), 12-Aug-1997.		**x-reference to IND 52,003 01/26/98**
[57] Mahl A. RAD001: 4-week oral toxicity study in rats (batch comparison). Novartis Pharma AG, Basel, Switzerland. Report No. 991094 (BS-697), 20-Sep-2000.	11	**8-3124**
[58] Schmid H, Allard G, Keller B, Weber K, Chevalier HJ. SDZ RAD Solid dispersion: A comparative 2-week oral (gavage) toxicity study in the rat with two different batches. RCC Itingen, Switzerland. RCC Project 634678 (203-077), 25-Aug-1997.		**x-reference to IND 52,003 01/26/98**
[59] Webley LJ. SDZ RAD: Oncogenicity study by oral gavage administration to Hanibm Wistar rats for 104 weeks. Huntingdon Life Sciences Ltd, Eye, England. Report No. SPM113/973228 (BS-468), 26-Oct-1999. Webley LJ. Additional pathology investigations to an oncogenicity study by oral gavage administration to Hanlbm Wistar rats for 104 weeks (Study number SPM/113). Huntingdon Life Sciences Ltd, Huntingdon, England. Report No. NVR053/00 3100 (BS-103), 02-Aug-2000.	12-16	**8-3502**

	Vol	Page No.
[60] Thomas H. SDZ RAD (SDZ 222-666): An oral 13-week investigative fertility study in male rats with 13 weeks recovery. Novartis Pharma AG, Basel, Switzerland. Report No. 7073R (203-094), 05-Oct-1998.	17	8-6011
[61] Chase KR. SDZ RAD: Oncogenicity study by oral gavage administration to CD-1 mice for104 weeks. Huntingdon Life Sciences Ltd, Eye, England. Report No. SPM118/973229 (BS-418), 08-Oct-1999.	18-24	8-6586
[62] Bartmann K. SDZ RAD (SDZ 222-666): An oral fertility dose-range-finding study in male rats. Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Report No. 7061R (203-058), 18-Sep-1996.		**x-reference to IND 52,003 11/15/96
[63] Bartmann K. SDZ RAD 666 (SDZ 222-666): An oral reproductive toxicity dose-range-finding study in female rats with toxicokinetics and placental transfer. Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Report No. 1060R (203-057), 18-Sep-1996.		**
[64] Thomas H. SDZ RAD (SDZ 222-666): An oral fertility and embryo-fetal development study in female rats. Novartis Pharma Ltd, Basel, Switzerland. Novartis Report No. 3074R (203-073), 25-Aug-1997.		x-reference to IND 52,003 01/26/98
[65] Bartmann K. SDZ RAD 666 (SDZ 222-666): An oral embryo-fetal development dose-range-finding study in rabbits with toxicokinetics and placental transfer. Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Study 2059K (203-056), 18-Sep-1996.		**
[66] Thomas H. SDZ RAD (SDZ 222-666): An oral embryo-fetal development study in rabbits. Novartis Pharma AG, Basel, Switzerland. Novartis Report No. 4070K (203-074), 02-Sep-1997.		x-reference to IND 52,003 01/26/98
[67] Youreneff M. RAD001: An oral pre- and postnatal development study in rats. Novartis Pharmaceuticals Corp., East Hanover, NY, USA. Report No. 987105 (US-75392), 06-Dec-1999.	25	8-9120
[68] Suter W. SDZ RAD 666: Mutagenicity test using Salmonella typhimurium. Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Report No. Mut.Bakt.27/95 (203-016), 19-Sep-1995.		**x-reference to IND 52,003 11/15/96
[69] Suter W. SDZ RAD 666 (SDZ 222-666): Mutagenicity test using Salmonella typhimurium (batch control). Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Report No. Mut.Bakt.10/96 (203-040), 30-May-1996.		**
[70] Suter W. SDZ RAD 666 (SDZ 222-666): Mutagenicity test using Salmonella typhimurium (batch control). Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Report No. Mut.Bakt.52/96 (203-062), 08-Oct-1996.		x-reference to IND 52,003 01/26/98

	Vol	Page No.
[71] Suter W. SDZ RAD (Solid dispersion): Mutagenicity test using Salmonella typhimurium. Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Report No. Mut.Bakt. 66/96 (203-063), 23-Oct-1996.		**x-reference to IND 52,003 01/26/98**
[72] Martus HJ. RAD001: Mutagenicity test using Salmonella typhimurium (batch control). Novartis Pharma AG, Basel, Switzerland. Report No. 001801 (BS-482), 02-Mar-2000).	**26**	**8-9486**
[73] Fellows M. SDZ RAD: Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells using the microtitre fluctuation technique. Corning Hazelton (Europe), Harrogate, England. Report No. 1463/4-1052 (203-046), 23-Jul-1996.		****x-reference to IND 52,003 11/15/96**
[74] Locher F. SDZ RAD 666: Chromosomal aberration test with V79 Chinese hamster cells. Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Report No. Z59 (203-025), 17-Jan-1996.		******
[75] Locher F. SDZ RAD (Solid dispersion): Chromosomal aberration test with V79 Chinese hamster cells. Novartis Pharma AG, Basel, Switzerland. Report No. Z63 (203-067), 13-Mar-1997.		**x-reference to IND 52,003 01/26/98**
[76] Pötter F. RAD001: Chromosome aberration test with V79 Chinese hamster cells. Novartis Pharma AG, Basel, Switzerland. Study 001831 (BS-725), 05-Jun-2000.	**26**	**8-9513**
[77] Suter W. SDZ RAD 666 (SDZ 222-666): Mouse bone marrow micronucleus test by the oral route. Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Report No. MK 36 (203-041), 28-May-1996.		******
[78] Jackson AM. SDZ RAD: Comparative study of ophthalmic toxicity by oral gavage administration to CD rats and Hanlbm rats for 4 weeks. Huntingdon Life Sciences Ltd, Eye, England. Report No. 96/SPM098/0796 (203-068), 14-Apr-1997.		**x-reference to IND 52,003 01/26/98**
[79] Längle UW. SDZ RAD 666: A local intravenous tolerability study in rabbits. Sandoz Pharma Ltd, Basel, Switzerland. Sandoz Study 80LTRB (203-031). 26-Jan-1996.		******
[80] Van Huygevoort AHBM. Primary skin irritation/corrosion study with RAD001 in the rabbit (4-hour semi-occlusive application). NOTOX B.V. 's-Hertogenbosch, The Netherlands. NOTOX Project 246781 (BS-811), 11-Jan-1999.	**26**	**8-9568**
[81] Van Huygevoort AHBM. Assessment of contact hypersensitivity to RAD001 in the albino guinea pig (Maximization test). NOTOX B.V. 's-Hertogenbosch, The Netherlands. NOTOX Project 246792 (BS-812), 11-Jan-1999.	**26**	**8-9577**

	Vol	Page No.
[82] Figueiredo J, Brüggen J, Muller M, Vaxelaire J, Hattenberger M, Lane H, O'Reilly T. Pharmacokinetics of RAD001 in BALB/c nu/nu mice bearing subcutaneous KB-31 human epidermoid tumors. Novartis Release Ready Report 2000;RD-2000-02553	26	8-9593
[83] O'Reilly T, Marti A, McMahon L, Lane HA. Pharmacokinetics of RAD001 in pancreatic tumor-bearing Lewis rats. Novartis Release Ready Study Report 2002;RD-2002-02884.	26	8-9607
[84] Hattenberger M, Boulay A, Lane HA, Maira M, O'Reilly T. In vitro antiproliferative activity of RAD001 against a broad panel of tumor cell lines. Novartis Release Ready Study Report 2002;RD-2002-03223.	2	8-295
[85] Vaxelaire J, Muller M, Hattenberger, Lane H, O'Reilly T. RAD001 is an effective antitumor agent in experimental A549 xenograft tumor model of lung cancer. Novartis Release Ready Report 2001;RD-2001-00848.	3	8-507
[86] Muller M, Vaxelaire J, Hattenberger M, Sedrani R, Lane H, O'Reilly T. RAD001 is an effective antitumor agent in experimental KB-31 xenograft tumor models of epidermoid cancer. Novartis Release Ready Report 2000;RD-2000-02549.	2	8-388
[87] Vaxelaire J, Muller M, Hattenberger M, Sedrani R, Lane H, O'Reilly T. RAD001 is active in vivo against xenograft tumors of HCT116 human colon carcinoma, a cell line resistant to RAD001 in vitro. Novartis Release Ready Report 2000;RD-2000-02550.	3	8-565
[88] Theuer A, Wood JM. RAD001: effects on endothelial and fibroblast cell proliferation. Novartis Release Ready Report 2001;RD-2001-00852.	2	8-357
[89] Wood JM, Schnell CR. RAD001: effects on angiogenesis-induced by growth factor-impregnated, subcutaneous implants in mice. Novartis Release Ready Report 2001; RD-2001-00853.	3	8-768
[90] Wood JM, Schnell CR. RAD001: effects in orthotopic B16/BL16 melanoma model in C57/BL/6 mice. Novartis Release Ready Report 2001; RD-2001-00854.	3	8-783
[91] Brüggen J, McMahon L, Lane HA, O'Reilly T. Pharmacokinetics of RAD001 in non-tumor bearing athymic BALB/c nu/nu mice. Novartis Release Ready Study Report 2002;RD-2002-02880.	26	8-9625
[92] Boulay A, Hattenberger M, O'Reilly T, Maira M, Lane HA. Comparison of the antiproliferative activity of RAD001 with activation of the PTEN/PI3 kinase/Akt/mTOR pathway in tumor cell lines. Novartis Release Ready Study Report 2002;RD-2002-03252	2	8-369
[93] RAD001: Phase 1 study in patients with advanced solid tumors, 2101/2, Novartis Pharma AG, Basel, Switzerland		Study in Progress (Europe)

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External Reports			
L1	Crowe A, Lemaire M. In vitro and in situ absorption of SDZ-RAD using a human intestinal cell line (Caco-2) and a single pass perfusion model in rats: comparison with rapamycin. Pharm Res 1998; 15: 1666-1672.	26	8-9651
L2	Calne RY, Collier DSJ, Lim S, Pollard SG, Samaan A, White DJG, Thiru S. Rapamycin for immunosuppression in organ allografting. The Lancet 1989; July 22:227.	26	8-9658
L3	Collier DSJ, Calne R, Thiru S, Lim S, Pollard SG, Barron P, Da Costa M, White DJG. Rapamycin in experimental renal allografts in dogs and pigs. Transplantation Proceedings 1990; 22(4):1674-1675.	26	8-9659
L4	Gunji Y, Ochiai T, Sakamoto K, Suzuki T, Nagata M, Nakajima K, Komori A, Asano T, Isono K, Hamaguchi K. Pathologic characteristics of vasculitis in renal transplant recipient dogs receiving immunosuppressive agents, FK 506, rapamycin or RS-61443. Transplantation Proceedings 1993; 25(1):752-753	26	8-9661
L5	Yanchar NL, Fedorak RN, Kneteman NM, Sigalet DL. Nutritional and intestinal effects of the novel immunosuppressive agents: deoxyspergualin, rapamycin, and mycophenolate mofetil. Clinical Biochemistry 1996; 9(4):363-369.	26	8-9663
L6	DiJoseph JF, Sehgal SN. Sirolimus: Side effect profile in animal studies. Principals in drug development in transplantation and autoimmunity, ed. by Liebermann R and Mukherjee A. 1996; R.G. Landes Company, Chapter 12.3, 289-94.	26	8-9670
L7	Chan CC, Martin DF, Xu D, Roberge FG. Side effects of rapamycin in the rat. Journal of Ocular Pharmacology and Therapeutics 1995; 11(2):177-181.	26	8-9676
L8	Vu MD, Qi S, Xu D, Wu J, Fitzsimmons WE, Sehgal SN, Dumont L, Busque S, Daloze P, Chen H. Tacrolimus (FK506) and sirolimus (rapamycin) in combination are not antagonistic but produce extended graft survival in cardiac transplantation in the rat. Transplantation 1997; 64(12):1853-1856.	26	8-9681
L9	Prakasam G, Yeh JK, Chen MM, Castro-Magana M, Liang CT, Aloia JF. Effects of growth hormone and testosterone on cortical bone formation and bone density in aged orchiectomized rats. Bone 1999; 24(5):491-497.	26	8-9685
L10	Chen MM, Yeh JK, Aloia JF. Histologic evidence: growth hormone completely prevents reduction in cortical bone gain and partially prevents cancellous osteopenia in the tibia of hypophysectomized rats. The Anatomical Record 1997; 249(2):163-172.	26	8-9692

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L11 Graeves P. Histopathology of preclinical toxicity studies: interpretation and relevance in drug safety evaluation. Elsevier, Amsterdam, 1990; 210-214.	**26**	**8-9702**
L12 Francesc V, Chambard JC, Pouysségur J. p70 S6 Kinase-mediated protein synthesis is a critical step for vascular endothelial cell proliferation. J Biol Chem 1999;274:26776-26782.	**26**	**8-9710**
L13 Yu Y, Sato JD. MAP kinases, phosphatidylinositol 3-kinase, and p70 S6 kinase mediate the mitogenic response of human endothelial cells to vascular endothelial growth factor. J Cell Physiol 1999;178:235-246.	**2**	**8-208**
L14 Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, Bruns CJ, Zuelke C, Farkas S, Anthuber M, Jauch KW, Geissler EK. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med 2002;8:128-135.	**2**	**8-220**
L15 Lesniak MS, Langer R, Brem H. Drug delivery to tumors of the central nervous system. Curr Neurol Neurosci Rep 2001; 1:210-216.	**26**	**8-9717**
L16 Papadopoulos MC, Saadoun S, Davies DC, Bell BA. Emerging molecular mechanisms of brain tumour oedema. Br J Neurosurg 2001; 15:101-108.	**26**	**8-9724**
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RAD001 IND # 66,279 Dec 19, 2002

Archives
cc: chron

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
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To:	Kevin Carl, Novartis	**From:**	Ann Staten, Project Manager
Fax:	973-781-5217	**Fax:**	301-827-4590
Phone:	973-781-8165	**Phone:**	301-594-0490
Pages:	1	**Date:**	December 19, 2002
Re:	IND 66,279 RAD001		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Mr. Carl,

Please refer to your Investigational New Drug Application (IND) submitted November 22, 2002 pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for RAD001.

We have completed the review of your IND and conclude it is reasonably safe to proceed with your proposed study based upon your December 19, 2002 agreement to correct the deficiency, which was forwarded to you by e-mail transmission on December 18, 2002.

Please let me know if you have any questions.

Sincerely,

Ann

APPENDIX L

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	04/08/2009	Amendment updates reference standards and retest period and storage temperature in support of upcoming clinical studies (PS).	813		CMC Amendment
66,279	RAD 001C	04/03/2009	Updated CMC for 0.25mg, 0.5mg, 0.75 mg and 1 mg tablets in support of upcoming clinical studies. (PS)	811		CMC Amendment
66,279	RAD 001C	03/19/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Irene Ghobrial, Dana Farber Cancer Institute, Boston, MA (PS).	801		Other
66,279	RAD 001C	03/17/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Joseph Sinning, Harold Leever Regional Cancer Center, Waterbury, CT (PS).	800		Other
66,279	RAD 001C	03/13/2009	Email Response to FDA Request including executive summary of final key results of Protocol CRAD001C2121 Regarding Bioavailability of everolimus.			Other
66,279	RAD 001C	03/12/2009	Provided executive summary of final key results of Protocol CRAD001C2121 Regarding Bioavailability of everolimus (PS).	798		Clinical Information Amendr
66,279	RAD 001C	03/12/2009	New Protocol CRAD001M2301 entitled "A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subpendymal giant cell astrocytomas (SEGA) associated with Tuberous Sclerosis Complex (TSC)" (PS).	799		New Protocol
66,279	RAD 001C	03/10/2009	Acknowledge Withdrawl of SN598 Special Protocol Assessment requested on May 1, 2008. Withdrawl requested on October 15, 2008.			Other
66,279	RAD 001C	03/10/2009	Acknowledge Withdrawl of SN579 Special Protocol Assessment requested on April 7, 2008. Withdrawl requested on November 13, 2008.			Other
66,279	RAD 001C	03/06/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Jennifer Chan, Dana-Farber Cancer Institute, Boston, MA (PS).	796		Other
66,279	RAD 001C	03/06/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Anne Beaven, Duke University Medical Center, Durham, NC (PS).	795		Other
66,279	RAD 001C	02/27/2009	Study CRAD001N2301 new protocol. (PS)	790		New Protocol
66,279	RAD 001C	02/24/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Denise Yardley, SCRI Oncology Research Consortium, Nashville, TN (PS).	786		Other
66,279	RAD 001C	02/20/2009	Annual Report covering the period of November 24, 2007 to November 24, 2008 (PS).	785		Annual Report
66,279	RAD 001C	02/19/2009	Amendment No. 3 to Protocol CRAD001L2201 (PS).	783		Change In Protocol
66,279	RAD 001C	02/18/2009	Request for Type B EOP2 meeting to discuss development plan of RAD001 for the treatment of patients with locally advanced or metastatic breast cancer. (PS)	781		Request for FDA Meeting
66,279	RAD 001C	02/11/2009	PHHO2008US15235; follow-up (PS)	780		Safety Report
66,279	RAD 001C	02/10/2009	PHHY2008DE25330; follow-up (PS)	779		Safety Report
66,279	RAD 001C	02/10/2009	PHHO2009IT00723; follow-up (PS)	778		Safety Report
66,279	RAD 001C	02/09/2009	PHHO2008US14020; follow-up (PS)	777		Safety Report
66,279	RAD 001C	02/09/2009	PHHO2009IT00723; follow-up (PS)	776		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	02/06/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Fury, Memorial Sloan-Kettering Cancer Center, NY. (PS)	774		Other
66,279	RAD 001C	02/06/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Wen W. Ma, Roswell Park Cancer Institute, Buffalo, NY. (PS)	775		Other
66,279	RAD 001C	02/05/2009	Studies CRAD001L2401,CRAD001N2201,CRAD001L2201,CRAD00 new investigator (PS).	773		New Investigator
66,279	RAD 001C	02/03/2009	Submission of Clinical Information Amendment providing for changes to the Investigator Brochure, Edition 7 Release Date: 21-Jan-2009 (PS)	772		Clinical Information Amendr
66,279	RAD 001C	01/29/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Sarah Ketchum, Mercy Oncology/Hematology Center Portland, ME (PS).	769		Other
66,279	RAD 001C	01/29/2009	PHHO2009IT00723; follow-up (PS)	771		Safety Report
66,279	RAD 001C	01/29/2009	PHHO2008FR13655; follow-up (PS)	770		Safety Report
66,279	RAD 001C	01/27/2009	PHHO2008FR13655 (PS)	768		Safety Report
66,279	RAD 001C	01/26/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Herbert Hurwitz, Duke University Medical Center Durham, NC (PS).	766		Other
66,279	RAD 001C	01/26/2009	PHHO2008US15235; follow-up (PS)	767		Safety Report
66,279	RAD 001C	01/21/2009	PHHO2008US14734 (PS)	765		Safety Report
66,279	RAD 001C	01/21/2009	PHHO2009IT00723 (PS)	764		Safety Report
66,279	RAD 001C	01/15/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Talpaz, Ann Arbor, MI. (PS)	763		Other
66,279	RAD 001C	01/15/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Jochem H. Lorch, Dana Farber Cancer Institute, Boston, MA (PS)	762		Other
66,279	RAD 001C	01/14/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Mark W. Kieran, Dana Farber Cancer Institute, Boston, MA (PS).	761		Other
66,279	RAD 001C	01/14/2009	PHHO2008US15235; follow-up (PS)	760		Safety Report
66,279	RAD 001C	01/13/2009	PHHO2008TR15236; follow-up (PS)	759		Safety Report
66,279	RAD 001C	01/09/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Herbert Hurwitz, Duke University Medical Center, Durham, NC (PS)	758		Other
66,279	RAD 001C	01/09/2009	PHHO2008TR15236; follow-up (PS)	757		Safety Report
66,279	RAD 001C	01/08/2009	Letter authorizing FDA to refer to IND 66,279 in support of IND filed by Dr. Zev A. Wainberg, David Gerffen School of Medicine at UCLA, Los Angeles, CA (PS).	756		Other
66,279	RAD 001C	01/07/2009	PHHO2008US14020; follow-up (PS)	755		Safety Report
66,279	RAD 001C	01/07/2009	PHHO2008US15235 (PS)	754		Safety Report
66,279	RAD 001C	01/07/2009	PHHO2008DE11094; follow-up (PS)	753		Safety Report
66,279	RAD 001C	01/05/2009	PHHO2008TR15236 (PS)	752		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	01/02/2009	PHHO2008DE11982; follow-up (PS)	751		Safety Report
66,279	RAD 001C	12/29/2008	PHHO2008US13880; follow-up (PS)	750		Safety Report
66,279	RAD 001C	12/26/2008	PHHO2008CH13360; follow-up (PS)	749		Safety Report
66,279	RAD 001C	12/26/2008	PHHO2008CH13379; follow-up (PS)	748		Safety Report
66,279	RAD 001C	12/18/2008	Letter authorizing FDA to refer to IND 66,279 in support of an IND filed by Dr. Zev A. Wainberg, David Gerffen School of Medicine at UCLA, Los Angeles, CA (PS).	746		General Correspondence
66,279	RAD 001C	12/17/2008	Letter authorizing FDA to refer to IND 66,279 in support of an IND filed by Dr. Mark H. Kirschbaum, City of Hope National Cancer Center, Duarte, CA. (PS)	745		General Correspondence
66,279	RAD 001C	12/16/2008	Studies CRAD001L2401,CRAD001N2201,CRAD001L2201,CRAD00 new investigator. (PS)	744		New Investigator
66,279	RAD 001C	12/15/2008	PHHO2007US20875; follow-up (PS)	743		Safety Report
66,279	RAD 001C	12/12/2008	PHHO2008BE12855; follow-up (PS)	742		Safety Report
66,279	RAD 001C	12/10/2008	Revision to letter authorizing FDA to refer to IND 66,279 in support of an IND filed by Dr. Bergsland, UCSF Comprehensive Cancer Center, San Francisco, CA (PS)	738		Other
66,279	RAD 001C	12/10/2008	Letter authorizing FDA to refer to IND 66,279 in support of an IND filed by Dr. Gilad Amiel, Baylor College of Medicine, Houston, TX (PS)	739		General Correspondence
66,279	RAD 001C	12/10/2008	Letter authorizing FDA to refer to IND 66,279 in support of an IND filed by Dr. Jeremy Abramson, MD, Massachusettes General Hospital Cancer Center, Boston, MA (PS)	740		General Correspondence
66,279	RAD 001C	12/10/2008	PHHO2008DE11094; follow-up (PS)	741		Safety Report
66,279	RAD 001C	12/09/2008	PHHO2008US14020; follow-up (PS)	736		Safety Report
66,279	RAD 001C	12/09/2008	PHHO2008DE11982 (PS)	737		Safety Report
66,279	RAD 001C	12/08/2008	PHHO2008IT09241; follow-up (PS)	735		Safety Report
66,279	RAD 001C	12/05/2008	PHHO2008US14020 (PS)	734		Safety Report
66,279	RAD 001C	12/04/2008	PHHO2008US13880 (PS)	733		Safety Report
66,279	RAD 001C	12/03/2008	The final internal meeting minutes from the DLBCL FDA end of phase II meeting to discuss a study in diffuse large B-cell lymphoma. (PS)			Other
66,279	RAD 001C	12/03/2008	PHHO2008DE11491; follow-up (PS)	732		Safety Report
66,279	RAD 001C	12/03/2008	Amendment No. 2 to Protocol CRAD001L2201(PS).	731		Change In Protocol
66,279	RAD 001C	12/02/2008	PHHO2008IT09241; follow-up (PS)	727		Safety Report
66,279	RAD 001C	12/02/2008	PHHO2008CH13360; follow-up (PS)	728		Safety Report
66,279	RAD 001C	12/02/2008	PHHO2008CH13379; follow-up (PS)	729		Safety Report
66,279	RAD 001C	12/02/2008	PHHO2008US14108 (PS)	730		Safety Report
66,279	RAD 001C	11/26/2008	PHHO2008CH13360; follow-up (PS)	725		Safety Report
66,279	RAD 001C	11/26/2008	PHHO2008CH13379; follow-up (PS)	726		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	11/25/2008	PHHO2007AU11574; follow-up (PS)	722		Safety Report
66,279	RAD 001C	11/25/2008	PHHO2008IT01481; follow-up (PS)	723		Safety Report
66,279	RAD 001C	11/25/2008	PHHO2008IT09241 (PS)	724		Safety Report
66,279	RAD 001C	11/21/2008	PHHO2008TW11206; follow-up (PS)	720		Safety Report
66,279	RAD 001C	11/21/2008	PHHO2008DE11094; follow-up (PS)	721		Safety Report
66,279	RAD 001C	11/19/2008	PHHO2008CH13379 (PS)	718		Safety Report
66,279	RAD 001C	11/19/2008	PHHO2008CH13360 (PS)	719		Safety Report
66,279	RAD 001C	11/18/2008	PHHO2008TW11206; follow-up (PS)	717		Safety Report
66,279	RAD 001C	11/17/2008	PHHO2008BE12855 (PS)	716		Safety Report
66,279	RAD 001C	11/14/2008	PHHO2008DE11491; follow-up (PS)	715		Safety Report
66,279	RAD 001C	11/13/2008	Withdrawal request for special protocol assessment submitted on April 7, 2008 (SN579) for protocol CRAD001M2301. (PS)	714		General Correspondence
66,279	RAD 001C	11/13/2008	Email Withdrawal of SPA Submitted 20080417			Other
66,279	RAD 001C	11/13/2008	PHHO2008US12593; follow-up (PS)	713		Safety Report
66,279	RAD 001C	11/12/2008	Study CRAD001L2401 change in protocol, amendment 2. (PS)	711		Change In Protocol
66,279	RAD 001C	11/12/2008	Amendment No. 3 to Protocol CRAD001C2116 (PS).	712		Change In Protocol
66,279	RAD 001C	11/11/2008	Email with FDA letter regarding pediatric studies attached.			Other
66,279	RAD 001C	11/11/2008	PHHO2008IT11948; follow-up (PS)	710		Safety Report
66,279	RAD 001C	11/10/2008	PHHY2008DE25330; follow-up (PS)	709		Safety Report
66,279	RAD 001C	11/10/2008	New Protocol CRAD001C2121 entitled "A randomized, open label, two-way crossover study investigating the relative bioavailability of a single 5 mg dose of everolimus administered as either 5x1 mg everolimus intact tablets or 5x1 mg everolimus tablets suspended in 30 mL of water to healthy subjects" (PS).	708		New Protocol
66,279	RAD 001C	11/06/2008	Letter authorizing FDA to refer to IND 66,279 in support of an IND filed by Dr. Lipton, Milton S. Hershey Medial Center, Hershey, PA. (PS)	706		Other
66,279	RAD 001C	11/06/2008	PHHO2008CA11400; follow-up (PS)	707		Safety Report
66,279	RAD 001C	11/05/2008	Letter authorizing FDA to refer to IND 66,279 in support of an IND filed by Dr. Glenn Kroog, Memorial Sloan-Kettering Cancer Center, NY. (PS)	705		General Correspondence
66,279	RAD 001C	11/04/2008	Study CRAD001L2401 new investigator. (PS)	704		New Investigator
66,279	RAD 001C	10/29/2008	PHHY2008SG20428 follow-up (PS)	703		Safety Report
66,279	RAD 001C	10/28/2008	Letter authorizing FDA to refer to IND 66,279 in support of an IND filed by Dr. Garland, Arizona Cancer Center, Tuscon, AZ. (PS)	700		General Correspondence
66,279	RAD 001C	10/28/2008	Letter authorizing FDA to refer to IND 66,279 in support of an IND filed by Dr. Bergsland, UCSF Comprehensive Cancer Center, San Francisco, CA. (PS)	701		General Correspondence

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	10/28/2008	Letter authorizing FDA to refer to IND 66,279 in support of an IND filed by Dr. George, Dana-Farber Cancer Institute, Boston, MA. (PS)	702		General Correspondence
66,279	RAD 001C	10/28/2008	PHHO2008DE11094 follow-up (PS)	698		Safety Report
66,279	RAD 001C	10/28/2008	PHHO2008DE12119 follow-up (PS)	699		Safety Report
66,279	RAD 001C	10/27/2008	PHHY2008DE25330 (PS)	697		Safety Report
66,279	RAD 001C	10/27/2008	PHHO2007US20875; follow-up (PS)	695		Safety Report
66,279	RAD 001C	10/27/2008	PHHO2008US12593 (PS)	696		Safety Report
66,279	RAD 001C	10/24/2008	PHHO2008DE11094 (PS)	694		Safety Report
66,279	RAD 001C	10/21/2008	PHHO2008DE12119 (PS)	693		Safety Report
66,279	RAD 001C	10/17/2008	E-mail from FDA. Conformation of Type A meeting (TC) on September 18, 2008 and follow-up questions. (PS)			Other
66,279	RAD 001C	10/16/2008	PHHO2008IT11948 (PS)	692		Safety Report
66,279	RAD 001C	10/16/2008	E-mail to FDA regarding withdrawal of SPA for protocol CRAD001M2302. (PS)			Other
66,279	RAD 001C	10/15/2008	This correspondence to the FDA is to withdrawal the request for special protocol assessment for study CRAD001M2302. (PS)	691		General Correspondence
66,279	RAD 001C	10/15/2008	New investigator to study CRAD001L2401 and new investigator to study CRAD001C2111. (PS)	690		New Investigator
66,279	RAD 001C	10/14/2008	Email to/from the FDA regarding the pending letter for the PPSR.			Other
66,279	RAD 001C	10/14/2008	Email from/to the FDA regarding the meeting minutes of the September 18, 2008 Type A meeting.			Other
66,279	RAD 001C	10/14/2008	PHHO2008DE11491 (PS)	688		Safety Report
66,279	RAD 001C	10/14/2008	PHHO2007US00556; follow-up (PS)	689		Safety Report
66,279	RAD 001C	10/10/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Dr. Matthew Fury, MD. (PS)	687		Other
66,279	RAD 001C	10/08/2008	PHHO2008CA04926; follow-up (PS)	686		Safety Report
66,279	RAD 001C	10/07/2008	Email from/to the FDA containing the word document of the EoP2 questions.			Other
66,279	RAD 001C	10/03/2008	EOP2 briefing book for the meeting scheduled for November 13, 2008. (PS)	681		Briefing Book
66,279	RAD 001C	10/03/2008	PHHO2008AR00668; follow-up (PS)	685		Safety Report
66,279	RAD 001C	10/02/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66279 for RAD001(everolimus) in support of an Investigational New Drug Application (IND) that will be filed by Kristin Zorn, M.D. (PS)	684		Other

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	10/02/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66279 for RAD001(everolimus) in support of an Investigational New Drug Application (IND) that will be filed by John D. Hainsworth, MD. (PS)	683		Other
66,279	RAD 001C	10/01/2008	Reference is made to the Letter of Authorization submitted on September 10, 2008 (SN 667) to authorize the FDA to refer to IND 66,279 for RAD001 (everolimus) in support of an Investigational New Drug Application (IND) that will be filed by Dr. David R. Gandara. With this submission Novartis would like to correct, that the principal investigator for the above mentioned study is Dr. Randeep Sangha, MD. (PS)	682		Other
66,279	RAD 001C	09/30/2008	PHHO2008TW11206 (PS)	679		Safety Report
66,279	RAD 001C	09/30/2008	PHHO2008CA11400 (PS)	680		Safety Report
66,279	RAD 001C	09/23/2008	PHHO2008US10695;Follow-Up (PS)	678		Safety Report
66,279	RAD 001C	09/23/2008	PHHO2008DE10143;Follow-Up (PS)	677		Safety Report
66,279	RAD 001C	09/19/2008	Email to/from the FDA regarding the Type A meeting scheduled for September 18, 2008.			Other
66,279	RAD 001C	09/19/2008	PHHO2008NO01190;Follow-Up (PS)	675		Safety Report
66,279	RAD 001C	09/18/2008	PHHY2008JP20446;Follow-Up (PS)	674		Safety Report
66,279	RAD 001C	09/18/2008	PHHY2008SG20428 (PS)	673		Safety Report
66,279	RAD 001C	09/17/2008	Email to/from the FDA regarding the pending PPSR.			Other
66,279	RAD 001C	09/16/2008	PHHO2008US10695 (PS)	672		Safety Report
66,279	RAD 001C	09/12/2008	PHHO1997FR03054 (PS)	671		Safety Report
66,279	RAD 001C	09/12/2008	Email from/to the FDA regarding the Type A meeting scheduled for September 18, 2008.			Other
66,279	RAD 001C	09/11/2008	PHHO1997NO02602 (PS)	670		Safety Report
66,279	RAD 001C	09/11/2008	Email from/to the FDA confirming the Type A meeting scheduled for September 18, 2008 and containing Novartis' follow-up questions.			Other
66,279	RAD 001C	09/10/2008	PHHO2008CA00612; follow-up (PS)	669		Safety Report
66,279	RAD 001C	09/10/2008	PHHO2007US21124; follow-up (PS)	668		Safety Report
66,279	RAD 001C	09/10/2008	Email from/to the FDA confirming the EoP2 meeting scheduled for November 13, 2008.			Other
66,279	RAD 001C	09/10/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66279 for RAD001(everolimus) in support of an Investigational New Drug Application (IND) that will be filed by David R. Gandara, MD. (PS)			Other
66,279	RAD 001C	09/09/2008	Email from the FDA containing the FDA's preliminary responses to Novartis' questions submitted in the meeting request submitted dated July 14, 2008.			Other

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	09/05/2008	New protocol RAD001O2101 entitled: "A phase 1 open label/phase 2 randomized, double-blind, multicenter study investigating the combination of RADOOl and sorafenib (Nexavar) in patients with advanced hepatocellular carcinoma". (PS)	666		New Protocol
66,279	RAD 001C	09/05/2008	Amendment No. 1 to protocol CRAD001L2201. (PS)	665		Change In Protocol
66,279	RAD 001C	09/04/2008	PHHO2007FR07389; follow-up (PS)	664		Safety Report
66,279	RAD 001C	09/03/2008	PHHO2008DE10143 (PS)	663		Safety Report
66,279	RAD 001C	09/02/2008	PHHO2007US21124;Follow-Up (PS)	660		Safety Report
66,279	RAD 001C	09/02/2008	PHHO2008FR08863;Follow-Up (PS)	661		Safety Report
66,279	RAD 001C	09/02/2008	PHHO2008CY09722;Follow-Up (PS)	662		Safety Report
66,279	RAD 001C	09/02/2008	Email to FDA following up on the pending SPAs for protocol M2301 (SEGA, submitted April 7, 2008), and protocol M2302 (Angyomyolipoma, submitted May 1, 2008).			Other
66,279	RAD 001C	08/29/2008	Request for Type B meeting to seek the agency's advice on the proposed development plan for RAD001 in patients with Diffuse Large B-Cell Lymphoma (DLBCL) and the acceptability of the design of the Phase III registration trial (Study CRAD001N2301), which will form the primary basis to support registration and approval of this indication. (PS)	659		Request for FDA Meeting
66,279	RAD 001C	08/28/2008	PHHO2008CA04926;Follow-Up (PS)	657		Safety Report
66,279	RAD 001C	08/28/2008	PHHO2008FR08863;Follow-Up (PS)	656		Safety Report
66,279	RAD 001C	08/28/2008	PHHO2008US05802; follow-up (PS)	658		Safety Report
66,279	RAD 001C	08/27/2008	New investigator to study CRAD001L2201 and CRAD001L2401. (PS)	655		New Investigator
66,279	RAD 001C	08/22/2008	At this time, Novartis is submitting an IND Amendment to provide updated Chemistry, Manufacturing and Controls infonnation for the drug product. An updated packaging site list is provided in this amendment. (PS)	653		CMC Amendment
66,279	RAD 001C	08/22/2008	PHHO2008AU08078;Follow-Up (PS)	654		Safety Report
66,279	RAD 001C	08/19/2008	PHHO2008CY09722;Follow-Up (PS)	652		Safety Report
66,279	RAD 001C	08/14/2008	New Investigator to Study CRAD001L2201 (PS)	651		New Investigator
66,279	RAD 001C	08/13/2008	Email to FDA informing them that the desk copies of the briefing documentation for the the Type A Meeting have been submitted.			Other
66,279	RAD 001C	07/31/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Michael K. Gibson, MD. (PS)	650		Other
66,279	RAD 001C	07/31/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Allan Lipton, MD. (PS)	649		Other
66,279	RAD 001C	07/31/2008	PHHO2008US05802;Follow-Up (PS)	648		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	07/28/2008	Fax FDA LETTER Informing Novartis that their meeting request dated July 14, 2008 has been granted.			Other
66,279	RAD 001C	07/25/2008	PHHO2008FR08382;Follow-Up (PS)	646		Safety Report
66,279	RAD 001C	07/22/2008	PHHO2008FR08382;Follow-Up (PS)	645		Safety Report
66,279	RAD 001C	07/21/2008	PHHO2008AU07680;Follow-Up (PS)	644		Safety Report
66,279	RAD 001C	07/16/2008	PHHO2008FR08382;Follow-Up (PS)	642		Safety Report
66,279	RAD 001C	07/16/2008	PHHO2008US07823; Follow-Up (PS)	643		Safety Report
66,279	RAD 001C	07/16/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RADOOI (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed byDaniel Cho, MD. (PS)	641		Other
66,279	RAD 001C	07/16/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RADOOI (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Charles A. Coltman, Jr. M.D. (PS)	640		Other
66,279	RAD 001C	07/14/2008	Request for Type A meeting to discuss the FDA's stance on whether the requested protocol change to include children under the age of 3 years is acceptable and to gain clarification on procedural aspects of a potential protocol change at this point in the SPA process. (PS)	639		Request for FDA Meeting
66,279	RAD 001C	07/10/2008	PHHO2007FR09520;Follow-Up (PS)	638		Safety Report
66,279	RAD 001C	07/09/2008	PHHO2008AU08078;Follow-Up (PS)	637		Safety Report
66,279	RAD 001C	07/03/2008	PHHO2007PL06777; Follow-Up (PS)	636		Safety Report
66,279	RAD 001C	07/03/2008	Email to FDA requesting advice on SPA submission on April 7, 2008, serial number 579.			Other
66,279	RAD 001C	07/03/2008	New Protocol to Study CRAD001L2201 entitled A randomized, open label, multi-center phase II study to compare bevacizumab plus RAD001 versus interferon alfa-2a plus bevacizumab for the first-line treatment of patients with metastatic clear cell carcinoma of the kidney. (PS)	635		New Protocol
66,279	RAD 001C	07/02/2008	PHHO2008DE05923;Follow-Up (PS)	632		Safety Report
66,279	RAD 001C	07/02/2008	PHHO2008US07899;Follow-Up (PS)	631		Safety Report
66,279	RAD 001C	07/02/2008	PHHO2007ES08365;Follow-Up (PS)	633		Safety Report
66,279	RAD 001C	07/02/2008	New Investigator to Study CRAD001C2324 (PS)	634		New Investigator
66,279	RAD 001C	07/01/2008	PHHO2008US07823;Follow-Up (PS)	630		Safety Report
66,279	RAD 001C	06/30/2008	PHHO2008US06493;Follow-Up (PS)	629		Safety Report
66,279	RAD 001C	06/27/2008	PHHO2008AU07680;Follow-Up (PS)	628		Safety Report
66,279	RAD 001C	06/26/2008	Amendment No. 1 to protocol CRAD001C2114. (PS)	626		Change In Protocol
66,279	RAD 001C	06/26/2008	PHHO2008CA00612;Follow-Up (PS)	627		Safety Report
66,279	RAD 001C	06/24/2008	PHHO2008CA00612;Follow-Up (PS)	625		Safety Report
66,279	RAD 001C	06/20/2008	PHHO2007FR03202;Follow-Up (PS)	624		Safety Report

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66,279	RAD 001C	06/19/2008	PHHO2008DE05923; Follow-Up (PS)	623		Safety Report
66,279	RAD 001C	06/17/2008	New Investigator to Study CRAD001C2410 (PS)	622		New Investigator
66,279	RAD 001C	06/16/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Dr. Maysa M. Abu-Khalaf, M.D. (PS)	621		Other
66,279	RAD 001C	06/13/2008	PHHO2007US21124;Follow-Up (PS)	620		Safety Report
66,279	RAD 001C	06/12/2008	PHHO2008DE05923;Follow-Up (PS)	619		Safety Report
66,279	RAD 001C	06/12/2008	PHHO2008US04833;Follow-Up (PS)	618		Safety Report
66,279	RAD 001C	06/10/2008	PHHO2008DE05923;Follow-Up (PS)	616		Safety Report
66,279	RAD 001C	06/10/2008	Amendment No. 1 to protocol CRAD001L2401. (PS)	617		Change In Protocol
66,279	RAD 001C	06/06/2008	This correspondence to the FDA contains a copy of the original PPSR for RAD 001 submitted on February 19, 2007 (SN 294), a copy of the revised PPSR submitted on August 13, 2007 (SN 379), a copy of the publication 'Phase I Study of Everolimus in Pediatric Patients With Refractory Solid Tumors' (Fouladi M et al. (2007) J Clin Oncology;25:4806-4812) and a copy of the Novartis draft of a Written Request following the new template (provided via e-mail on June 02, 2008). (PS)	613		General Correspondence
66,279	RAD 001C	06/06/2008	PHHO2008US06493;Follow-Up (PS)	615		Safety Report
66,279	RAD 001C	06/06/2008	PHHO2008US01900;Follow-Up (PS)	614		Safety Report
66,279	RAD 001C	06/06/2008	FDA LETTER Responding to Novartis' request for special protocol assessment submitted on May 1, 2008.			Other
66,279	RAD 001C	06/05/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Richard M. Stone, M.D. (PS)	612		Other
66,279	RAD 001C	06/03/2008	PHHO2007DE20351;Follow-Up (PS)	611		Safety Report
66,279	RAD 001C	06/02/2008	PHHO2007FR14620;Follow-Up (PS)	610		Safety Report
66,279	RAD 001C	06/02/2008	Email to FDA containing the new templated of the revised written request.			Other
66,279	RAD 001C	05/30/2008	PHHO2008AR00668;Follow-Up (PS)	609		Safety Report
66,279	RAD 001C	05/29/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Dr. Roberto Pili, M.D. (PS)	608		Other
66,279	RAD 001C	05/22/2008	This submission is in response to the FDA request received on April 17, 2008, requesting a list of all manufacturing and testing sites, their CFN/FEI numbers and contact person's information, involved in the production of the clinical trial material for the treatment protocol CRAD001L2401. (PS)	605		Response to FDA Request

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	05/22/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Susan M. Chang, MD. (PS)	606		Other
66,279	RAD 001C	05/22/2008	New investigator to study CRAD001C2116, CRAD001C2241, CRAD001C2410. (PS)	607		New Investigator
66,279	RAD 001C	05/09/2008	FDA LETTER Informing Novartis that they may proceed with the treatment protocol for use in patients with metastic carcinoma of the kidney who have progressed despite vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy.			Other
66,279	RAD 001C	05/09/2008	PHHO2007FR14620;Follow-Up (PS)	604		Safety Report
66,279	RAD 001C	05/09/2008	New investigators to study CRAD001C2324. (PS)	603		New Investigator
66,279	RAD 001C	05/07/2008	Email to FDA responding to their fax dated May 6, 2008.			Response to FDA Request
66,279	RAD 001C	05/07/2008	New investigators to study RAD001C2324. (PS)	601		New Investigator
66,279	RAD 001C	05/07/2008	This correspondence to the FDA contains Novartis' response to the FDA comments dated May 6, 2008 regarding the informed consent. (PS)	602		General Correspondence
66,279	RAD 001C	05/06/2008	Fax FDA LETTER Requesting information regarding the Informed Consent submitted with the treatment protocol.			Other
66,279	RAD 001C	05/06/2008	This correspondence to the FDA is to re-submit the trade name Afinitor for trademark review in light of the upcoming NDA submission in the treatment of patients with advanced renal cell carcinoma. (PS)	600		General Correspondence
66,279	RAD 001C	05/06/2008	Email to FDA regarding the submission of the updated tradename review.			Other
66,279	RAD 001C	05/05/2008	Email to FDA informing them of Novartis' response to their comments on treatment protocol CRA001L2401 (FDA Faxes dated 23 and 29 April 2008). Also includes a copy of the draft protocol amendment.			Other
66,279	RAD 001C	05/01/2008	PHHO2008DE03857; follow-up (PS)	597		Safety Report
66,279	RAD 001C	05/01/2008	Email to FDA informing them that Novartis has submitted the request for SPA for study CRAD001M2302. Also providing the FDA with the names of three 3treating physicians of angiomyolipoma patients.			Other
66,279	RAD 001C	05/01/2008	Request for special protocol assessment for study CRAD001M2302. (PS)	598		Other
66,279	RAD 001C	04/30/2008	PHEH2000US08591;Follow-Up (PS)	595		Safety Report
66,279	RAD 001C	04/30/2008	PHHO2008US04833; follow-up (PS)	596		Safety Report
66,279	RAD 001C	04/29/2008	New protocol CRAD001N2201 entitled: 'An open-label, single-arm phase II study of RAD001 in patients with refractory mantle cell lymphoma". (PS)	592		New Protocol
66,279	RAD 001C	04/29/2008	PHHO2008CA04926;Follow-Up (PS)	593		Safety Report
66,279	RAD 001C	04/29/2008	PHHO2008JP04055;Follow-Up (PS)	594		Safety Report
66,279	RAD 001C	04/29/2008	Fax FDA LETTER Requesting additional information on the treatment protocol submitted on March 26, 2008.			Other

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	04/28/2008	PHHO2008US04833; Follow-Up (PS)	591		Safety Report
66,279	RAD 001C	04/25/2008	PHHO2007IT19720; Follow-Up (PS)	590		Safety Report
66,279	RAD 001C	04/24/2008	Fax FDA LETTER Requesting additional clinical information on the treatment protocol submitted March 26, 2008.			Other
66,279	RAD 001C	04/23/2008	PHHO2008US01900; follow-up (PS)	589		Safety Report
66,279	RAD 001C	04/23/2008	Fax to FDA responding to their April 17, 2008 request for additional CMC information.			Response to FDA Request
66,279	RAD 001C	04/22/2008	PHHO2008US04833 (PS)	587		Safety Report
66,279	RAD 001C	04/22/2008	PHHO2008US04735 (PS)	586		Safety Report
66,279	RAD 001C	04/22/2008	Amendment No. 3 to protocol CRAD001J2101. (PS)	588		Change In Protocol
66,279	RAD 001C	04/22/2008	Email to FDA containing the new draft WR template for the PPSR submitted on August 13, 2007, serial number 379.			Other
66,279	RAD 001C	04/21/2008	PHHO2008IT01481; follow-up (PS)	585		Safety Report
66,279	RAD 001C	04/18/2008	PHHO2008DE03857; follow-up (PS)	584		Safety Report
66,279	RAD 001C	04/17/2008	Fax FDA LETTER Requesting additional CMC information on the treatment protocol submitted March 26, 2008.			Other
66,279	RAD 001C	04/15/2008	PHHO2008JP04055 (PS)	583		Safety Report
66,279	RAD 001C	04/15/2008	HA meeting minutes of the April 3, 2008 Pre-NDA meeting between Novartis and the FDA to discuss the planned NDA for RAD011 for metastatic renal cell carcinoma (mRCC) and advanced pancreatic neuroendocrine tumors (pNET).			FDA/Novartis Meeting Minu
66,279	RAD 001C	04/14/2008	Email to FDA containing the e-mail trail on the topic Special Protocol Assessment (SPA) for clinical study protocol CRAD001M2301 entitled 'A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with Tuberous Sclerosis Complex (TSC), and for clinical study protocol CRAD001M2302 'A randomized, double-blind, placebo-controlled study of RAD0001 in the treatment of Angiomyolipomata in patients with either			Other
66,279	RAD 001C	04/14/2008	At this time Novartis is providing a CMC information amendment to provide updated information, manufacturing sites, stability programs and other CMC changes to the drug product. (PS)	582		CMC Amendment
66,279	RAD 001C	04/11/2008	PHHO2007FR18497; follow-up (PS)	581		Safety Report
66,279	RAD 001C	04/08/2008	PHHO2008IT01481; follow-up (PS)	580		Safety Report
66,279	RAD 001C	04/07/2008	FDA and Novartis email correspondence. Novartis has submitted request for SPA on April 7, 20008; relevant to protocol CRAD001M2301. Cover letter of this submission is appended (PS)			Other
66,279	RAD 001C	04/07/2008	Protocol CRAD001M2301 request for SPA. (PS)	579		Other
66,279	RAD 001C	04/04/2008	Email correspondence to FDA regarding Pre-NDA meeting for RAD001 and providing electronic copies of the handouts which we brought to the meeting: the background slides to Novartis' follow- up questions, and the draft Table of Contents of the RAD001 eCTD (PS)			Other
66,279	RAD 001C	04/04/2008	PHHO2008DE03857; follow-up (PS)	578		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	04/02/2008	FDA email with appended responses and comments, in preparation for Pre-NDA meeting of April, 3 2008 (PS)			Other
66,279	RAD 001C	04/02/2008	Email between FDA and Novartis related to outstanding CMC and Clinical questions and comments pertaining to discussion set for Pre-NDA meeting on April 3, 2008 (PS)			Other
66,279	RAD 001C	04/02/2008	FDA email providing a list of attendees for Pre-NDA meeting (PS)			Other
66,279	RAD 001C	03/31/2008	Email to FDA containing an updated list of Novartis participants for the Pre-NDA meeting scheduled on April 3, 2008.			Other
66,279	RAD 001C	03/31/2008	Email from FDA regarding the revised FDA template letter and containing an updated PPSR template.			Other
66,279	RAD 001C	03/28/2008	Email to FDA containing the revised FDA template letter, with regard to the PPSR.			Other
66,279	RAD 001C	03/28/2008	PHHO2008DE03857 (PS)	577		Safety Report
66,279	RAD 001C	03/27/2008	PHhO2008US01990; follow-up (PS)	576		Safety Report
66,279	RAD 001C	03/26/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Eileen O'Reilly, M.D. (PS)	571		Other
66,279	RAD 001C	03/26/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Chong-Xian Pan, MD, PhD. (PS)	572		Other
66,279	RAD 001C	03/26/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Matthew I. Milowsky, MD. (PS)	573		Other
66,279	RAD 001C	03/26/2008	New protocol CRAD001L2401 entitled: "An open-label, multi-center, expanded access study of RAD001 in patients with metastatic carcinoma of the kidney who have progressed despite vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy". (PS)	574		New Protocol
66,279	RAD 001C	03/26/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Jochen H. Lorch, M.D., M.S. (PS)	575		Other
66,279	RAD 001C	03/25/2008	PHHO2007NO19319 follow-up (PS)	570		Safety Report
66,279	RAD 001C	03/25/2008	PHHO2007US21124 follow-up (PS)	569		Safety Report
66,279	RAD 001C	03/25/2008	Email to FDA responding to their request for an electronic copy of the request for trade name review, which was submitted on September 24, 2007.			Response to FDA Request
66,279	RAD 001C	03/21/2008	Novartis Pharmaceticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) for treatment use in a single patient that will be filed by Dr. Shawn Glisson. (PS)	568		Other

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	03/20/2008	PHHO2007US20563; follow-up (PS)	566		Safety Report
66,279	RAD 001C	03/20/2008	New investigator to study CRAD001C2242 and CRAD001C2325. New investigators to study CRAD001C2324. (PS)	567		New Investigator
66,279	RAD 001C	03/20/2008	Email to FDA regarding the submission of a treatment protocol intended to allow for expanded access to RAD001 for the treatment of patients with metastatic renal cell carcinoma (mRCC) who have progressed despite VEGFr TKI therapy.			Other
66,279	RAD 001C	03/19/2008	Email to/from the FDA regarding the establishment of the secure e-mail.			Other
66,279	RAD 001C	03/18/2008	Email to FDA containing the cover letter for the Pre-NDA briefing book and the the briefing book amendment.			Other
66,279	RAD 001C	03/17/2008	PHHO2007US21124;Follow-Up (PS)	565		Safety Report
66,279	RAD 001C	03/13/2008	Email to the FDA containing an electronic copy of the amendment to the Pre-NDA Briefing book that was submitted on March 13, 2008.			Briefing Book
66,279	RAD 001C	03/13/2008	Email to the FDA containing questions regarding the pending PPSR and pending pre-market evaulation of trademark.			Other
66,279	RAD 001C	03/13/2008	This correspondence to the FDA contains an amendment to the Pre-NDA briefing book for the April 3, 2008 Pre-NDA meeting. (PS)	564		General Correspondence
66,279	RAD 001C	03/12/2008	PHHO2008AU01363 (PS)	563		Safety Report
66,279	RAD 001C	03/12/2008	Email to the FDA containing the Pre-NDA questions and cover letter, as well as the list of Novartis attendees for the meeting scheduled April 3, 2008.			Other
66,279	RAD 001C	03/12/2008	Email to FDA regarding the planned SPAs for SEGa and AML studies.			Other
66,279	RAD 001C	03/10/2008	Email to/from the FDA regarding the planned SPA for SEGA and AML studies and the delay until in submission.			Other
66,279	RAD 001C	03/07/2008	PHHO2007US21124; follow-up (PS)	561		Safety Report
66,279	RAD 001C	03/07/2008	PHHO2007NO19319; follow-up (PS)	562		Safety Report
66,279	RAD 001C	03/05/2008	Briefing book for Pre-NDA meeting scheduled for April 3, 2008. (PS)	560		Briefing Book
66,279	RAD 001C	03/05/2008	Email to FDA informing them that the Pre-NDA briefing book was submitted on March 3, 2008.			Other
66,279	RAD 001C	03/04/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Jennifer Chan, MD. (PS)	559		Other
66,279	RAD 001C	03/03/2008	PHHO2008AR00668 (PS)	558		Safety Report
66,279	RAD 001C	02/28/2008	PHHO2008US02416 (PS)	556		Safety Report
66,279	RAD 001C	02/28/2008	PHHO2008IT01481; follow-up (PS)	557		Safety Report
66,279	RAD 001C	02/27/2008	PHHO2007IT19720; follow-up (PS)	554		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	02/26/2008	Amendment No. 2 and 3 to protocol CRAD001C2111. (PS)	553		Change In Protocol
66,279	RAD 001C	02/25/2008	PHHO2007FR13915; follow-up (PS)	552		Safety Report
66,279	RAD 001C	02/20/2008	PHHO2007NO19319; follow-up (PS)	548		Safety Report
66,279	RAD 001C	02/20/2008	PHHO2007IT19720; follow-up (PS)	549		Safety Report
66,279	RAD 001C	02/20/2008	PHHO2007FR14001; follow-up (PS)	550		Safety Report
66,279	RAD 001C	02/19/2008	PHHO2008FR02098 (PS)	545		Safety Report
66,279	RAD 001C	02/19/2008	PHHO2007FR14620; follow-up (PS)	546		Safety Report
66,279	RAD 001C	02/15/2008	Novartis is herewith providing the Statistical Analysis Plan for protocol CRAD001C2239 prior to data base lock. (PS)	544		Other
66,279	RAD 001C	02/14/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Sunil Sharma, MD. (PS)	542		Other
66,279	RAD 001C	02/14/2008	PHHO2008US01900 (PS)	543		Safety Report
66,279	RAD 001C	02/13/2008	Amendment No. 1 and 2 to protocol CRad001J2101. (PS)	540		Change In Protocol
66,279	RAD 001C	02/13/2008	Amendment No. 1 and 2 to protocol CRAD001C2116. (PS)	541		Change In Protocol
66,279	RAD 001C	02/12/2008	PHHO2008IT01481 (PS)	538		Safety Report
66,279	RAD 001C	02/12/2008	New investigators to study CRAD001C2324. (PS)	539		New Investigator
66,279	RAD 001C	02/08/2008	PHHO2007FR17369; follow-up (PS)	536		Safety Report
66,279	RAD 001C	02/08/2008	PHHO2007JP19109; follow-up (PS)	537		Safety Report
66,279	RAD 001C	02/08/2008	Email to FDA informing them of Novartis' intent to submit SPAs for SEGA and AML studies.			General Correspondence
66,279	RAD 001C	02/07/2008	PHHO2007FR14001; follow-up (PS)	534		Safety Report
66,279	RAD 001C	02/07/2008	PHHO2007FR13915 (PS)	535		Safety Report
66,279	RAD 001C	02/06/2008	PHHO2007IT19720; follow-up (PS)	533		Safety Report
66,279	RAD 001C	02/06/2008	Email from/to the FDA regarding the Pre-NDA meeting request submitted on January 30, 2008.			Other
66,279	RAD 001C	02/05/2008	PHBS2007BE07399; follow-up (PS)	532		Safety Report
66,279	RAD 001C	01/31/2008	PHHO2007FR18943; Follow-Up (PS)	529		Safety Report
66,279	RAD 001C	01/31/2008	PHHO2007NO19319; Follow-Up (PS)	528		Safety Report
66,279	RAD 001C	01/28/2008	PHHO2007FR18943; follow-up (PS)	524		Safety Report
66,279	RAD 001C	01/28/2008	PHHO2007FR20512; follow-up (PS)	525		Safety Report
66,279	RAD 001C	01/28/2008	PHHO2007FR18940; follow-up (PS)	526		Safety Report
66,279	RAD 001C	01/25/2008	PHHO2007NO19319; follow-up (PS)	523		Safety Report
66,279	RAD 001C	01/23/2008	PHHO2007DE20351;Follow-Up (PS)	520		Safety Report
66,279	RAD 001C	01/23/2008	PHHO2007IT19720 (PS)	521		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	01/22/2008	PHHO2007FR11090; follow-up (PS)	518		Safety Report
66,279	RAD 001C	01/22/2008	PHHO2007FR12501; follow-up (PS)	519		Safety Report
66,279	RAD 001C	01/21/2008	PHHO2007US17617;Follow-Up (PS)	517		Safety Report
66,279	RAD 001C	01/16/2008	PHHO2007US20875;Follow-Up (PS)	516		Safety Report
66,279	RAD 001C	01/15/2008	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Svetomir Markovic, MD, Ph.D. (PS)	515		Other
66,279	RAD 001C	01/09/2008	New investigator to study CRAD001C2324 and new investigator to study CRAD001C2325. (PS)	514		New Investigator
66,279	RAD 001C	01/04/2008	PHHO2007JP17929;Follow-Up (PS)	513		Safety Report
66,279	RAD 001C	01/04/2008	PHHO2007US21124;Follow-Up (PS)	512		Safety Report
66,279	RAD 001C	01/02/2008	PHHO2007FR18943;Follow-Up (PS)	510		Safety Report
66,279	RAD 001C	01/02/2008	PHHO2007JP19109;Follow-Up (PS)	508		Safety Report
66,279	RAD 001C	01/02/2008	PHHO2007FR11090;Follow-Up (PS)	511		Safety Report
66,279	RAD 001C	12/27/2007	PHHO2007US20563;Follow-Up (PS)	507		Safety Report
66,279	RAD 001C	12/27/2007	PHHO2007FR19560;Follow-Up (PS)	506		Safety Report
66,279	RAD 001C	12/24/2007	PHHO2007DE20351;Follow-Up (PS)	504		Safety Report
66,279	RAD 001C	12/24/2007	PHHO2007FR20512; Follow-Up (PS)	503		Safety Report
66,279	RAD 001C	12/24/2007	PHHO2007US13764;Follow-Up (PS)	505		Safety Report
66,279	RAD 001C	12/20/2007	This clinical information amendment contains updated Investigator's Brochure, Edition 6, which replaces Edition 5. (PS)	502		Clinical Information Amendr
66,279	RAD 001C	12/20/2007	PHHO2007FR19560;Follow-up (PS)	500		Safety Report
66,279	RAD 001C	12/20/2007	PHHO2007DE20052;Follow-Up (PS)	501		Safety Report
66,279	RAD 001C	12/18/2007	PHHO2007FR18943; follow-up (PS)	496		Safety Report
66,279	RAD 001C	12/18/2007	PHHO2007CA19062 (PS)	497		Safety Report
66,279	RAD 001C	12/18/2007	PHHO2007DE20052 (PS)	499		Safety Report
66,279	RAD 001C	12/18/2007	New investigator to study CRAD001C2324, CRAD001C2325, CRAD001C2410. (PS)	498		New Investigator
66,279	RAD 001C	12/17/2007	PHHO2007US06570 (PS)	495		Safety Report
66,279	RAD 001C	12/13/2007	PHHO2007US17944; follow-up (PS)	493		Safety Report
66,279	RAD 001C	12/13/2007	PHHO2007JP19109; follow-up (PS)	494		Safety Report
66,279	RAD 001C	12/12/2007	PHBS2007TR02235;Follow-Up (PS)	492		Safety Report
66,279	RAD 001C	12/11/2007	PHHO2007FR19043; Follow-Up (PS)	490		Safety Report
66,279	RAD 001C	12/11/2007	PHHO2007JP17929;Follow-Up (PS)	491		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	12/10/2007	PHHO2007FR19560 (PS)	488		Safety Report
66,279	RAD 001C	12/10/2007	PHHO2007FR18940 (PS)	487		Safety Report
66,279	RAD 001C	12/10/2007	Amendment No. 1 to protocol CRAD001C2241. (PS)	489		Change In Protocol
66,279	RAD 001C	12/07/2007	PHHO2007FR17914; follow-up (PS)	485		Safety Report
66,279	RAD 001C	12/07/2007	This correspondence to the FDA is to inform them that Dr. Myra Herrle has changed her responsibilities and that, effective immediately, Sibylle Jennings will be the Regulatory Affairs contact for this IND, specifically for the request for orphan drug designation for RAD001 (everolimus) for the treatment of renal carcinoma submitted October 8, 2007, Reference No. 07-2511, and for the request of orphan designation for RAD001 (everolimus) for treatment of patients with gastroenteropancreatic	486		General Correspondence
66,279	RAD 001C	12/06/2007	PHHO2007FR18497; follow-up (PS)	480		Safety Report
66,279	RAD 001C	12/06/2007	PHHO2007NO19319 (PS)	481		Safety Report
66,279	RAD 001C	12/06/2007	PHHO2007JP17929; follow-up (PS)	482		Safety Report
66,279	RAD 001C	12/06/2007	PHHO2007FR11090; follow-up (PS)	483		Safety Report
66,279	RAD 001C	12/06/2007	New investigators to study CRAD001C2242, CRAD001C2324 and CRAD001C2325. (PS)	484		New Investigator
66,279	RAD 001C	12/05/2007	PHHO2007CA19062; follow-up (PS)	477		Response to FDA Request
66,279	RAD 001C	12/05/2007	PHHO2000NO08769 (PS)	478		Safety Report
66,279	RAD 001C	12/05/2007	PHHO2007FR18943 (PS)	479		Safety Report
66,279	RAD 001C	12/04/2007	PHHO2007JP19109 (PS)	475		Safety Report
66,279	RAD 001C	12/04/2007	This correspondence to the FDA is to inform them that Dr. Myra Herrle has transferred responsibilities for this IND to Sibylle Jennings effective immediately. (PS)	476		General Correspondence
66,279	RAD 001C	11/30/2007	New investigators to Study CRAD001C2242 and new investigator to Study CRAD001C2325. (PS)	473		New Investigator
66,279	RAD 001C	11/30/2007	PHHO2007TW16075 (PS)	472		Safety Report
66,279	RAD 001C	11/30/2007	PHHO2007CA19062 (PS)	471		
66,279	RAD 001C	11/30/2007	New investigator to study CRAD001C2101 and new investigators to study CRAD001C2242. (PS)	474		New Investigator
66,279	RAD 001C	11/29/2007	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by John W. Sweetenham, MD. (PS)	469		Other
66,279	RAD 001C	11/29/2007	PHHO2006US22078; follow-up (PS)	470		Safety Report
66,279	RAD 001C	11/28/2007	PHHO2007FR17369; follow-up (PS)	466		Safety Report
66,279	RAD 001C	11/28/2007	PHHO2007US17617; follow-up (PS)	467		Safety Report
66,279	RAD 001C	11/28/2007	PHHO2007FR19043 (PS)	468		Safety Report
66,279	RAD 001C	11/27/2007	PHHO2007CA19062 (PS)	465		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	11/21/2007	PHHO2007FR17914; follow-up (PS)	461		Safety Report
66,279	RAD 001C	11/21/2007	PHHO2007FR18497 (PS)	462		Safety Report
66,279	RAD 001C	11/21/2007	PHHO2007FR11090 (PS)	463		Safety Report
66,279	RAD 001C	11/21/2007	Please note that this serial number is a request for Orphan drug designation and was issued Orphan number 072541 by the FDA and therefore can be located in REDI under this number not IND 66,279 as originally submitted.	464		Other
66,279	RAD 001C	11/20/2007	PHHO2007FR03202; follow-up (PS)	460		Safety Report
66,279	RAD 001C	11/15/2007	PHHO2007ES08365; follow-up (PS)	459		Safety Report
66,279	RAD 001C	11/12/2007	PHHO2007JP17793; follow-up (PS)	458		Safety Report
66,279	RAD 001C	11/09/2007	PHHO2007FR17914 (PS)	454		Safety Report
66,279	RAD 001C	11/09/2007	PHHO2007JP17929 (PS)	455		Safety Report
66,279	RAD 001C	11/09/2007	New investigator to study CRAD001J2101. (PS)	457		New Investigator
66,279	RAD 001C	11/09/2007	New investigators to Study CRAD001C2242. (PS)	456		New Investigator
66,279	RAD 001C	11/08/2007	PHHO2007AU14332; follow-up (PS)	452		Safety Report
66,279	RAD 001C	11/08/2007	PHHO2007US17944 (PS)	453		Safety Report
66,279	RAD 001C	11/07/2007	PHHO2007CA15784; follow-up (PS)	451		Safety Report
66,279	RAD 001C	11/05/2007	PHHO2007US17617 (PS)	449		Safety Report
66,279	RAD 001C	11/05/2007	PHHO2007ES08365; follow-up (PS)	450		Safety Report
66,279	RAD 001C	11/02/2007	PHHO2007US12809; follow-up (PS)	448		Safety Report
66,279	RAD 001C	11/01/2007	PHHO2007SE15401; follow-up (PS)	447		Safety Report
66,279	RAD 001C	10/30/2007	PHHO2007FR17369 (PS)	445		Safety Report
66,279	RAD 001C	10/30/2007	PHHO2007JP17793 (PS)	446		Safety Report
66,279	RAD 001C	10/24/2007	PHHO2007FR03202 FOLLOW-UP (PS)	442		Safety Report
66,279	RAD 001C	10/24/2007	PHHO2007CA17142 (PS)	443		Safety Report
66,279	RAD 001C	10/18/2007	PHHO2007FR03202 folow-up (PS)	440		Safety Report
66,279	RAD 001C	10/18/2007	New investigators to Study CRAD001C2325. (PS)	441		New Investigator
66,279	RAD 001C	10/18/2007	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by John D. Hainsworth. (PS)	439		Other
66,279	RAD 001C	10/17/2007	PHHO2007US13977;Follow-Up (PS)	438		Safety Report
66,279	RAD 001C	10/16/2007	PHHO2007US12809; Follow-Up (PS)	437		Safety Report
66,279	RAD 001C	10/15/2007	PHHO2007CA15784; follow-up (PS)	436		Safety Report
66,279	RAD 001C	10/12/2007	PHHO2007US16146 (PS)	434		Safety Report
66,279	RAD 001C	10/12/2007	PHHO2007FR0302; follow-up (PS)	435		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	10/10/2007	PHHO2007FR03202; follow-up (PS)	433		Safety Report
66,279	RAD 001C	10/09/2007	PHHO2007DE15860 (PS)	432		Safety Report
66,279	RAD 001C	10/08/2007	PHHO2007US13977 (PS)	431		Safety Report
66,279	RAD 001C	10/08/2007	PHHO2007US15872; follow-up (PS)	430		Safety Report
66,279	RAD 001C	10/05/2007	PHHO2007US13764;Follow-Up (PS)	429		Safety Report
66,279	RAD 001C	10/04/2007	PHHO2007CA15784;Follow-Up (PS)	428		Safety Report
66,279	RAD 001C	10/04/2007	PHHO2007US15872;Follow-Up (PS)	427		Safety Report
66,279	RAD 001C	10/03/2007	PHHO2007US12809 (PS)	426		Safety Report
66,279	RAD 001C	10/02/2007	Email to FDA containing the draft slides for the EoP2 meeting to discuss development in TSC (SEGA + AML).			Other
66,279	RAD 001C	10/02/2007	Novartis meeting minutes on October 2, 2007. Type EOP2 meeting, to discuss proposed trials for TSC and sponsor's questions. (PS)			FDA/Novartis Meeting Minu
66,279	RAD 001C	09/28/2007	PHHO2004BE07879; follow-up (PS)	423		Safety Report
66,279	RAD 001C	09/28/2007	Amendment No. 4 to protocol CRAD001C2111 (PS)			Change In Protocol
66,279	RAD 001C	09/28/2007	This correspondence to the FDA is to correct the IND number listed on box 6 of the 1571. (PS)	425		General Correspondence
66,279	RAD 001C	09/27/2007	PHHO2007FR03202; follow-up (PS)	422		Safety Report
66,279	RAD 001C	09/26/2007	Email to FDA containing a word document of questions posed in the briefing book.			Other
66,279	RAD 001C	09/26/2007	Email to FDA containing the revised FDA template letter.			Other
66,279	RAD 001C	09/25/2007	Email to FDA containing the documentation sent to the FDA requesting Tradename Review for RAD001.			Other
66,279	RAD 001C	09/25/2007	PHHO2007AU14332; follow-up (PS)	419		Safety Report
66,279	RAD 001C	09/25/2007	PHHO2007SE15401 (PS)	420		Safety Report
66,279	RAD 001C	09/25/2007	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Mary-Ellen Taplin, MD (PS)	421		Other
66,279	RAD 001C	09/24/2007	At this time, Novartis is submitting documentation to the Oncology Division in support of the current strategy of two brand names for the active ingredient everolimus for the transplant and oncology indications. Novartis is hereby requesting pre-market evaluation of the trademark AFINITOR. (PS)	418		General Correspondence
66,279	RAD 001C	09/21/2007	PHHO2007AU14332 (PS)	417		Safety Report
66,279	RAD 001C	09/20/2007	PHHO2007US07788; follow-up (PS)	415		Safety Report
66,279	RAD 001C	09/20/2007	PHHO2007AU11574; follow-up (PS)	416		Safety Report
66,279	RAD 001C	09/19/2007	PHHO2007ES08365; follow-up (PS)	414		Safety Report
66,279	RAD 001C	09/18/2007	PHHO2007FR14001; follow-up (PS)	412		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	09/18/2007	PHHO2007FR14620 (PS)	413		Safety Report
66,279	RAD 001C	09/17/2007	Email from FDA containing the FDA letter informing Novartis of the FDA's formal written request.			Other
66,279	RAD 001C	09/14/2007	New investigators to Study CRAD001C2242, CRAD001C2325 and new investigator to Study CRAD001C2324. (PS)	411		New Investigator
66,279	RAD 001C	09/13/2007	PHHO2004BE07879; follow-up (PS)	410		Safety Report
66,279	RAD 001C	09/12/2007	Email to/from the FDA regarding the due date for the PPSR.			Other
66,279	RAD 001C	09/11/2007	PHHO2007FR14001; follow-up (PS)	409		Safety Report
66,279	RAD 001C	09/10/2007	PHHO2004US12965; follow-up (PS)	408		Safety Report
66,279	RAD 001C	09/10/2007	FDA LETTER responding to serial number 368, SPA submitted on July 26, 2007.			Other
66,279	RAD 001C	09/07/2007	PHHO2004BE07879; follow-up (PS)	407		Safety Report
66,279	RAD 001C	09/06/2007	PHHO2007BE13048; follow-up (PS)	401		Safety Report
66,279	RAD 001C	09/06/2007	PHHO2007BE12170; follow-up (PS)	402		Safety Report
66,279	RAD 001C	09/06/2007	Novartis Pharmaceuticals Corporation,hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Vassiliki Papadimitrakopoulou. (PS)	406		Other
66,279	RAD 001C	09/06/2007	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Suleiman Alfred Massarweh (PS)	403		Other
66,279	RAD 001C	09/06/2007	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Shanthi Marur, MD. (PS)	404		Other
66,279	RAD 001C	09/06/2007	Novartis Pharmaceuticals Corporation hereby authorizes the 'Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Bo Lu, MD, Ph.D. (PS)	405		Safety Report
66,279	RAD 001C	09/05/2007	PHHO2007FR14001 (PS)	400		
66,279	RAD 001C	08/31/2007	PHHO2007US11543;Follow-Up (PS)	399		Safety Report
66,279	RAD 001C	08/30/2007	PHHO2004BE07879;Follow-Up (PS)	398		Safety Report
66,279	RAD 001C	08/28/2007	PHHO2007FR10519;Follow-Up (PS)	397		Safety Report
66,279	RAD 001C	08/27/2007	PHHO2007US11397;Follow-Up (PS)	396		Safety Report
66,279	RAD 001C	08/23/2007	PHHO2007BE13048;Follow-Up (PS)	394		Safety Report
66,279	RAD 001C	08/23/2007	PHHO2007FR10519;Follow-Up (PS)	393		Safety Report
66,279	RAD 001C	08/21/2007	PHHO2007FR09520;Follow-Up (PS)	391		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	08/21/2007	This correspondence to the FDA is to submit the December 22, 2006 letter and amendment 1 of the protocol CRAD001C2325. (PS)	392		General Correspondence
66,279	RAD 001C	08/20/2007	Email from FDA approving the compassionate use request.			Other
66,279	RAD 001C	08/20/2007	PHHO2007BE12170;Follow-Up (PS)	388		Safety Report
66,279	RAD 001C	08/17/2007	PHHO2007BE13048;Follow-Up (PS)	386		Safety Report
66,279	RAD 001C	08/17/2007	PHHO2007AU11574;Follow-Up (PS)	387		Safety Report
66,279	RAD 001C	08/16/2007	PHHO2007FR12501;Follow-Up (PS)	384		Safety Report
66,279	RAD 001C	08/15/2007	PHHO2007US09880;Follow-Up(PS)	383		Safety Report
66,279	RAD 001C	08/15/2007	PHHO2007IT12077;Follow-Up (PS)	381		Safety Report
66,279	RAD 001C	08/15/2007	PHHO2007FR10519;Follow-Up (PS)	382		Safety Report
66,279	RAD 001C	08/14/2007	Attached please find a copy of documentation sent via email to Ms. Dottie Pease on August 13, 2007 in support of a. request for Compassionate Use of RAD001 (in combination with bevacizumab) for a single patient diagnosed with advanced carcinoid cancer in November 2006. The patient in question, is being treated by Seth Cohen, MD at Monmouth Medical Center in Long Branch, NJ. (PS)	380		General Correspondence
66,279	RAD 001C	08/13/2007	Proposed Pediatric Study Request submitted for the treatment of patients with refractory brain and musculoskeletal cancers (PS)	379		Other
66,279	RAD 001C	08/10/2007	PHHO2007FR12501;Follow-Up (PS)	377		Safety Report
66,279	RAD 001C	08/10/2007	PHHO2004BE07879;Follow-Up (PS)	378		Safety Report
66,279	RAD 001C	08/07/2007	PHHO2007BE12170;Follow-Up (PS)	376		Safety Report
66,279	RAD 001C	08/06/2007	New investigators to Study CRAD001C2241 and CRAD001C2325 and new investigator to Study CRAD001C2242 and CRAD001C2116 (PS)	375		New Investigator
66,279	RAD 001C	08/03/2007	PHHO2007FR09520;Follow-Up (PS)	374		Safety Report
66,279	RAD 001C	08/02/2007	Email to the FDA responding to their request for a word document detailing the original questions asked of FDA with CRAD001C2325 SPA.			Other
66,279	RAD 001C	08/02/2007	PHHO2007US11543;Follow-Up (PS)	373		Safety Report
66,279	RAD 001C	08/01/2007	PHHO2007FR03202;Follow-Up (PS)	372		Safety Report
66,279	RAD 001C	08/01/2007	Email from/to the FDA regarding the electronic version of the IRC.			Other
66,279	RAD 001C	07/31/2007	PHHO2007PL06777; follow-up (PS)	370		Safety Report
66,279	RAD 001C	07/31/2007	PHHO2007IT12077 (PS)	371		Safety Report
66,279	RAD 001C	07/31/2007	PHHO2007US04089; follow-up (PS)	369		Safety Report
66,279	RAD 001C	07/30/2007	Email to/from the FDA regarding the FDA request for additional information on the PPSR.			Response to FDA Request
66,279	RAD 001C	07/27/2007	Email to/from the FDA regarding serial number 368, SPA submitted on July 26, 2007.			Other

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	07/26/2007	PHHO2007US07788; follow-up (PS)	366		Safety Report
66,279	RAD 001C	07/26/2007	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Sandy Srinivas, MD (PS)	367		Other
66,279	RAD 001C	07/26/2007	Amendment No. 2 to SPA, Protocol CRAD001C2325 (PS)	368		Change In Protocol
66,279	RAD 001C	07/25/2007	FDA LETTER Informing Novartis that the FDA is unable to issue a written request based on the February 19, 2007, Pediatric study request			Other
66,279	RAD 001C	07/24/2007	PHHO2007US07788 (PS)	365		Safety Report
66,279	RAD 001C	07/24/2007	PHHO2007US11543 (PS)	364		Safety Report
66,279	RAD 001C	07/23/2007	This correspondence to the FDA is regarding the written request and as to whether or not the FDA has any information as to the status of the PPSR. (PS)	363		General Correspondence
66,279	RAD 001C	07/20/2007	PHHO2007US11397; follow-up (PS)	362		Safety Report
66,279	RAD 001C	07/17/2007	Email to FDA regarding the meeting package for the August 14, 2007 meeting.			Other
66,279	RAD 001C	07/17/2007	Resubmission of protocol CRAD001C2324 for Special Protocol Assessment (PS)	361		Other
66,279	RAD 001C	07/17/2007	PHHO2007US11397 (PS)	360		Safety Report
66,279	RAD 001C	07/16/2007	Briefing book for Type B meeting which is scheduled for August 14, 2007 to discuss the plan for development and registration (sNDA) of RAD001 in patients with subependymal giant cell astrocytomas (SEGA) and angiomyolipoma (AML) associated with either tuberous sclerosis complex (TSC) or sporadic lymphangioleiomyomatosis (LAM). (PS)	359		Briefing Book
66,279	RAD 001C	07/11/2007	Email to/from the FDA regarding the May 31, 2007 meeting request.			Request for FDA Meeting
66,279	RAD 001C	07/11/2007	PHRM2007FR01778 (PS)	358		Safety Report
66,279	RAD 001C	07/09/2007	PHHO2007ES08365;Follow-Up (PS)	356		Safety Report
66,279	RAD 001C	07/09/2007	PHHO2007PL06777;Follow-Up (PS)	357		Safety Report
66,279	RAD 001C	07/03/2007	New protocol CRAD001C2118 entitled: "A blinded, randomized, placebo and active controlled, single-dose crossover study to investigate the effect of RAD001 on cardiac intervals in healthy volunteers" (PS)	353		New Protocol
66,279	RAD 001C	07/03/2007	New investigator to Study CRAD001C211, CRAD001C2241, CRAD001C2325 and CRAD001J2101 (PS)	354		New Investigator
66,279	RAD 001C	07/03/2007	PHHO2005US14500. (PS)	355		Safety Report
66,279	RAD 001C	06/25/2007	PHHO2007US09880;Follow-Up (PS)	352		Safety Report
66,279	RAD 001C	06/21/2007	PHHO2007PL06777;Follow-Up (PS)	351		Safety Report
66,279	RAD 001C	06/21/2007	PHHO2007FR07389;Follow-Up (PS)	350		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	06/20/2007	Email from/to FDA containing Novartis' draft questions and concept protocol to help facilitate the FDA's review of Novartis' meeting request.			Other
66,279	RAD 001C	06/19/2007	PHBS2007BE07399;Follow-Up (PS)	348		Safety Report
66,279	RAD 001C	06/13/2007	TELECON with FDA to discuss the email received on June 12, 2007 from Dottie Pease.			Memo of Record (telephone report)
66,279	RAD 001C	06/13/2007	PHHO2007FR07389;Follow-Up (PS)	347		Safety Report
66,279	RAD 001C	06/12/2007	Email from FDA regarding the meeting request submitted on May 31, 2007.			Other
66,279	RAD 001C	06/08/2007	FDA LETTER Responses to serial number 320, for a special clinical protocol assessment submitted on April 30, 2007.			Other
66,279	RAD 001C	06/07/2007	PHHO2006US22078;Follow-Up (PS)	346		Safety Report
66,279	RAD 001C	06/06/2007	PHHO2007PL06777; Follow-Up (PS)	345		Safety Report
66,279	RAD 001C	06/06/2007	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Scott K. Kuwada, MD (PS)	343		Other
66,279	RAD 001C	06/06/2007	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by James C. Yao, MD (PS)	344		Other
66,279	RAD 001C	06/05/2007	PHHO2006US22078; Follow-Up (PS)	341		Safety Report
66,279	RAD 001C	06/05/2007	PHBS2007BE07399;Follow-Up (PS)	342		Safety Report
66,279	RAD 001C	06/04/2007	New investigator to Study CRAD001C2240 and new investigators to Study CRAD001C2325 (PS)	340		New Investigator
66,279	RAD 001C	05/31/2007	Novartis hereby is formally requesting a Type B meeting with the Division of Oncology Drug Products to discuss the development plan and registration strategy for RAD001 (everolimus) in Tuberous Sclerosis Complex (TSC) and sporadic lymphangioleiomyomatosis (LAM). (PS)	339		Request for FDA Meeting
66,279	RAD 001C	05/30/2007	Email from FDA containing the FDA responses to Novartis' questions for the SPA meeting scheduled for June 7, 2007			Other
66,279	RAD 001C	05/30/2007	Email to FDA confirming that Novartis would still like to have the scheduled meeting on June 7, 2007			Other
66,279	RAD 001C	05/30/2007	PHHO2007ES08365;Follow-up (PS)	338		Safety Report
66,279	RAD 001C	05/25/2007	PHHO2007PL06777;Follow-up (PS)	337		Safety Report
66,279	RAD 001C	05/24/2007	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Ravi D Rao, M.B.B.S (PS)	335		Other
66,279	RAD 001C	05/24/2007	New investigator to Study CRAD001C2114 and CRAD001C2116 and new investigators to Study CRAD001C2242 and CRAD001C2325 (PS)	336		New Investigator

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	05/23/2007	Email to FDA responding to their request for a completed template summarizing information from PPSR submitted to FDA on Feb 15, 2007.			Response to FDA Request
66,279	RAD 001C	05/23/2007	PHBS2007BE07399; Follow-up (PS)	334		Safety Report
66,279	RAD 001C	05/22/2007	PHHO2007PL06777; follow-up (PS)	333		Safety Report
66,279	RAD 001C	05/21/2007	Novartis Pharmaceuticals Corporation hereby authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Jann N. Sarkaria, M.D. (PS)	332		Other
66,279	RAD 001C	05/18/2007	PHHO2007FR07389; Follow-up (PS)	331		Safety Report
66,279	RAD 001C	05/18/2007	PHRM2007FR01407;Follow-up (PS)	330		Safety Report
66,279	RAD 001C	05/18/2007	PHBS2007BE07399;Follow-up (PS)	329		Safety Report
66,279	RAD 001C	05/16/2007	PHHO2006US11747; follow-up (PS)	328		Safety Report
66,279	RAD 001C	05/15/2007	PHBS2007BE07399 (PS)	327		Safety Report
66,279	RAD 001C	05/15/2007	New investigators to Study CRAD001C2116, CRAD001J2101, CRAD001C2240 and CRAD001C2325 (PS)	326		New Investigator
66,279	RAD 001C	05/09/2007	PHHO2007FR07389 (PS)	325		Safety Report
66,279	RAD 001C	05/08/2007	Email to FDA containing the questions for the June 7, 2007 meeting.			Other
66,279	RAD 001C	05/08/2007	Email to FDA regarding the EOP2 meeting request and briefing book (ES)			Request for FDA Meeting
66,279	RAD 001C	05/08/2007	PHHO2007DE07018 (PS)	323		Safety Report
66,279	RAD 001C	05/08/2007	Briefing book for Type A meeting which is scheduled for June 7, 2007 (PS)	324		Briefing Book
66,279	RAD 001C	05/03/2007	PHHO2007PL06777 (PS)	322		Safety Report
66,279	RAD 001C	05/02/2007	New investigator to Study CRAD001C2325 (PS)	321		New Investigator
66,279	RAD 001C	04/27/2007	Request for Special Protocol Assessment for study CRAD001C2324 (PS)	320		Other
66,279	RAD 001C	04/23/2007	PHHO2007DE03665; follow-up (PS)	319		Safety Report
66,279	RAD 001C	04/20/2007	Email from FDA with a tentative meeting date for April 16, 2007 meeting request.			Other
66,279	RAD 001C	04/20/2007	New investigator to Study CRAD001C2239 and CRAD001C2325. New investigators to Study CRAD001C2240 and CRAD001C2241 (PS)	318		New Investigator
66,279	RAD 001C	04/18/2007	Email from FDA informing Novartis that the submission does not qualify for an SPA since the study has already started.			Other
66,279	RAD 001C	04/16/2007	Email to the FDA regarding the dates of the FDA letters received containing their feedback on the SPA for CRAD001C2240.			Other
66,279	RAD 001C	04/16/2007	Request for Type A meeting to discuss the Special Protocol Assessment Clinical Protocol CRAD001C2239 (PS)	317		Request for FDA Meeting

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	04/13/2007	New protocol CRaD001C2410 entitled: "A Pilot Multicenter Phase I/II Trial of RAD001 in patients with Recurrent Glioblastoma Multiforme" (PS)	316		New Protocol
66,279	RAD 001C	04/11/2007	PHHO2007US00556; follow-up (PS)	315		Safety Report
66,279	RAD 001C	04/09/2007	Novartis Pharmaceuticals Corporation authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Walter Stadler, MD (PS)	314		General Correspondence
66,279	RAD 001C	04/09/2007	General correspondence to the FDA to provide clarity around recent communications that have a significant impact on Novartis' development planning while continuing to work within the regulatory framework of 21 CFR 312 (PS)			General Correspondence
66,279	RAD 001C	04/03/2007	PHHO2007US4089; follow-up (PS)	313		Safety Report
66,279	RAD 001C	03/30/2007	Email response to FDA's request for an electronic copy of the final signed version of the Independent Radiological Review Charter for Protocol CRAD001C2240 which incorporates the FDA's feedback received via fax on December 7, 2006.			Response to FDA Request
66,279	RAD 001C	03/30/2007	Email to FDA regarding the final signed IRC for CRAD001C2240.			Response to FDA Request
66,279	RAD 001C	03/30/2007	PHHO2007US05182 (PS)	312		Safety Report
66,279	RAD 001C	03/27/2007	PHHO2006US20476;Follow-up (PS)	311		Safety Report
66,279	RAD 001C	03/26/2007	Study CRAD001C2239, CRAD001C2240 new investigators and Study CRAD001C2241 New investigator (PS)	310		New Investigator
66,279	RAD 001C	03/19/2007	New investigators to Study CRAD001C2240 and new investigator to Study CRAD001C2325 (PS)	309		New Investigator
66,279	RAD 001C	03/15/2007	PHHO2007US04089; follow-up (PS)	307		Safety Report
66,279	RAD 001C	03/15/2007	PHHO2007CA02219; follow-up (PS)	308		Safety Report
66,279	RAD 001C	03/14/2007	PHHO2007US04215 (PS)	306		Safety Report
66,279	RAD 001C	03/13/2007	PHHO2007US04089 (PS)	305		Safety Report
66,279	RAD 001C	03/12/2007	FDA LETTER Comments on the December 20, 2006, serial number 267 SPA and January 25, 2007, serial number 280 amendment.			Other
66,279	RAD 001C	03/08/2007	Amendment No. 1 to SPA Protocol CRAD001C2240 (PS)	304		Change In Protocol
66,279	RAD 001C	03/08/2007	New investigator to Study CRAD001C2239 and CRAD001C2240. New investigators to Study CRAD001C2325 (PS)	303		New Investigator
66,279	RAD 001C	03/07/2007	PHHO2007DE03665 (PS)	302		Safety Report
66,279	RAD 001C	02/28/2007	PHHO2008FR02098; follow-up (PS)	555		Safety Report
66,279	RAD 001C	02/26/2007	Novartis Pharmaceuticals Corporation authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Dr, Ana Maria Gonzalez-Angulo, M.D. (PS)	298		Other

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	02/26/2007	Novartis Pharmaceuticals Corporation authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Bert O'Neil , M.D. (PS)	299		Other
66,279	RAD 001C	02/26/2007	Novartis Pharmaceuticals Corporation authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Srdan Verstovsek, M,D., Ph.D. (PS)	300		Other
66,279	RAD 001C	02/26/2007	Novartis Pharmaceuticals Corporation authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Johanna Bendell, M.D. (PS)	301		Other
66,279	RAD 001C	02/22/2007	FDA LETTER Responses to the November 6, 2006, serial number 252, request for SPA.			Other
66,279	RAD 001C	02/22/2007	PHHO2007CA02219; follow-up (PS)	296		Safety Report
66,279	RAD 001C	02/22/2007	This Annual report covers the period December 25, 2005 through December 24, 2006 (PS)	297		Annual Report
66,279	RAD 001C	02/20/2007	Email from FDA responding to Novartis' question regarding the PPSR being submitted.			Other
66,279	RAD 001C	02/19/2007	Proposed Pediatric Study Request submiited for the treatment of refractory cancers in a pediatric population (ages 3-16) (Protocol No. CRAD001C2244) (PS)	294		Other
66,279	RAD 001C	02/19/2007	New investigators to Study CRAD001C2114, CRAD001C2240 and CRAD001C2241 (PS)	295		New Investigator
66,279	RAD 001C	02/19/2007	This annual report covers the period November 27, 2006 through November 26, 2007. (PS)	547		Annual Report
66,279	RAD 001C	02/15/2007	PHBS2006AT07989; follow-up (PS)	293		Safety Report
66,279	RAD 001C	02/13/2007	At this time, Novartis is submitting an IND amendment to provide updated information on the manufacturing sites, stability programs, and other CMC changes. The summary of changes and the updated IND sections are included in this submission (PS)	292		CMC Amendment
66,279	RAD 001C	02/09/2007	PHHO2007CA02219; follow-up (PS)	290		Safety Report
66,279	RAD 001C	02/09/2007	New Protocol RAD001C2242 entitled: "An open-label, multicenter Phase 1 study investigating the combination of RAD001, cetuximab and irinotecan as second-line therapy after FOLFOX (or XELOX) plus bevacinunab (if given as part of local standard practice) in patients with metastatic colorectal adenocarcinoma" (PS)	291		New Protocol
66,279	RAD 001C	02/08/2007	Novartis Pharmaceuticals Corporation authorizes FDA to refer to IND 66279 for RAD001 (everolimus) in support of an Investigational New Drug Application (IND) that will be filed by Dr. Mark Stein (PS)	289		Other
66,279	RAD 001C	02/08/2007	PHHO2007CA02219; follow-up (PS)	288		Safety Report
66,279	RAD 001C	02/07/2007	PHHO2007CA02219 (PS)	287		Safety Report
66,279	RAD 001C	02/06/2007	Novartis Pharmaceuticals Corporation authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Daniel George, MD (PS)	285		Other

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	02/06/2007	Novartis Pharmaceuticals Corporation authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Jorae A. Ciarcia. MD (PS)	286		Other
66,279	RAD 001C	02/05/2007	New investigators to Study CRAD001C2239 and CRAD001C2240 (PS)	284		New Investigator
66,279	RAD 001C	02/01/2007	PHHO2004BE07879; follow-up (PS)	283		Safety Report
66,279	RAD 001C	01/29/2007	This submissions contains copies of the materials sent on January 25, 2007, serial number 280 (PS)	282		General Correspondence
66,279	RAD 001C	01/26/2007	Email to FDA informing them that the materials sent via email have been sent directly to them instead of the central document room.			Response to FDA Request
66,279	RAD 001C	01/26/2007	PHHO2006US22076; follow-up (PS)	281		Safety Report
66,279	RAD 001C	01/25/2007	PHHO2007US00556; follow-up (PS)	279		Safety Report
66,279	RAD 001C	01/19/2007	PHHO2006US22076 (PS)	278		Safety Report
66,279	RAD 001C	01/18/2007	New investigator/Sub investigator to Study CRAD001C2111 (PS)	276		New Investigator
66,279	RAD 001C	01/18/2007	PHHO2007US00556 (PS)	277		Safety Report
66,279	RAD 001C	01/17/2007	Email to FDA informing them of the upcoming Novartis FDA CRADA meeting.			Other
66,279	RAD 001C	01/16/2007	Email from FDA replying to the meeting cancellation of the January 18, 2007 Type A meeting.			Other
66,279	RAD 001C	01/16/2007	New investigator to Study CRAD001C2239 and CRAD001C2325. New investigators to Study CRAD001C2240 (PS)	275		New Investigator
66,279	RAD 001C	01/09/2007	This correspondence is to provide the FDA with Novartis' questions for the Type A meeting which is scheduled for January 18, 2007 (ES)			General Correspondence
66,279	RAD 001C	01/03/2007	Email to FDA containing serial number 274, an addendum to the briefing book (ES)			General Correspondence
66,279	RAD 001C	01/03/2007	The addendum the the briefing book contains simulation data which is highly relevant to the planned discussions and the conclusions are supportive of the Novartis position as stated in the protocol. Please note that this submission in REDI only contains the cover letter and 1571, as this is all we received for archiving). (PS)	274		Other
66,279	RAD 001C	01/01/2007	Email from FDA responding to Novartis' questions regarding the FDA information request for the simulation methods.			Other
66,279	RAD 001C	12/28/2006	PHHO2006FR20729; Follow-up	273		Safety Report
66,279	RAD 001C	12/22/2006	Email from FDA with responses to Novartis' questions regarding protocol CRAD001C2325			Other
66,279	RAD 001C	12/22/2006	PHHO2005DE16006; Follow-Up	272		Safety Report
66,279	RAD 001C	12/21/2006	New investigator to Study CRAD001C2239 and CRAD001C2241, new investigators to Study CRAD001C2240 (PS)	271		New Investigator
66,279	RAD 001C	12/21/2006	PHHO2006FR20729; Follow-up	270		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	12/21/2006	PHBS2006ES19190; Follow-Up	269		Safety Report
66,279	RAD 001C	12/21/2006	PHBS2006ES19166; Follow-Up	268		Safety Report
66,279	RAD 001C	12/20/2006	Amendment No. 2 to Protocol CRAD001C2239 (PS)	267		Change In Protocol
66,279	RAD 001C	12/18/2006	PHHO2006FR20566; Follow-Up	266		Safety Report
66,279	RAD 001C	12/18/2006	PHHO2006IT15311; Follow-Up	265		Safety Report
66,279	RAD 001C	12/13/2006	Novartis Pharmaceuticals Corporation authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Gabriela Chiorean, MD (PS)	264		Other
66,279	RAD 001C	12/12/2006	In response to FDA request the email contains the questions q posed in BB submitted with SPA for CRAD001C2325 (RAD001 in Carcinoid IND66,279) on Nov 6, 2006 (Serial 252) (ES)			Response to FDA Request
66,279	RAD 001C	12/12/2006	PHHO2006US17466; follow-up (PS)	263		Safety Report
66,279	RAD 001C	12/12/2006	New investigator to Study CRAD001C2111, CRAD001C2239, and new investigators to CRAD001C2241 (PS)	262		New Investigator
66,279	RAD 001C	12/08/2006	PHHO2006IT15311; follow-up (PS)	260		Safety Report
66,279	RAD 001C	12/08/2006	This correspondence is to inform the FDA of the transfer of specific obligations to a contract research organization for clinical drug supply management of selected sites in protocol CRAD001C2240 (PS)	261		General Correspondence
66,279	RAD 001C	12/07/2006	New investigators to Study CRAD001C2239 (PS)	259		New Investigator
66,279	RAD 001C	12/07/2006	Fax from FDA containing the Medical imaging responses to serial number 249.			Other
66,279	RAD 001C	12/06/2006	PHHO2006US11747; follow-up (PS)	258		Safety Report
66,279	RAD 001C	11/21/2006	Email from FDA confirming the postponement of the November 27, 2006teleconference to January 18, 2007.			Other
66,279	RAD 001C	11/16/2006	Email response to the FDA request for a copy of the draft IRC charter for CRAD001C2239 protocol.			Response to FDA Request
66,279	RAD 001C	11/15/2006	Amendment No. 1 to Protocol RAD001C2235 (PS)	257		Change In Protocol
66,279	RAD 001C	11/09/2006	PHHO2004US12965; follow-up (PS)	256		Safety Report
66,279	RAD 001C	11/07/2006	This submission contains RAD001C Investigator's Brochure Edition 5 (PS)	253		Clinical Information Amendr
66,279	RAD 001C	11/07/2006	New investigator to Study CRAD001C2206 (PS)	254		New Investigator
66,279	RAD 001C	11/07/2006	PHHO2006US17466; Follow-Up (PS)	255		Safety Report
66,279	RAD 001C	11/06/2006	Request for special protocol assessment for Study CRAD001C2325 (PS)	252		Other
66,279	RAD 001C	10/31/2006	PHHO2006US17466 (PS)	251		Safety Report
66,279	RAD 001C	10/24/2006	Briefing Book is being submitted in preparation for the Type A meeting to gain clarification on FDA's responses , provide clarification on Novartis position and ensure agreement on any additional modifications which may be required to allow for a positive agency determination regarding protocol CRAD001C2240 and allow the study to proceed (PS)	249		Briefing Book

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	10/24/2006	PHBS2006ES15520; follow-up (PS)	250		Safety Report
66,279	RAD 001C	10/23/2006	Email responding to FDA that Novartis acknowledges receipt of the e-mail and the proposed date of the meeting for November 27th 2PM.			Other
66,279	RAD 001C	10/23/2006	Email to FDA regarding the number of copies needed of the briefing book and the meeting date of November 10, 2006 for the Type A meeting.			Other
66,279	RAD 001C	10/23/2006	PHHO2006US11747; follow-up (PS)	248		Safety Report
66,279	RAD 001C	10/23/2006	Novartis Pharmaceuticals Corporation authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Andrew X. Zhu, MD, PhD (PS)	247		Other
66,279	RAD 001C	10/20/2006	Email response to the FDA request for an electronic copy of the Type A meeting request.			Request for FDA Meeting
66,279	RAD 001C	10/17/2006	PHBS2006S15520; Follow-up (PS)	246		Safety Report
66,279	RAD 001C	10/13/2006	Novartis Pharmaceuticals Corporation authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Barbara Burtness, MD (PS)	245		Other
66,279	RAD 001C	10/09/2006	Type A meeting request to gain further clarification on the responses received by the FDA, particularly for questions 3, 7 and 11. More specifically Novartis wishes to identify any additional modifications to the proposed pivotal study, analysis plan and independent radiological review charter necessary to adequately meet the requirements for a regulatory submission of phase III protocol CRAD001C2240 data in support of approval of RAD001 for the treatment of patients with metastatic renal cell carcinomas who have	244		Request for FDA Meeting
66,279	RAD 001C	10/06/2006	PHHO2006IT15311 (PS)	243		Safety Report
66,279	RAD 001C	10/03/2006	New investigator to Study No. RAD001C2239 (PS)	241		New Investigator
66,279	RAD 001C	10/03/2006	PHHO2006IT15311 (PS)	242		Safety Report
66,279	RAD 001C	09/29/2006	PHHO2006IT09039; Follow Up (PS)	240		Safety Report
66,279	RAD 001C	09/27/2006	Addressing issues raised per September 26, 2006 phone call noting discrepancies between information Novartis submitted and the FDA website so that Entry 506-0814195-3 can be released. (PS)			Other
66,279	RAD 001C	09/25/2006	New investigator to Study No. RAD001C2206 and new investigators to Study No. RAD001C2239 (PS)	239		New Investigator
66,279	RAD 001C	09/19/2006	New Protocol RAD001J2101 entitled: "A phase Ib study investigating the combination of AD001 with trastuzumab and paclitaxel in patients with HER2-overexpressing metastatic breast cancer" (PS)	238		New Protocol
66,279	RAD 001C	09/15/2006	FDA LETTER response to SPA for CRAD001C2240 (PS)			Other
66,279	RAD 001C	09/13/2006	New Protocol RAD001C2114 entitled, "A two-step phase 1 study investigating the combination of RAD001 with carboplatin, paclitaxel and bevacizumab in non-small-cell lung cancer (NSCLC) patients not treated previously with systemic therapy (PS)	236		New Protocol

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	09/13/2006	New Protocol RAD001C2116 entitled: " A phase Ib study investigating the combination of RAD001 with cisplatin and etoposide in patients with extensive-stage small-cell lung cancer not previously treated with chemotherapy" (PS)	237		New Protocol
66,279	RAD 001C	09/07/2006	TELECON with FDA on September 7, 2006 to discuss the request for ane e-copy of the CRAD001C2240 SPA and the timelines for FDA review/response of Oncology PPSR (PS)			Memo of Record (telephone report)
66,279	RAD 001C	09/07/2006	Email regarding the request from FDA for an electronic copy fo the SPA for protocol CRAD001C2240 (PS)			Response to FDA Request
66,279	RAD 001C	08/31/2006	PHHO2006US02640; follow-up (PS)	234		Safety Report
66,279	RAD 001C	08/31/2006	Novartis Pharmaceuticals Corporation hereby authorizes the FDA to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by John D. Hainsworth, M.D. (PS)	235		Other
66,279	RAD 001C	08/29/2006	New investigator to Study No. CRAD001C2206 (PS)	233		New Investigator
66,279	RAD 001C	08/23/2006	Email response to FDA request for TOC and and electronic copy of the 11 protocol specific questions listed in section 5 of the briefing book submitted on July 28, 2006 (PS)			Response to FDA Request
66,279	RAD 001C	08/22/2006	New Protocol, RAD001C2241 entitled, "A single arm, multicenter phase II study of RAD001 in patients with metastatic colorectal adenocarcinoma whose cancer has progressed despite prior therapy with an anti- EGFR antibody (if appropriate), bevacizumab, fluoropyrimidine, oxaliplatin, and irinotecan- based regimens (PS)	231		New Protocol
66,279	RAD 001C	08/18/2006	PHHO2006BE00473; follow-up (PS)	228		Safety Report
66,279	RAD 001C	08/18/2006	PHHO2006DE09301; follow-up (PS)	229		Safety Report
66,279	RAD 001C	08/18/2006	PHHO2006US11747; follow-up (PS)	230		Safety Report
66,279	RAD 001C	08/17/2006	PHHO2006US11747; follow-up (PS)	227		Safety Report
66,279	RAD 001C	08/16/2006	PHHO2006BE00473 (PS)	226		Safety Report
66,279	RAD 001C	08/15/2006	PHHO2006US11747 (PS)	225		Safety Report
66,279	RAD 001C	08/04/2006	New investigator to Study CRAD001C2239 (PS)	224		New Investigator
66,279	RAD 001C	07/28/2006	Request for special protocol assessment for Study CRAD001C2240 (PS)	223		Other
66,279	RAD 001C	07/28/2006	PHHO2006DE09652; follow-up (PS)	222		Safety Report
66,279	RAD 001C	07/27/2006	Amendment No. 2 to Protocol CRAD001JC2222 (PS)	221		Change In Protocol
66,279	RAD 001C	07/26/2006	PHHO2006CA03486; follow-up (PS)	220		Safety Report
66,279	RAD 001C	07/25/2006	PHHO2006DE09859; follow-up (PS)	219		Safety Report
66,279	RAD 001C	07/21/2006	Documentation FDA position: Pediatric Exclusivity requirements NDA submission for active moiety.			Other
66,279	RAD 001C	07/21/2006	PHHO2006DE09652; follow-up (PS)	218		Safety Report
66,279	RAD 001C	07/20/2006	PHHO2006DE09652; follow-up (PS)	215		Safety Report
66,279	RAD 001C	07/20/2006	PHHO2006IT09039; follow-up (PS)	216		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	07/20/2006	PHHO2006DE09301; Follow Up (PS)	217		Safety Report
66,279	RAD 001C	07/19/2006	PHHO2006DE09652; follow-up (PS)	214		Safety Report
66,279	RAD 001C	07/17/2006	PHHO2006IT09039; follow-up (PS)	213		Safety Report
66,279	RAD 001C	07/11/2006	At the request of the principal investigator for the study, Novartis Pharmaceuticals Corporation is hereby amending this letter to reflect a change in principal investigator for the study. Novartis authorizes the Food and Drug Administration to refer to IND 66,279 RAD001 (everolimus) Tablets in support of an Investigational New Drug Application (IND) that will be filed by Alice Elizabeth Guardino, M.D., Ph.D. (PS)	212		Other
66,279	RAD 001C	07/07/2006	FDA LETTER (email) FDA Response to questions on briefing book for Type A Meeting scheduled for July 11,2006 (CRAD001C2239 SPA follow-up).	203		Other
66,279	RAD 001C	07/07/2006	PHHO2006DE09652 Follow Up	210		Safety Report
66,279	RAD 001C	07/07/2006	Referencing General Correspondence letter of Authorization SN156. Novartis is amending this letter to reflect a change in address and study title.			Safety Report
66,279	RAD 001C	07/05/2006	PHBS2006AT07989 Follow Up	209		Safety Report
66,279	RAD 001C	06/27/2006	PHBS2006AT07989 Follow up	206		Safety Report
66,279	RAD 001C	06/27/2006	PHHO2006DE09859 Follow Up	207		Safety Report
66,279	RAD 001C	06/27/2006	PHNU2006DE02164 (PS)	208		Safety Report
66,279	RAD 001C	06/22/2006	Referencing General Correspondence Letter of Authorization SN 157. Novartis Pharmaceutical Corporation is hereby amending this letter.			General Correspondence
66,279	RAD 001C	06/21/2006	PHHO2006DE09301 Follow Up	204		Safety Report
66,279	RAD 001C	06/20/2006	Type A meeting briefing book to support the discussion for a special protocol assessment for CRAD001C2239 submitted on April 3, 2006 (Serial No. 183). (PS)	203		Briefing Book
66,279	RAD 001C	06/19/2006	Referencing an authorization to the FDA by Novartis to refer to IND 66,279 RAD001.			General Correspondence
66,279	RAD 001C	06/19/2006	Referencing an authorization to the FDA by Novartis to refer to IND 66,279 RAD001.			General Correspondence
66,279	RAD 001C	06/16/2006	PHHO2006IT09039 Follow Up	200		Safety Report
66,279	RAD 001C	06/16/2006	Email responding to the FDA request for the questions which will be presented in the briefing document for the FDA Type A meeting scheduled for July 11, 2006.			Other
66,279	RAD 001C	06/14/2006	PHHO2006IT07069 Follow Up	198		Safety Report
66,279	RAD 001C	06/13/2006	7 Day Safety Report PHHO2006IT09039 (PS)			Safety Report
66,279	RAD 001C	06/05/2006	Request for Type A Meeting to gain clarification on responses and modifications to the analysis regarding treatment with RAD001 alone or in combination with Sandostatin for patients with NET, who failed treatment with cytotoxic chemotherapy			Request for FDA Meeting

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	06/02/2006	Reference is made to IND 66,279 Annual Report for RAD001 dated February 24, 2006 regarding the clinical review reported to the FDA for a Phase II Study of RAD001C			Response to FDA Request
66,279	RAD 001C	05/30/2006	Protocol C2111 Amendment 1 and Protocol C2206 Amendment 5. (PS)	195		Change In Protocol
66,279	RAD 001C	05/23/2006	PHBS2006ES06880 Follow Up	194		Safety Report
66,279	RAD 001C	05/19/2006	PHHO2006IT07069 Follow Up	193		Safety Report
66,279	RAD 001C	05/19/2006	FDA LETTER responding to the April 3, 2006, serial number 182, request for SPA.			Other
66,279	RAD 001C	05/18/2006	Referencing General Correspondence Letter of Authorization SN 158. Novartis is amending the letter for the purpose of reflecting changes in the protocol title.			General Correspondence
66,279	RAD 001C	05/18/2006	Email to FDA following receipt of their responses, accepting the option of canceling the scheduled face-to-face meeting.			Request for FDA Meeting
66,279	RAD 001C	05/17/2006	Email from FDA with their responses to Novartis' questions for the EOP 1-2 meeting.			Other
66,279	RAD 001C	05/11/2006	PHHO2006IT07069 Follow Up	191		Safety Report
66,279	RAD 001C	05/01/2006	Amendment No. 1 to Protocol 2222.	190		Change In Protocol
66,279	RAD 001C	04/21/2006	Email response to FDA request for a summary document outlining the requested information for the pivotal and supportive trials to be submitted for approval of RAD001.			Response to FDA Request
66,279	RAD 001C	04/13/2006	Amendment to Letter of Authorization, dated November 22, 2005 (SN153) in support of an IND that will be filed by Gerber Wulf, MD, PhD.	188		General Correspondence
66,279	RAD 001C	04/13/2006	Study 2235 update to new investigator address	189		New Investigator
66,279	RAD 001C	04/12/2006	Submitted 14 desk copies of the briefing book and appendices in anticipation of a possible meeting on May 20 or June 12, 2006 to discuss the development plan and registration strategy for RAD001 (everolimus) in advanced metastatic renal cancer.	187		Request for FDA Meeting
66,279	RAD 001C	04/10/2006	PHHO2005FR20026	186		Safety Report
66,279	RAD 001C	04/07/2006	Request for Type B meeting to discuss the development plan and registration strategy for RAD001 in advanced metastatic renal cancer.	185		Request for FDA Meeting
66,279	RAD 001C	04/07/2006	Email to FDA responding to request for a word document with the list of questions submitted in the briefing book for the SPA for protocol CRAD001C2239.			Other
66,279	RAD 001C	04/05/2006	PHHO2005US06739	184		Safety Report
66,279	RAD 001C	04/04/2006	Email to FDA responding to their request for desk copies of the SPA as well as the indication.			Response to FDA Request
66,279	RAD 001C	04/03/2006	Request for Special Protocol Assessment for CRAD001C2239.	183	2239	Other
66,279	RAD 001C	03/15/2006	PHNR2006AU00570	182		Safety Report
66,279	RAD 001C	03/15/2006	PHNR2006AU00570 Follow Up			Safety Report
66,279	RAD 001C	03/14/2006	PHHO2005US19658	181		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	03/14/2006	PHHO2005US19658 Follow Up			Safety Report
66,279	RAD 001C	03/08/2006	PHHO2006CA03486	180		Safety Report
66,279	RAD 001C	03/08/2006	PHHO2006CA03486 Follow Up			Safety Report
66,279	RAD 001C	02/27/2006	This submission addresses FDA concerns regarding a number of adverse events associated with a clinical study of RAD001C in patients with renal cancer, which were submitted by Dr. Amato under private IND 71,586.	179		General Correspondence
66,279	RAD 001C	02/24/2006	This Annual Report covers the period December 25, 2004 throughNovember 25, 2005. Includes clinical study information, abstract of published papers on RAD001 (Oncology) and Appendix 1.	178		Annual Report
66,279	RAD 001C	02/23/2006	Dr. George Demetri: Malignant neoplasm progression, ascites, cholelithiasis, pleural effusion, dyspnoea; Follow-up#1.	177	2206	Safety Report
66,279	RAD 001C	02/06/2006	[FRANCE] Dr. Jean-Charles Soria: Mental disorder, back pain, delusional disorder, persecutory type, myalgia; Follow-up#2.	176	2235	Safety Report
66,279	RAD 001C	02/01/2006	[FRANCE] Dr. Jacques Dantal: Respiratory tract infection, lung disorder, fluid overload; Follow-up#1.	175	2420	Safety Report
66,279	RAD 001C	01/24/2006	[FRANCE] Dr. Jacques Dantal: Lung disorder.	174	2420	Safety Report
66,279	RAD 001C	01/18/2006	The current submission provides response to questions raised by FDA and includes detailed data from protocol 2206, which were identified as critical to resolve the clinical hold deficiencies for Dr. Ryan's IND 73,986.	173	2206	Response to Clinical Hold
66,279	RAD 001C	01/18/2006	[FRANCE] Dr. Jean-Charles Soria: Back pain, mental disorder, delusional disorder, persecutory type, myalgia; Follow-up#1.	172	2235	Safety Report
66,279	RAD 001C	01/18/2006	This submission provides response to questions raised by FDA and includes detailed data from protocol 2206, which were identified as critical to resolve the clinical hold deficiencies for Dr. Ryan's IND 73,986.	173		Response to Clinical Hold
66,279	RAD 001C	01/11/2006	Dr. Howard Sher: Muscular weakness, myopathy steroid, hydrocephalus, cognitive deterioration, general physical health deterioration, mood altered, depression, cardiovascular disorder, fall; Follow-up#2.	171	2408	Safety Report
66,279	RAD 001C	01/10/2006	E-MAIL from FDA containing response to NVS questions for discussion during January 12, 2006 meeting.			Other
66,279	RAD 001C	01/03/2006	[BELGIUM] Dr. Van Oosterom: Gastritis haemorrhagic, right ventricular failure, pulmonary hypertension, anaemia, haematochezia, general physical health deterioration; Follow-up#1.	170	2206	Safety Report
66,279	RAD 001C	12/30/2005	[FRANCE] Dr. Jean-Charles Soria: Back pain, mental disorder, delusional disorder, persecutory type, myalgia.	169	C2235	Safety Report
66,279	RAD 001C	12/23/2005	Michelle Roos: Hyponatraemia, vomiting, diarrhoea, viral infection, dehydration.	168	AUS15	Safety Report
66,279	RAD 001C	12/22/2005	Dr. Howard Sher: Muscular weakness, myopathy steroid, hydrocephalus, fall; Follow-up#1.	167	2408	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	12/21/2005	NVS acknowledges receipt of FDA response dated July 7. 2005 to Special Protocol Assessment requested for CRAD001C2223, which was submitted to FDA on May 11, 2005, and hereby requests additional information on statistical procedures outlined in the protocol.	166		General Correspondence
66,279	RAD 001C	12/20/2005	Dr. Alex Adjei: Pulmonary embolism, malignant neoplasm progression, chest pain, dyspnoea, respiratory failure, productive cough; Follow-up#2.	165	US15	Safety Report
66,279	RAD 001C	12/19/2005	Dr. Howard Sher: Muscular weakness, fall.	163	2408	Safety Report
66,279	RAD 001C	12/19/2005	This submission provides the Edition 4 of the Investigators' Brochure, which replaces Edition 3, dated 30-Aug-2004. Also included is the summary of changes, outlining the updates incorporated in Edition 4.	164		Clinical Information Amendr
66,279	RAD 001C	12/16/2005	Novartis is amending the Letter of Authorization submitted to the Agency on November 22, 2005, SN 151, in support of an IND that will be filed by Charles A. Coltman, Jr., MD.	162		General Correspondence
66,279	RAD 001C	12/06/2005	This submission provides the briefing book and appendices, including cited references, for the January 12, 2006 meeting to discuss the development plan and registration strategy for RAD001 in carcinoid tumors and pancreatic neuroendocrine tumors. Three copies were forward to the Division of Oncology, as well as fourteen desk copies.	161		General Correspondence Response to FDA Request
66,279	RAD 001C	12/06/2005	E-MAIL detailing questions presented in briefing document for the FDA meeting scheduled for January 12, 2006.			Other
66,279	RAD 001C	12/02/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Tiffany Svahn, MD.	160		General Correspondence
66,279	RAD 001C	12/02/2005	This letter authorizes FDA to refer to this IND in support of IND that will be filed by Robert. J. Motzer, MD.	159		General Correspondence
66,279	RAD 001C	12/02/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Jonathan Rosenberg, MD.	158		General Correspondence
66,279	RAD 001C	12/02/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Chandra Belani, MD.	157		General Correspondence
66,279	RAD 001C	12/02/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Robert Figlin, MD.	156		General Correspondence
66,279	RAD 001C	12/02/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by John. D. Hainsworth, MD.	155		General Correspondence
66,279	RAD 001C	11/22/2005	Richard Stone: Pneumonitis, nausea, dyspnoea, hypoxia, pleural effusion, performance status decreased, cough, pulmonary fibrosis, fatigue, productive cough, respiratory distress; Follow-up#4.	154	2207	Safety Report
66,279	RAD 001C	11/22/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Lyndsay N. Harris, MD.	153		General Correspondence
66,279	RAD 001C	11/22/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Shirish. M. Gadgeel, MD.	151		General Correspondence
66,279	RAD 001C	11/22/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Philip. J. Gold. MD.	150		General Correspondence
66,279	RAD 001C	11/22/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by John R. Murren. MD.	149		General Correspondence
66,279	RAD 001C	11/22/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Milind Javle. MD.	148		General Correspondence

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	11/22/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Mitchell Gross, MD.	152		General Correspondence
66,279	RAD 001C	11/17/2005	[GERMANY] Prof. Struber: Renal impairment, immunosuppressant drug level increased, blood creatinine increased, drug interaction; Follow-up#1.	146	DE06	Safety Report
66,279	RAD 001C	11/14/2005	Dr. Judith Wolf: Hyponatraemia, condition aggravated, anorexia, nausea, asthenia, muscle spasms, hypotension.	145	2409	Safety Report
66,279	RAD 001C	11/11/2005	Dr. Lauren Abrey: International normalised ratio increased, haematuria, drug interaction; Follow-up#1.	143	C2408	Safety Report
66,279	RAD 001C	11/11/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Christopher Ryan, MD.	144		General Correspondence
66,279	RAD 001C	11/01/2005	New Investigator to Study No. 2222: Dr. Stephen M. Schultz, MD.	142	2222	New Investigator
66,279	RAD 001C	11/01/2005	Dr. Lauren Abrey: International normalised ratio increased, haematuria.	141	C2408	Safety Report
66,279	RAD 001C	10/31/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Francisco J. Esteva, MD.	140		General Correspondence
66,279	RAD 001C	10/31/2005	This letter authorizes FDA to refer to this IND in support of an IND that will bi filed by Lawrence S. Blaszkowsky, MD.	139		Safety Report
66,279	RAD 001C	10/31/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Dr. Deborah Toppmeyer.	138		General Correspondence
66,279	RAD 001C	10/31/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Amanda Psyrri, MD.	137		General Correspondence
66,279	RAD 001C	10/31/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Nooper Raje, MD.	136		General Correspondence
66,279	RAD 001C	10/31/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Leonard B. Saltz, MD.	135		General Correspondence
66,279	RAD 001C	10/31/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Manuel Hidalgo, MD., Ph.D.	134		General Correspondence
66,279	RAD 001C	10/26/2005	E-MAILS to/from FDA requesting a meeting date. FDA scheduled a meeting for January 12, 2006 and requested the background package by December 8, 2005.			Request for FDA Meeting
66,279	RAD 001C	10/17/2005	This correspondence is a request for a Type B meeting with the Division of Oncology Drug Products to discuss the development plan and registration strategy for RAD001 in carcinoid tumors and pancreatic neuroendocrine tumors.	133		Request for FDA Meeting
66,279	RAD 001C	10/14/2005	[GERMANY] Prof. Struber: Renal impairment, drug interaction, immunosuppressant drug level increased, blood creatinine increased.	132	ADE06	Safety Report
66,279	RAD 001C	10/04/2005	Dr. Alex Adjei: Pulmonary embolism, chest pain, dyspnoea, respiratory failure, productive cough; Follow-up#1.	131	AUS15	Safety Report
66,279	RAD 001C	09/28/2005	New Investigator to Study No. 2222: Dr. Hope S. Rugo.	130	2222	New Investigator
66,279	RAD 001C	09/28/2005	Dr. Alex Adjei: Pulmonary embolism, chest pain, dyspnoea, respiratory failure, productive cough.	129	AUS15	Safety Report
66,279	RAD 001C	09/27/2005	This letter authorizes FDA to refer to this IND in support of an IND that will befiled by Mario Sznol, MD.	128		General Correspondence
66,279	RAD 001C	09/27/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Christopher W. Ryan, MD.	127		General Correspondence

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	09/27/2005	New Investigator to Study No. 2222: Dr. Victor Vogel, MD.	126	2222	New Investigator
66,279	RAD 001C	09/26/2005	Richard Stone, MD: Pneumonitis, nausea, dyspnoea, hypoxia, pleural effusion, performance status decreased, cough, pulmonary fibrosis, fatigue, productive cough, respiratory distress; Follow-up#3.	125	2207	Safety Report
66,279	RAD 001C	09/23/2005	Richard Stone. MD: Pneumonia bacterial, diarrhoea, supraventricular tachycardia, hypokalaemia, pleural effusion, hypoxia, dyspnoea, crackles lung, troponin increased; Follow-up#2.	124	2207	Safety Report
66,279	RAD 001C	09/01/2005	TELECON from FDA regarding an authorization letter for an Investigator's IND for Dr. Khuri. NVS had submitted the information to FDA on August 31, 2005 (SNs 121 and 122), however, the letters were not received at this time, therefore, NVS faxed the information to the Division, as per their request.			General Correspondence
66,279	RAD 001C	08/31/2005	This letter authorizes FDA to refere to this IND in support of an IND that will be filed by Fadio Khuri, MD.	122		General Correspondence
66,279	RAD 001C	08/31/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Fadio Khuri, MD.	121		General Correspondence
66,279	RAD 001C	08/31/2005	This Annual Report covers the period December 25, 2003 to December 24, 2004. The addendum provides clarification on the 15-day safety reports submitted (section 1.1.6) during the relevant period.	120		Annual Report
66,279	RAD 001C	08/31/2005	E-MAIL from FDA responding to NVS telephone request regarding dual reporting of safety reports, in which FDA stated that all SAEs for oncology, as well as transplantation, be reported to both Divisions.			Other
66,279	RAD 001C	08/25/2005	Richard Stone MD: Pneumonitis, nausea, drug interaction potentiation, dyspnoea, hypoxia, pleural effusion, performance status decreased, cough, pulmonary fibrosis; Follow-up#2.	119	2207	Safety Report
66,279	RAD 001C	08/19/2005	Amendment No. 4 to Study No. 2206.	117	2206	Change In Protocol
66,279	RAD 001C	08/18/2005	New Investigator to Study No. 2235: Drs. S. Sharma, V. Papadimitrakopulou.	116	2235	New Investigator
66,279	RAD 001C	08/10/2005	Amendment No. 5 to Study No. 2101.	115	2101	Change In Protocol
66,279	RAD 001C	08/09/2005	Dr. Francis Giles: Leukocytoclastic vasculitis, hyperglycaemia, oedema peripheral, calcinosis, pain, erythema, rash, eschar; Follow-up#1	114	2406	Safety Report
66,279	RAD 001C	08/05/2005	[GREAT BRITAIN] Dr. Ian Judson: Gastrointestinal haemorrhage, bone marrow depression, cardiac arrest, malignant neoplasm progression, melaena, vomiting, haemoglobin decreased, platelet count decreased, dyspnoea, abdominal pain, loss of consciousness; Follow-up#5	113	2101	Safety Report
66,279	RAD 001C	08/05/2005	[AUSTRALIA] Dr. Dan Chambers: Vasculitis gastrointestinal, leukocytoclastic vasculitis, dermatitis allergic, neutropenia, white blood cell count decreased, diarrhoea, vomiting, intestinal ischaemia, biopsy intestine abnormal, biopsy colon abnormal, petechiae, biopsy skin abnormal; Follow-up#1	112		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	08/03/2005	[AUSTRALIA] Dr. Dan Chambers: Vasculitis gastrointestinal, leukocytoclastic vasculitis, dermatitis allergic, neutropenia, white blood cell count decreased, diarrhoea, vomiting, intestinal ischaemia, biopsy intestine abnormal, biopsy colon abnormal, petechiae, biopsy skin abnormal.	110		Safety Report
66,279	RAD 001C	08/03/2005	Correspondence responding to FDA feedback dated July 7,2005, regarding the May 11, 2005 Special Protocol Assessment request.	111		General Correspondence
66,279	RAD 001C	08/02/2005	This correspondence informs the FDA that the regulatory responsibilities for this product have been transferred to a new manager.	109		General Correspondence
66,279	RAD 001C	07/26/2005	New Investigator to Study No. 2222: Dr. Rachel A. Borso.	108	2222	New Investigator
66,279	RAD 001C	07/14/2005	Howard Burris. MD: Mental status changes, anaemia; Follow-up#2.	107	2101	Safety Report
66,279	RAD 001C	07/07/2005	FDA LETTER containing responses to questions contained in the May 11, 2005, request for a special protocol assessment.			
66,279	RAD 001C	07/06/2005	Dr. Judith Wolf: Hyperglycaemia.	106	2409	Safety Report
66,279	RAD 001C	07/01/2005	Dr. L. Miller: Cardiac tamponade, anastomotic leak, unresponsive to verbal stimuli, fall, cardiac arrest, accelerated idioventricular rhythm: Follow-up#5	105	2403	Safety Report
66,279	RAD 001C	06/30/2005	[GREAT BRITAIN] Prof. Ian Judson: Cryptogenic organizing pneumonia, lung infiltration, dyspnoea, dyspnoea exertional; Follow-up#2	104	2101	Safety Report
66,279	RAD 001C	06/29/2005	New Investigator to Study No. 2111: Dr. Vali Papadimitrakopoulou.	103	2111	New Investigator
66,279	RAD 001C	06/29/2005	E-mail to FDA regarding SPA status.			
66,279	RAD 001C	06/21/2005	[AUSTRALIA] Dr. Josette Eris: Drug exposure during pregnancy, premature rupture of membranes, normal delivery, hypertension; Follow-up#1.	102	A2307	Safety Report
66,279	RAD 001C	06/17/2005	This amendment contains supportive documentation for two new tablet strengths, 1.25 mg (6001322.001) and 2.5 mg (3747250.004).	100		CMC Amendment
66,279	RAD 001C	06/09/2005	This Letter authorizes FDA to refer to this IND in support of an IND that will be filed by Anjali S. Advani, MD.	099		General Correspondence
66,279	RAD 001C	06/09/2005	Submission of Investigator's Brochure, Edition 3, replacing Edition 2 dated 11-nov-2002.	098		Clinical Information Amendr
66,279	RAD 001C	06/08/2005	Howard Burris, MD: Mental status changes, anaemia; Follow-up#1.	097	C2101	Safety Report
66,279	RAD 001C	06/02/2005	Dr. L. Miller: Cardiac tamponade, Anastomotic leak, unresponsive to verbal stimuli, fall, cardiac arrest, accelerated idioventricular rhythm; Follow-up#4.	096	A2403	Safety Report
66,279	RAD 001C	06/02/2005	[GREAT BRITAIN] Dr. Ian Judson: Gastrointestinal haemorrhage, bone marrow depression, circulatory collapse, cardiac arrest, malignant neoplasm progression, melaena, vomiting, haemoglobin decreased, platelet count decreased, dyspnoea, abdominal pain, loss of consciousness; Follow-up#4.	095	2101	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	06/01/2005	[AUSTRALIA] Dr. Steve Chadban: Drug exposure during pregnancy, cerebral ventricle dilatation, renal disorder, umbilical cord vascular disorder.	094	A2307E1	Safety Report
66,279	RAD 001C	06/01/2005	[AUSTRALIA] Dr. Josette Eris: Drug exposure during pregnancy, premature rupture of membranes, normal delivery, hypertension.	093	A2307	Safety Report
66,279	RAD 001C	05/31/2005	[GREAT BRITAIN] Dr. Ian Judson: Gastrointestinal haemorrhage, bone marrow depression, circulatory collapse, cardiac arrest, malignant neoplasm progression, melaena, vomiting, haemoglobin decreased, platelet count decreased, dyspnoea, abdominal pain, loss of consciousness; Follow-up#3.	092	2101	Safety Report
66,279	RAD 001C	05/31/2005	E-mails to/from FDA regarding SPA questions.			
66,279	RAD 001C	05/26/2005	[SWITZERLAND] Dr. D. Uehlinger: Eye haemorrhage, Retinal detachment, eye operation; Follow-up#1.	091	A2307E1	Safety Report
66,279	RAD 001C	05/16/2005	Dr. L. Miller: Cardiac tamponade, anastomotic leak, unresponsive to verbal stimuli, fall, cardiac arrest, accelerated idioventricular rhythm; follow-up#3	090	2403	Safety Report
66,279	RAD 001C	05/12/2005	Submission of a revised page of the Briefing Book submitted May 11, 2005.	089		General Correspondence
66,279	RAD 001C	05/12/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Dr. Douglas Yee, MD.	088		General Correspondence
66,279	RAD 001C	05/12/2005	Richard Stone, MD: Interstitial lung disease, pneumonitis, nausea, drug interaction potentiation, dyspnoea, hypoxia, pleural effusion, performance ststus decreased, cough, pulmonary fibrosis: Follow-up#1	087	2207	Safety Report
66,279	RAD 001C	05/11/2005	In reference to the End-of-Phase 2 meeting held October 25, 2004, this submissions contains a request for special protocol assessment for Phase 3 study No. C2223.	086		
66,279	RAD 001C	05/11/2005	Richard Stone. MD: Pneumonia, diarrhoea, dyspnoea, hypoxia, pleural effusion, crackles lung; Follow-up#1.	085	2207	Safety Report
66,279	RAD 001C	05/06/2005	[SWITZERLAND] Dr. D. Uehlinger: Eye haemorrhage, retinal detachment, eye operation.	084	A2307	Safety Report
66,279	RAD 001C	05/06/2005	Richard Stone. MD: Pneumonia, hypoxia, diarrhoea, pleural effusion, dyspnoea, crackles lung.	083	2207	Safety Report
66,279	RAD 001C	05/05/2005	Dr. L. Miller: Cardiac tamponade, anastomic leak, unresponsive to verbal stimuli, fall, cardiac arrest, accelerated idioventricular rhythm; Follow-up#2.	082	2403	Safety Report
66,279	RAD 001C	05/04/2005	Richard Stone. MD: Interstitial disease, pneumonitis, nausea, dyspnoea, hypoxia, pleural effusion, performance status decreased, cough, pulmonary fibrosis.	081	2207	Safety Report
66,279	RAD 001C	05/03/2005	Dr. L. Miller: Cardiac tamponade, anastomotic leak, unresponsive to verbal stimuli, fall, cardiac arrest, accelerated idioventricular rhythm; Follow-up#1	080	A2403	Safety Report
66,279	RAD 001C	04/28/2005	Dr. L. Miller: Cardiac tamponade, anastomotic leak, unresponsive to verbal stimuli, fall.	079	A2403	Safety Report
66,279	RAD 001C	04/27/2005	[GREAT BRITAIN] Prof. Ian Judson: Cryptogenic organizing pneumonia, lung infiltration, dyspnoea, dyspnoea exertional; Follow-up#1	078	2101	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	04/26/2005	Dr. Ian Judson: Cardiac arrest, malignant neoplasm progression, circulatory collapse, bone marrow depression, gastrointestinal haemorrhage, haemoglobin decreased, platelet count decreased, dyspnoea, abdominal pain, loss of cinsciousness, vomiting, melaena; Follow-up#2.	077	2101	Safety Report
66,279	RAD 001C	04/25/2005	[GERMANY] Peter Reichardt: Neoplasm progression, tumour haemorrhage, haemoglobin decreased, blood lactate dehydrogenase increased, blood potassium increased, blood uric acid increased, hyperbilirubinaemia, blood creatinine increased; Follow-up#1.	076	2206	Safety Report
66,279	RAD 001C	04/20/2005	E-mail to FDA regarding SPA and list of investigators participating in study 2223.			
66,279	RAD 001C	04/18/2005	[GERMANY] Peter Reichardt: Tumor lysis syndrome, tumour haemorrhage, haemoglobin decreased, blood lactate dehydrogenase increased, blood potassium increased, blood uric acid increased, hyperbilirubinaemia, blood creatinine increased.	075	2206	Safety Report
66,279	RAD 001C	04/11/2005	New Protocol to Study No. 2111 entitled, "A combined phase 1 and 2 study investigating the combination of RAD001 and erlotinib in patients with advanced NSCLC previously treated only with chemotherapy. This trial combines erlotinib (Tarceva), an approved agent for loccaly advanced or metastatic NSCL after failure of at least one prior chemotherapy regimen, with the investigational drug RAD001. The erlotinib tablets used in the studies are supplied by OSIPharmaceuticals. OSI submitted a letter of	074	2111 2235	New Protocol
66,279	RAD 001C	04/08/2005	[GERMANY] Dr. Kaltenhaeuser: Septic shock, peripheral occlusive disease, vasculitis, drug level decreased, skin ulcer, haemoglobin decreased, C-reactive protein increased.	073		Safety Report
66,279	RAD 001C	04/08/2005	James Yao: Hypoglycaemia, feeling abnormal, confusional state.	072	BUS52	Safety Report
66,279	RAD 001C	04/06/2005	Howard A. Burris,III, MD: Epistaxis, platelet count decreased, bleeding time prolonged.	071	2101	Safety Report
66,279	RAD 001C	04/06/2005	[SPAIN] Dr. Tabemero: Malignant neoplasm progression, stomatitis, drug inffective, enterocolitis, abdominal pain, anorexia, vomiting, constipation, skin lesion, metastases to peritoneum, performance status decreased, respiratory disorder, hypoalbuminaemia, generalised oedema.	070	2107	Safety Report
66,279	RAD 001C	04/06/2005	[BELGIUM] Dr. Van Oosterom: Gastritis haemorrhagic, thrombocytopenia, anaemia, nausea, vomiting, melaena.	069	2206	Safety Report
66,279	RAD 001C	04/06/2005	Dr. Meir Wetzler, MD: Cardiac failure congestive, asthma, dyspnoea, oedema peripheral, eyelid oedema, weight increased, dilatation atrial, ventricular hypertrophy.	068	2207	Safety Report
66,279	RAD 001C	04/06/2005	[BELGIUM] Dr. Van Oosterom: Gastritis haemorrhagic, right ventricular failure, pulmonary hypertension, aaemia, haematochezia, general physical health deterioration.	067	2206	Safety Report
66,279	RAD 001C	04/06/2005	E-mails to/from FDA regarding a sample CRF requirement for an SPA.			
66,279	RAD 001C	04/04/2005	TELECON with FDA regarding CIOMS VI safety reporting requirements and investigator notifications.			Memo of Record (telephone report)
66,279	RAD 001C	04/01/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Ingrid Mayer, MD.	066		General Correspondence

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	04/01/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Mary-Ellen Taplin, MD.	065		General Correspondence
66,279	RAD 001C	04/01/2005	E-mail to FDA regarding submission date for SPA for Study 2223.			
66,279	RAD 001C	03/28/2005	This amendment provides for the following dosage forms and or pharmaceutical intermediate: RAD001 5 mg Tablets and RAD001 9.09% Solid Dispersion.	064		CMC Amendment
66,279	RAD 001C	03/21/2005	[GREAT BRITAIN] Dr. Ian Judson: Cardiac arrest, malignant neoplasm progression, circulatory collapse, bone marrow depression, gastrointestinal haemorrhage, haemoglobin decreased, platelet count decreased, dyspnoea, abdominal pain, loss of consciousness, vomiting, melaena: Follow-up#1.	063	2101	Safety Report
66,279	RAD 001C	03/15/2005	[GREAT BRITAIN] Dr. Ian Judson: Cardiac arrest, malignant neoplasm progression, circulatory collapse, bone marrow depression, circulatory collapse, bone marrow depression, gastrointestinal haemorrhage, haemoglobin decreased, platelet count decreased, dyspnoea, abdominal pain, loss of consciousness, vomiting, melaena.	062	2101	Safety Report
66,279	RAD 001C	03/08/2005	Dr. George Demetri: Malignant neoplasm progression, ascites, drug interaction, cholelithiasis, pleural effusion, dyspnoea.	061	C2206	Safety Report
66,279	RAD 001C	02/23/2005	This Annual Report covers the period December 25, 2003 through December 23, 24, 2004. Includes clinical study information, general investigation plan for the coming year and a investigator brochure.	060		Annual Report
66,279	RAD 001C	02/01/2005	[GREAT BRITAIN] Prof. Ian Judson: Criptogenic organizing pneumonia, lung infiltration, dyspnoea, dyspnoea exertional.	059	2101	Safety Report
66,279	RAD 001C	01/28/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Robert J. Amato, MD.	058		General Correspondence
66,279	RAD 001C	01/28/2005	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by Gini Fleming, MD.	057		General Correspondence
66,279	RAD 001C	01/24/2005	New Investigator to Study No. 2106: Dr. David A. Reardon, MD.	056	2106	New Investigator
66,279	RAD 001C	01/24/2005	This letter authorizes FDA to refer to the IND that will be filed by Daniel George, MD.	055		General Correspondence
66,279	RAD 001C	01/14/2005	E-mail to FDA regarding the action items from the October 25, meeting.			
66,279	RAD 001C	12/21/2004	New Investigator to Study No. 2207: Drs. S. Petersdorf, R. M. Stone, S. Goldberg.	054	2207	New Investigator
66,279	RAD 001C	12/17/2004	E-mails to/from FDA regarding delay of SPA request.			
66,279	RAD 001C	12/08/2004	Howard Burris. MD: Mental status changes, anaemia.	053		Safety Report
66,279	RAD 001C	12/07/2004	Dr. Francis Giles: Leukocytoclastic vasculitis, hyperglycaemia, oedema peripheral, calcinosis, pain, erythema, rash eschar.	052	2406	Safety Report
66,279	RAD 001C	12/01/2004	New Investigator to Study No. 2207: Dr. Charles A. Schiffer, MD.	051	2207	New Investigator

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	11/23/2004	In reference to the End-of-Phase 2 meeting held on October 25, 2004, this correspondence notifies the Agency of Novartis' intent to request a Special Protocol Assessment for a pivotal Phase 3 study, CRAD001C2223.	050		General Correspondence
66,279	RAD 001C	11/19/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed T. Witzig, MD.	048		General Correspondence
66,279	RAD 001C	11/16/2004	E-mails to/from FDA concerning the clinical pharmacology review of submission dated July 30, 2004.			
66,279	RAD 001C	11/15/2004	Dr. Vincent Miller: Multi-organ failure, chest pain, back pain, asthenia, diarrhoea, hypotension.	047	C2406	Safety Report
66,279	RAD 001C	11/15/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed D. A. Reardon and H. S. Friedman.	046		General Correspondence
66,279	RAD 001C	11/15/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed T. Witzig, MD.	045		General Correspondence
66,279	RAD 001C	11/11/2004	New protocol to Study No. 2222 entitled, "A phase 2, double-blind, randomized, placebo-controlled, multi-center study assessing the value of adding RAD001 to letrozole (Femara) as preoperative therapy of primary breast cancer in postmenopausal women.	044	2222	New Protocol
66,279	RAD 001C	11/09/2004	E-mail from FDA stating that there are no comments from the clinical pharmacology review of the July 30, 2004 submission for Study 2106.			
66,279	RAD 001C	10/29/2004	E-mails to/from FDA regarding October 25 meeting minutes.			
66,279	RAD 001C	10/25/2004	FDA minutes of the EOP2 meeting held on October 25, 2004.			FDA/Novartis Meeting Minu
66,279	RAD 001C	10/19/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by P. O'Dwyer, MD.	043		General Correspondence
66,279	RAD 001C	10/19/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by E. Riveria, MD.	042		General Correspondence
66,279	RAD 001C	10/07/2004	New Investigator to Study No. 2207. Dr. Brian J. Druker, MD.	041	2207	New Investigator
66,279	RAD 001C	09/23/2004	New Investigator to Study No. 2101: Dr. V. A. Papadimitrakopoulou; Study No. 2207: Dr. R. A. Larson.	040	2101 2207	New Investigator
66,279	RAD 001C	09/22/2004	E-mails to/from FDA regarding End-of-Phase 2 meeting.			
66,279	RAD 001C	09/20/2004	This Briefing Book is being submitted in preparation for a Type B (End-of-Phase 2) meeting scheduled for October 21, 2004.	039		Briefing Book
66,279	RAD 001C	09/20/2004	E-mail to FDA containing electronic version of documents requested from End-of-Phase 2 Briefing Book.			
66,279	RAD 001C	08/31/2004	FAX from FDA contained information on the EOP2 meeting requested (Serial No. 037).			
66,279	RAD 001C	08/25/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by S. N. Markovic, MD.	038		General Correspondence
66,279	RAD 001C	08/18/2004	This correspondence requests a Type B meeting with the Division to discuss a development plan and registration strategy for RAD001 in combination therapy for advanced breast cancer.	037		Request for FDA Meeting

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	08/11/2004	This correspondence re-submits a letter of authorization dated August 31, 2004, Serial No. 031 with the correct name of the investigator: T. Cloughesy, MD.	036		General Correspondence
66,279	RAD 001C	08/03/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by M. Prados, MD.	035		General Correspondence
66,279	RAD 001C	08/03/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by A. Yung, MD.	034		General Correspondence
66,279	RAD 001C	08/03/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by P. Wen, MD.	033		General Correspondence
66,279	RAD 001C	08/03/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by H. S. Friedman, MD.	032		General Correspondence
66,279	RAD 001C	08/03/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by C. L. Sawyers, MD.	031		General Correspondence
66,279	RAD 001C	07/30/2004	New Protocol to Study No. 2106 entitled, "A phase IB/II, multicenter, two-arm, dose escalation study of oral AEE788 administered in combination with oral RAD001 on a continuous once daily dosing schedule in adult patients with first or second recurrent or relapsing glioblastoma multiforme."	030	2106	New Protocol
66,279	RAD 001C	07/29/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by J. C. Yao, MD	029		General Correspondence
66,279	RAD 001C	07/27/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by A. Adjei, MD.	028		General Correspondence
66,279	RAD 001C	07/23/2004	New Investigator to Study No. 2207: Dr. Meir Wetzler, MD.	027	2207	New Investigator
66,279	RAD 001C	07/22/2004	This correspondence informs the Division that the regulatory responsibilities have been transferred to a new regulatory manager, C. Vanderlinden.	026		General Correspondence
66,279	RAD 001C	06/17/2004	New Protocol: Study No. 2207 entitled, "A phase I-II study of RAD001 in combination with imatinib (Glivec/Gleevec) in patients with chronic myelogenous leukemia (CML) in chronic phase who are not in complete cytogenic response to imatinib-alone at Study entry.	025	2207	New Protocol
66,279	RAD 001C	06/07/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by M. Fouladi, MD.	023		General Correspondence
66,279	RAD 001C	05/24/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by H. Hurwitz, MD.	022		General Correspondence
66,279	RAD 001C	05/18/2004	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by D. Franz, MD.	021		General Correspondence
66,279	RAD 001C	05/11/2004	E-mails to/from FDA regarding the response to FDA comments for Study 2107			
66,279	RAD 001C	04/27/2004	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by D. George, MD.	020		General Correspondence
66,279	RAD 001C	04/06/2004	Amendment No. 1 to Study No. 2107.	019	2107	Change In Protocol
66,279	RAD 001C	03/25/2004	This letter authorizes FDA to refer this IND in support of an IND to be sponsored by J. Wolf.	018		General Correspondence
66,279	RAD 001C	02/10/2004	New Investigator to Study No. 2107: Dr. Howard A. Burris.	016	2107	New Investigator
66,279	RAD 001C	01/29/2004	This letter authorizes FDA to refer to this IND in support of two INDs that will be filed by Memorial Sloan-Kettering Cancer Center.	015		General Correspondence

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	01/15/2004	This correspondence authorizes the FDA to refer to this IND in support of an IND that will be filed by F. Giles, MD.	014		General Correspondence
66,279	RAD 001C	01/09/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by H. Scher, MD.	013		General Correspondence
66,279	RAD 001C	01/09/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by V. A. Miller, MD.	012		General Correspondence
66,279	RAD 001C	01/07/2004	New protocol: Study No. 2107 entitled, A" phase 1b study investigating safety, tolerability and molecular pharmacodynamic effects of RAD001 monotherapy in patients with solid cancers.	011	2107	New Protocol
66,279	RAD 001C	12/15/2003	New Investigator to Study No. 2101: Dr. Howard. A. Burris, III, MD.	010	2101	New Investigator
66,279	RAD 001C	12/01/2003	FAX from FDA containing comments from the clinical pharmacology review on Serial No. 006 dated March 7, 2003.			
66,279	RAD 001C	10/07/2003	New protocol and Amendment No. 1, No. 2, and No. 3, to Study No. 2101: entitled, "A phase Ib study of RAD001 in combination with gemcitabine, investigating safety, tolerability pharmacokinetics and pharmacodynamics in patients with advanced solid tumors.	009	2101	New Protocol
66,279	RAD 001C	05/02/2003	Amendments No. 1 and 2 to Study No. 2206.	007	2206	Change In Protocol
66,279	RAD 001C	03/07/2003	Response to comments from the Pharmacology Reviewer on Serial No. 005 received February 25, 2002.	006		Response to FDA Request
66,279	RAD 001C	03/05/2003	FDA LETTER stating that the proposed clinical study may proceed and also contains recommendations and/or requests for information in reference to the original IND.			
66,279	RAD 001C	02/25/2003	FAX from FDA containing comments from the clinical pharmacology review on Serial No. 005.			
66,279	RAD 001C	01/17/2003	This correspondence responds to comments received from the Pharmcology Reviewer regarding Study RAD001.	005		Response to FDA Request
66,279	RAD 001C	12/31/2002	FAX from FDA containing comments from the Medical Reviewer on Serial No. 003, dated December 19, 2002.			
66,279	RAD 001C	12/30/2002	FAX from FDA containing comments from the Chemistry review.			
66,279	RAD 001C	12/19/2002	FAX from FDA which states that the review of the IND is completed and that the proposed clinical study may begin based on the December 19, 2002 agreement to correct the deficiency.			
66,279	RAD 001C	12/19/2002	E-mail to FDA in response to the deficiency and comments received December 18, 2002.			
66,279	RAD 001C	12/19/2002	FAX from FDA containing comments from the Medical review.			
66,279	RAD 001C	12/19/2002	Response to comments received from the Medical Reviewer regarding Study No. 2206.	003		Response to FDA Request
66,279	RAD 001C	12/18/2002	E-mail from FDA containing a deficiency and comments on the original IND.			
66,279	RAD 001C	12/18/2002	Response to FDA for a statement of clarification to allow cross referencing of IND 52,003 (Division of Special Pathogens and Immunologic Drug Products).	002		Response to FDA Request

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
66,279	RAD 001C	12/06/2002	This submission responds to an FDA request for desk copies of relevant sections of the original IND.	001		Response to FDA Request
66,279	RAD 001C	11/22/2002	This original IND for RAD001 is being developed as an antiproliferative drug with applications as an immunosuppressant and anticancer agent. Protocol: Study No. RAD001C2206 entitled, "A phase I-II, open-label study of RAD001 in combination with Glivec (imatinib) in patients with Glivec-refractory/resistant gastrointestinal stromal tumors". Investigator: G. Demetri, MD.	000	C2206	Original IND

REF	PROD	DATE	DESCRIPTION	SUP	TYPE
22-334	Afinitor	04/07/2009	Final printed labeling as requested in the approval letter dated March 30, 2009 for S000 in Structured product labeling format. Also includes the final printed carton and container labels (eCTD-seq0046).	000	Labeling
22-334	Afinitor	03/30/2009	FDA LETTER approving the new drug application submitted June 27, 2008. This new drug application provides for the use of Afinitor (everolimus) tablets for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.		
22-334	Afinitor	03/27/2009	Final proposed labeling of US PI as received from FDA on March 25, 2009. Also includes agreement to Post-Marketing Commitments received on March 26, 2009 (eCTD-seq0045).		Labeling
22-334	Afinitor	03/20/2009	Response to FDA Request received March 18, 2009 regarding adverse event table (eCTD-seq0043).		Clinical
22-334	Afinitor	03/12/2009	Response to FDA request for time-to-treatment-failure analysis combining the PFS events per investigator with events based on treatment discontinuation. Also providing a by-patient listing explaining differences between the dates for PFS events and the main reasons for treatment discontinuation (eCTD-seq0042)		Clinical
22-334	Afinitor	03/11/2009	Response to CMC information request received on March 9 and 10, 2009 (eCTD-seq0041).		CMC
22-334	Afinitor	03/10/2009	Response to request for clinical and statistical information received via email on March 6, 2009 (eCTD-seq0040).		Clinical
22-334	Afinitor	03/03/2009	Response to request for proposed PMR timelines and clinical information request received via email on March 2, 2009. (eCTD-seq0039).		Clinical
22-334	Afinitor	02/27/2009	Response to FDA Request Updated Proposed Label Requested on February 23, 2009 (eCTD-seq0038).		Labeling
22-334	Afinitor	02/25/2009	Response to FDA request for Statistical information dated February 24, 2009 (eCTD-seq0037).		Other
22-334	Afinitor	02/23/2009	Response to FDA CMC infomation email request dated Febraury 19, 2009. Response to FDA Clinical information email request dated February 19, 2009 and February 20, 2009 (eCTD-seq0036).		Clinical CMC
22-334	Afinitor	02/20/2009	Corrected cover letter for seq. 0034 regarding incorrect "Document Status" (sent Feb. 17, 2009). Cover sheet was marked "draft", but information was final (eCTD-seq-0035).		General Corresponden
22-334	Afinitor	02/18/2009	Response to FDA regarding Clinical Information request (eCTD-seq0034).		Other
22-334	Afinitor	02/17/2009	Investigators Prof. Stephanie Oudard and Prof. Camillo Pota response to FDA inspectional observations. Inspections were held Dec. 8-12, 2009 and Dec. 15-19, 2009 respectively (eCTD-seq0033).		General Corresponden
22-334	Afinitor	02/10/2009	Response to clinical information request of February 9, 2009 (eCTD-seq0032)		Clinical
22-334	Afinitor	02/06/2009	Email Response to Statistical Request Regarding Sequence 31		Other
22-334	Afinitor	01/20/2009	Response to FD-483 observations from FDA Inspection November 17-21, 2008, CFN 9611204 Novartis Pharma AG, Site Basel (eCTD-seq0029).		CMC
22-334	Afinitor	12/22/2008	Response to DRISK Comments on PPI (eCTD-seq0027)		Labeling
22-334	Afinitor	12/10/2008	Response to Clinical Pharmacology Information Request received by e-mail on December 7, 2008. Novartis is providing all requested bio-analytical reports (eCTD-seq0026)		Clinical

REF	PROD	DATE	DESCRIPTION	SUP TYPE
22-334	Afinitor	12/05/2008	Response to clinical pharmacology information request received via email on November 4, 2008, discussed at a telecon on November 5, 2008 and November 26, 2008. Submission also includes a revised Financial Disclosure Certification. (eCTD-seq0025).	Clinical
22-334	Afinitor	11/26/2008	This submission is in response to information requests received October 10 and November 13, 2008. Novartis providing the RECIST CRFs for 93 patients and the eCRF screenshots for 210 patients as agreed. (eCTD-0024)	Clinical
22-334	Afinitor	11/11/2008	Response to FDA question about number of patients with post study treatment in raw and derived datasets. (eCTD-0022)	General Corresponden
22-334	Afinitor	10/31/2008	Novartis is providing the written response to the information Request referenced herein. (eCTD-0021).	CMC
22-334	Afinitor	10/28/2008	With this submission Novartis is providing the third and last part of the response to the Information Requests received via email on September 22, and September 23, 2008, which addresses the request to quantify missing tumor assessments both for site (local) evaluations and evaluations carried out by independent review (central) and compare the missing patterns between the two sources. (eCTD-seq0019)	Clinical
22-334	Afinitor	10/24/2008	This amendment is in response to the FDA request received via email on October 9, 2008 and includes the combined datasets for the C2101-02 PK data analysis including concentration data that was missing in the datasets for this study submitted in the original NDA. Novartis is also re-submitting the updated PK datasets with nominal time for clinical oncology studies C1101, C2104, C2108, C2207, and C2222. Also With this submission Novartis is submitting a revised version of the population PK study report which we submitted with the 90-Day Safety Update [September 30, 2008, sequenee 0011, CTD	Clinical
22-334	Afinitor	10/21/2008	This amendment contains the response to the FDA request received by email on September 22, 2008 for the by-patient listing of all discrepancies between the central and local reviews, with the incorporation of a comments column to document potential explanations. (eCTD-seq0017)	Clinical
22-334	Afinitor	10/21/2008	This correspondence to the FDA is to inform them of the minor descrepancies discoverd for protocol deviations codes as"E 08-Patient has a severe and/or uncontrolled medical condition" for 3 patients at Dr, Robert Motzer's site (number 513) at Memorial Sloan-Kettering Cancer Center (York, US) which are incorrect. (eCTD-seq0018)	General Corresponden
22-334	Afinitor	10/17/2008	This amendment contains the additional datasets for study C2107 requested by email on October 8, 2008, as well as the request by email on October 9, 2008 for the resubmission of the dataset for study C2119. (eCTD-seq0016)	Clinical
22-334	Afinitor	10/14/2008	This amendment contains the respone to the information request received by email on October 2, 2008 for the datasets for studies C2107 and C2239. (eCTD-seq0015)	Clinical
22-334	Afinitor	09/29/2008	Response to FDA request received via email on September 22 and 23, 2008. (eCTD-seq0013)	Clinical
22-334	Afinitor	09/29/2008	Response to FDA request received via email on August 29, 2008. At this time Novartis is submitting the responses to the unanswered questions in the CMC information request. (eCTD-seq0012)	CMC
22-334	Afinitor	09/18/2008	Response to Division of Scientific Investigation request regarding information for Everolimus. The response includes information from Study 2240 Centers 0513 and 0606 and 0756. (ES)	Other
22-334	Afinitor	09/11/2008	This correspondence to the FDA is to follow-up on the question about reader concordance raised at the applicant orientation meeting. (eCTD-seq0009)	General Corresponden

REF	PROD	DATE	DESCRIPTION	SUP TYPE
22-334	Afinitor	09/09/2008	This amendment is in response to the information request made via email on August 28, 2008 for the list of drug substance batches (pre-clinical and clinical) used to support NDA 22-334 and the batch data for one drug substance batch that has not been submitted. (eCTD-seq0010)	CMC
22-334	Afinitor	09/07/2008	Novartis is submitting an Amending to the Pending NDA for providing registration stability update and a shelf life extension for the 5mg and 10mg Afinitor® (everolimus) Tablets. Also included in this submission is a correction of the name and address of a quality control and stability testing site for the 5mg and 10mg Afinitor® (everolimus) Tablets. The updated address was also provided in the Establishment Information included in the Amendment Sequence 0006, submission date of 29-Aug-2008. (eCTD-seq0007)	CMC
22-334	Afinitor	09/05/2008	This amendment is in response to the CMC information request received via email on August 29, 2008. (eCTD-seq0008)	CMC
22-334	Afinitor	08/29/2008	At this time, Novartis is submitting an amendment in response to the information requeat received dated 22-Jul-2008, to provide complete updated drug substance information to NDA No. 22-334. This amendment is submitted in accordance to the agreements reached in the teleconference held between Novartis associates and FDA representatives from the Division of Special Pathogens and Transplant Products, and the Oncology Drug Products Division to discuss the requirements for transfer of responsibility for NDA review of the everolimus drug substance information in support of the Afinitor	CMC
22-334	Afinitor	08/26/2008	This amendment contains a 60 day efficacy update of the pivotal Phase III study CRAD001C2240, which is provided as an amendment to 2.7.3 Summary of Clinical Efficacy. (eCTD-seq0005)	Clinical
22-334	Afinitor	08/21/2008	This amendment to the pending NDA is in response to the emails received on July 31 and August 12, 2008 for the datasets of the thorough QT study C2118. (eCTD-seq0004)	Clinical
22-334	Afinitor	08/20/2008	Novartis meeting minutes submitted to the FDA of the August 13, 2008 meeting between Novartis and the FDA to discuss and agree on the requirements for transfer of responsibility for NDA review of the everolimus drug substance information in support of the Afinitor NDA CMC review. (eCTD-seq0003)	FDA/Novartis Meeting Minutes
22-334	Afinitor	08/04/2008	This amendment to the pending NDA is in response to the FDA requested received via email on July 24, 2008 and July 25, 2008. (eCTD-seq0002)	Clinical
22-334	Afinitor	07/29/2008	This amendment to the pending NDA is in response to the FDA request received July 17, 2008 for the annotated label with each line numbered. (eCTD-seq0001)	Labeling
22-334	Afinitor	06/27/2008	Original NDA for the treatment of advanced renal cell carcinoma (RCC). (eCTD-seq0000)	Original NDA

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	04/08/2009	Amendment updates reference standards and retest period and storage temperature in support of upcoming clinical studies (PS).	885		CMC Amendment
52,003	Certican®	04/03/2009	Updated CMC for 0.25mg, 0.5mg, 0.75 mg and 1 mg tablets in support of upcoming clinical studies. (PS)	884		CMC Amendment
52,003	Certican®	03/27/2009	Response to FDA request to submit final study reports CRAD001A B158, B158E1 and B158E2. (PS)	880		Response to FDA Request
52,003	Certican®	03/25/2009	Request for teleconference to help guide Novartis and clarify FDA recommendations from February 19, 2009 communication for exposure-response analyses. (PS)	0879		Request for FDA Meeting
52,003	Certican®	03/04/2009	7-day safety report PHHO2009US02442			Safety Report
52,003	Certican®	03/04/2009	Clinical information amendment - Revised Statistical Plan CRAD001A2309. (PS)	872		Clinical Information Amendr
52,003	Certican®	02/19/2009	7-day safety report PHHO2009US01705 (PS)			Safety Report
52,003	Certican®	02/11/2009	PHHO2008US15235; follow-up (PS)	865		Safety Report
52,003	Certican®	02/10/2009	PHHY2008DE25330; follow-up (PS)	864		Safety Report
52,003	Certican®	02/10/2009	PHHO2009IT00723; follow-up (PS)	863		Safety Report
52,003	Certican®	02/09/2009	PHHO2009IT00723; follow-up (PS)	862		Safety Report
52,003	Certican®	02/09/2009	PHHO2008US14020; follow-up (PS)	861		Safety Report
52,003	Certican®	02/04/2009	CRAD001H2304,CRAD001A2309,CRAD001A2310,CRAD0(new investigator (PS)	860		New Investigator
52,003	Certican®	01/30/2009	Submission to gain preliminary advice from FDA on future development program for Certican in combination with reduced exposure tacrolimus in renal transplantation. Note cover letter incorrectly states date as 1/30/2008.(PS)	859		Clinical Information Amendr
52,003	Certican®	01/29/2009	PHHO2008FR13655; follow-up (PS)	858		Safety Report
52,003	Certican®	01/29/2009	PHHO2009IT00723; follow-up (PS)	857		Safety Report
52,003	Certican®	01/27/2009	7-day safety report PHHO2008FR13655 (PS)			Safety Report
52,003	Certican®	01/27/2009	PHHO2008FR13655 (PS)	856		Safety Report
52,003	Certican®	01/26/2009	PHHO2008US15235; follow-up (PS)	855		Safety Report
52,003	Certican®	01/21/2009	7-day safety report PHHO2008US14734. (PS)			Safety Report
52,003	Certican®	01/21/2009	PHHO2008US14734 (PS)	854		Safety Report
52,003	Certican®	01/21/2009	PHHO2009IT00723 (PS)	853		Safety Report
52,003	Certican®	01/14/2009	PHHO2008US15235; follow-up (PS)	852		Safety Report
52,003	Certican®	01/13/2009	PHHO2008TR15263; follow-up (PS)	851		Safety Report
52,003	Certican®	01/12/2009	Annual Report covering the period November 15, 2007 to November 14, 2008. (PS)	850		Annual Report
52,003	Certican®	01/09/2009	PHHO2008TR15236; follow-up (PS)	849		Safety Report
52,003	Certican®	01/07/2009	PHHO2008US14020; follow-up (PS)	848		Safety Report
52,003	Certican®	01/07/2009	PHHO2008DE11094; follow-up (PS)	847		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	01/07/2009	PHHO2008US15235 (PS)	846		Safety Report
52,003	Certican®	01/06/2009	Clinical information amendment - updated statistical analysis plan for study CRAD001A2309. (PS)	845		Clinical Information Amendr
52,003	Certican®	01/05/2009	PHHO2008TR15236 (PS)	844		Safety Report
52,003	Certican®	01/02/2009	PHHO2008DE11982; follow-up (PS)	843		Safety Report
52,003	Certican®	12/29/2008	PHHO2008US13880; follow-up (PS)	842		Safety Report
52,003	Certican®	12/26/2008	PHHO2008CH13360; follow-up (PS)	841		Safety Report
52,003	Certican®	12/26/2008	PHHO2008CH13379; follow-up (PS)	840		Safety Report
52,003	Certican®	12/18/2008	Clinical information amendment - proposals for PK/PD statistical methods/table shells. (PS)	839		Clinical Information Amendr
52,003	Certican®	12/15/2008	PHHO2007US20875; follow-up (PS)	838		Safety Report
52,003	Certican®	12/12/2008	PHHO2008BE12855; follow-up (PS)	837		Safety Report
52,003	Certican®	12/10/2008	PHHO2008DE11094; follow-up (PS)	836		Safety Report
52,003	Certican®	12/09/2008	PHHO2008US14020; follow-up (PS)	834		Safety Report
52,003	Certican®	12/09/2008	PHHO2008DE11982 (PS)	835		Safety Report
52,003	Certican®	12/08/2008	PHHO2008IT09241; follow up (PS)	833		Safety Report
52,003	Certican®	12/05/2008	PHHO2008US14020 (PS)	832		Safety Report
52,003	Certican®	12/04/2008	PHHO2008US13880 (PS)	831		Safety Report
52,003	Certican®	12/03/2008	PHHO2008DE11491; follow-up (PS)	830		Safety Report
52,003	Certican®	12/02/2008	PHHO2008IT09241; follow-up (PS)	826		Safety Report
52,003	Certican®	12/02/2008	PHHO2008CH13360; follow-up (PS)	827		Safety Report
52,003	Certican®	12/02/2008	PHHO2008CH13379; follow-up (PS)	828		Safety Report
52,003	Certican®	12/02/2008	PHHO2008US14108 (PS)	829		Safety Report
52,003	Certican®	11/26/2008	PHHO2008CH13379; follow-up (PS)	824		Safety Report
52,003	Certican®	11/26/2008	PHHO2008CH13360; follow-up (PS)	825		Safety Report
52,003	Certican®	11/25/2008	PHHO2008IT01481; follow-up (PS)	821		Safety Report
52,003	Certican®	11/25/2008	PHHO2008IT09241 (PS)	822		Safety Report
52,003	Certican®	11/25/2008	PHHO2007AU11574; follow-up (PS)	823		Safety Report
52,003	Certican®	11/21/2008	PHHO2008DE11094; follow-up (PS)	819		Safety Report
52,003	Certican®	11/21/2008	PHHO2008TW11206; follow-up (PS)	820		Safety Report
52,003	Certican®	11/19/2008	PHHO2008CH13379 (PS)	817		Safety Report
52,003	Certican®	11/19/2008	PHHO2008CH13360 (PS)	818		Safety Report
52,003	Certican®	11/18/2008	PHHO2008TW11206; follow-up (PS)	816		Safety Update
52,003	Certican®	11/17/2008	PHHO2008BE12855 (PS)	815		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	11/14/2008	PHHO2008DE11491; follow-up (PS)	814		Safety Report
52,003	Certican®	11/13/2008	PHHO2008US12593; follow-up (PS)	813		Safety Report
52,003	Certican®	11/11/2008	PHHO2008IT11948; follow-up (PS)	812		Safety Report
52,003	Certican®	11/10/2008	PHHY2008DE25330; follow-up (PS)	811		Safety Report
52,003	Certican®	11/06/2008	Study CRAD001H2304 new investigator. (PS)	809		New Investigator
52,003	Certican®	11/06/2008	PHHO2008CA11400; follow-up (PS)	810		Safety Report
52,003	Certican®	10/29/2008	PHHY2008SG20428 follow-up (PS)	808		Safety Report
52,003	Certican®	10/28/2008	PHHO2008DE11094 follow-up (PS)	806		Safety Report
52,003	Certican®	10/28/2008	PHHO2008DE12119 follow-up (PS)	807		Safety Report
52,003	Certican®	10/27/2008	PHHY2008DE25330 follow-up (PS)	805		Safety Report
52,003	Certican®	10/27/2008	PHHO2007US20875; follow-up (PS)	803		Safety Report
52,003	Certican®	10/27/2008	PHHO2008US12593 (PS)	804		Safety Report
52,003	Certican®	10/24/2008	PHHO2008DE11094; follow-up (PS)	802		Safety Report
52,003	Certican®	10/21/2008	PHHO2008DE12119 (PS)	801		Safety Report
52,003	Certican®	10/20/2008	7-day safety report PHHO2008DE11094 (PS)			Safety Report
52,003	Certican®	10/16/2008	7-Day safety report PHHO2008DE12119. (PS)			Safety Report
52,003	Certican®	10/16/2008	PHHO2008IT11948 (PS)	800		Safety Report
52,003	Certican®	10/14/2008	PHHO2008DE11491 (PS)	798		Safety Report
52,003	Certican®	10/14/2008	PHHO2007US00556; follow-up (PS)	799		Safety Report
52,003	Certican®	10/08/2008	PHHO2008CA04926; follow-up (PS)	796		Safety Report
52,003	Certican®	10/03/2008	PHHO2008AR00668; follow-up (PS)	795		Safety Report
52,003	Certican®	09/30/2008	PHHO2008TW11206 (PS)	793		Safety Report
52,003	Certican®	09/30/2008	PHHO2008CA11400 (PS)	794		Safety Report
52,003	Certican®	09/23/2008	PHHO2008US10695 follow-up (PS)	791		Safety Report
52,003	Certican®	09/23/2008	PHHO2008DE10143 follow-up (PS)	792		Safety Report
52,003	Certican®	09/19/2008	PHHO2008NO01190 (PS)	790		Safety Report
52,003	Certican®	09/18/2008	PHHY2008SG20428 (PS)	788		Safety Report
52,003	Certican®	09/18/2008	PHHY2008JP20446 (PS)	789		Safety Report
52,003	Certican®	09/16/2008	PHHO2008US10695 (PS)	787		Safety Report
52,003	Certican®	09/15/2008	7-Day Safety report PHHY2008SG20428 (PS)			Safety Report
52,003	Certican®	09/15/2008	7-day safety report PHHO2008US12593 (PS)			Safety Report
52,003	Certican®	09/12/2008	PHHO1997FR03054 (PS)	786		Safety Report
52,003	Certican®	09/11/2008	PHHO1997NO02606 follow-up (PS)	785		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	09/10/2008	PHHO2007US21124 follow-up (PS)	783		Safety Report
52,003	Certican®	09/10/2008	PHHO2008CA00612 follow-up (PS)	784		Safety Report
52,003	Certican®	09/08/2008	Study CRAD001A2310 change in protocol, amendment 7. (PS)	782		Change In Protocol
52,003	Certican®	09/04/2008	PHHO2007FR07389 follow-up (PS)	781		Safety Report
52,003	Certican®	09/03/2008	PHHO2008DE10143 (PS)	780		Safety Report
52,003	Certican®	09/02/2008	PHHO2008CY09722 follow-up (PS)	777		Safety Report
52,003	Certican®	09/02/2008	PHHO2008FR08863 follow-up (PS)	778		Safety Report
52,003	Certican®	09/02/2008	PHHO2007US21124 follow-up (PS)	779		Safety Report
52,003	Certican®	08/29/2008	Study CRAD001H2304,CRAD001A2309, CRAD001A2401 new investigator (PS)	776		New Investigator
52,003	Certican®	08/28/2008	PHHO2008FR08863 (PS)	773		Safety Report
52,003	Certican®	08/28/2008	PHHO2008CA04926 follow-up (PS)	774		Safety Report
52,003	Certican®	08/28/2008	PHHO2008US05802 follow-up (PS)	775		Safety Report
52,003	Certican®	08/22/2008	PHHO2008AU08078 follow-up (PS)	772		Safety Report
52,003	Certican®	08/20/2008	7-Day IND Safety Notifiction PHHO2008FR08863 (PS)			Safety Report
52,003	Certican®	08/19/2008	PHHO2008CY09722 (PS)	771		Safety Report
52,003	Certican®	07/31/2008	PHHO2008FR08382 follow-up (PS)	769		Safety Report
52,003	Certican®	07/31/2008	PHHO2008US05802 (PS)	770		Safety Report
52,003	Certican®	07/29/2008	7-Day IND Safety Notification PHHO2008US05802 (PS)			Safety Report
52,003	Certican®	07/25/2008	PHHO2008FR08382 follow-up (PS)	768		Safety Report
52,003	Certican®	07/22/2008	PHHO2008FR08382 follow-up (PS)	767		Safety Report
52,003	Certican®	07/21/2008	PHHO2008AU07680 follow-up (PS)	766		Safety Report
52,003	Certican®	07/16/2008	PHHO2008FR08382 (PS)	764		Safety Report
52,003	Certican®	07/16/2008	PHHO2008US07823 follow-up (PS)	765		Safety Report
52,003	Certican®	07/10/2008	PHHO2007FR09520 follow-up (PS)	763		Safety Report
52,003	Certican®	07/09/2008	PHHO2008AU08078 (PS)	762		Safety Report
52,003	Certican®	07/03/2008	Study CRAD001H2304 new investigator. (PS)	760		New Investigator
52,003	Certican®	07/03/2008	PHHO2007PL06777 follow-up (PS)	761		Safety Report
52,003	Certican®	07/02/2008	PHHO2008DE05923 follow-up (PS)	757		Safety Report
52,003	Certican®	07/02/2008	PHHO2007ES08365 follow-up (PS)	758		Safety Report
52,003	Certican®	07/02/2008	PHHO2008US07899 (PS)	759		Safety Report
52,003	Certican®	06/30/2008	PHHO2008US06493 follow-up (PS)	755		Safety Report
52,003	Certican®	06/27/2008	PHHO2008AU07680 (PS)	754		Safety Report

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52,003	Certican®	06/26/2008	PHHO2008CA00612 follow-up (PS)	753		Safety Report
52,003	Certican®	06/20/2008	PHHO2007FR03202 follow-up (PS)	751		Safety Report
52,003	Certican®	06/19/2008	PHHO2008DE05923 follow-up (PS)	750		Safety Report
52,003	Certican®	06/13/2008	PHHO2007US21124 follow-up (PS)	749		Safety Report
52,003	Certican®	06/12/2008	PHHO2008US04833 follow-up (PS)	747		Safety Report
52,003	Certican®	06/12/2008	PHHO2008DE05923 follow-up (PS)	748		Safety Report
52,003	Certican®	06/10/2008	PHHO2008DE05923 (PS)	746		Safety Report
52,003	Certican®	06/09/2008	Study CRAD001H2304 new investigator. (PS)	745		New Investigator
52,003	Certican®	06/06/2008	Response to address FDA statistical comments, a copy of the DMC charter and additional comments in response to FDA letter dated November 29, 2007. (PS)	742		Clinical Information Amendr Response to FDA Request
52,003	Certican®	06/06/2008	PHHO2008US01900 follow-up (PS)	744		Safety Report
52,003	Certican®	06/03/2008	PHHO2007DE20351 follow-up (PS)	741		Safety Report
52,003	Certican®	06/02/2008	PHHO2007FR14620 follow-up (PS)	740		Safety Report
52,003	Certican®	05/30/2008	PHHO2008AR00668 follow-up (PS)	739		Safety Report
52,003	Certican®	05/09/2008	PHHO2007FR14620 follow-up (PS)	738		Safety Report
52,003	Certican®	05/01/2008	PHHO2008DE03857 follow-up (PS)	737		Safety Report
52,003	Certican®	04/30/2008	PHEH2000US08591 follow-up (PS)	735		Safety Report
52,003	Certican®	04/30/2008	PHHO2008US04833 follow-up (PS)	736		Safety Report
52,003	Certican®	04/29/2008	PHHO2008CA04926 (PS)	733		Safety Report
52,003	Certican®	04/29/2008	PHHO2008JP04055 follow-up (PS)	734		Safety Report
52,003	Certican®	04/28/2008	PHHO2008US04833 follow-up (PS)	732		Safety Report
52,003	Certican®	04/25/2008	PHHO2007IT19720 follow-up (PS)	731		Safety Report
52,003	Certican®	04/23/2008	PHHO2008US01900 follow-up (PS)	730		Safety Report
52,003	Certican®	04/22/2008	PHHO2008US04735 (PS)	728		Safety Report
52,003	Certican®	04/22/2008	PHHO2008US04833 (PS)	729		Safety Report
52,003	Certican®	04/21/2008	PHHO2008IT01481 follow-up (PS)	727		Safety Report
52,003	Certican®	04/18/2008	PHHO2008DE03857 follow-up (PS)	726		Safety Report
52,003	Certican®	04/15/2008	PHHO2008JP04055 (PS)	725		Safety Report
52,003	Certican®	04/15/2008	Per FDA request, submission of statistical analysis plan prior to database lock for study CRAD001A2309. (PS)	724		Clinical Information Amendr Response to FDA Request
52,003	Certican®	04/11/2008	PHHO2007FR18497 follow-up (PS)	723		Safety Report
52,003	Certican®	04/08/2008	PHHO2008IT01481 follow-up (PS)	722		Safety Report
52,003	Certican®	04/04/2008	PHHO2008DE03857 follow-up (PS)	721		Safety Report
52,003	Certican®	04/03/2008	Study CRAD001A2401 new investigator. (PS)	720		New Investigator

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	04/01/2008	Submission to FDA of notification from the study Data Monitoring Committee and a copy of the communication sent to study investigators. (PS)	719		Clinical Information Amendr
52,003	Certican®	03/28/2008	PHHO2008DE03857 (PS)	718		Safety Report
52,003	Certican®	03/27/2008	PHHO2008US01900 follow-up (PS)	717		Safety Report
52,003	Certican®	03/25/2008	PHHO2007US2114 follow-up (PS)	715		Safety Report
52,003	Certican®	03/25/2008	PHHO2007NO19319 follow-up (PS)	716		Safety Report
52,003	Certican®	03/21/2008	Study CRAD001A2401 new investigator (PS)	714		New Investigator
52,003	Certican®	03/20/2008	PHHO2007US20563 follow-up (PS)	713		Safety Report
52,003	Certican®	03/17/2008	PHHO2007US21124 follow-up (PS)	712		Safety Report
52,003	Certican®	03/12/2008	PHHO2008AU01363 (PS)	711		Safety Report
52,003	Certican®	03/07/2008	PHHO2007US21124 follow-up (PS)	709		Safety Report
52,003	Certican®	03/07/2008	PHHO2007NO19319 follow-up (PS)	710		Safety Report
52,003	Certican®	03/03/2008	PHHO2008AR00668 (PS)	708		Safety Report
52,003	Certican®	02/28/2008	PHHO2008FR02098 FOLLOW-UP (PS)	705		Safety Report
52,003	Certican®	02/28/2008	PHHO2008US02416 (PS)	706		Safety Report
52,003	Certican®	02/28/2008	PHHO2008IT01481 FOLLOW-UP (PS)	707		Safety Report
52,003	Certican®	02/27/2008	PHHO2007IT19720 FOLLOW-UP (PS)	704		Safety Report
52,003	Certican®	02/25/2008	PHHO2007FR13915 follow-up (PS)	703		Safety Report
52,003	Certican®	02/21/2008	PHHO2008US01900 follow-up (PS)	701		Safety Report
52,003	Certican®	02/21/2008	Study CRAD001A2401 new investigator. (PS)	702		New Investigator
52,003	Certican®	02/20/2008	PHHO2007FR14001 FOLLOW-UP (PS)	698		Safety Report
52,003	Certican®	02/20/2008	PHHO2007IT19720 FOLLOW-UP (PS)	699		Safety Report
52,003	Certican®	02/20/2008	PHHO2007NO19319 (FOLLOW-UP) (PS)	700		Safety Report
52,003	Certican®	02/19/2008	PHHO2008FR02098 (PS)	696		Safety Report
52,003	Certican®	02/19/2008	PHHO2007FR14620 FOLLOW-UP (PS)	697		Safety Report
52,003	Certican®	02/14/2008	PHHO2008US01900 (PS)	695		Safety Report
52,003	Certican®	02/13/2008	Letter of cross reference granting permission to FDA/HFD-590 to allow representatives from the CDRH Interventional Cardiology Devices Branch to review and discuss those parts of our documents relevant for Abbott Vascular's XIENCE V application. (PS)	694		Other
52,003	Certican®	02/12/2008	PHHO2008IT01481 (PS)	693		Safety Report
52,003	Certican®	02/08/2008	PHHO2007JP19109 FOLLOW-UP (PS)	692		Safety Report
52,003	Certican®	02/08/2008	PHHO2007FR17369 FOLLOW-UP (PS)	691		Safety Report
52,003	Certican®	02/07/2008	PHHO2007FR14001 FOLLOW-UP (PS)	689		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	02/07/2008	PHHO2007FR13915 (PS)	690		Safety Report
52,003	Certican®	02/06/2008	PHHO2007IT19720 FOLLOW-UP (PS)	688		Safety Report
52,003	Certican®	01/31/2008	PHHO2007NO19319 FOLLOW-UP (PS)	685		Safety Report
52,003	Certican®	01/31/2008	PHHO2007FR18943 FOLLOW-UP (PS)	686		Safety Report
52,003	Certican®	01/28/2008	PHHO2007FR18943 FOLLOW-UP (PS)	682		Safety Report
52,003	Certican®	01/28/2008	PHHO2007FR20512 FOLLOW-UP (PS)	683		Safety Report
52,003	Certican®	01/28/2008	PHHO2007FR18940 FOLLOW-UP (PS)	684		Safety Report
52,003	Certican®	01/25/2008	Studies CRAD001A2309 and CRAD001A2310 change in protocol, amendment 3. (PS)	680		Change In Protocol
52,003	Certican®	01/25/2008	PHHO2007NO19319 FOLLOW-UP (PS)	681		Safety Report
52,003	Certican®	01/23/2008	PHHO2007DE20351 FOLLOW-UP (PS)	677		Safety Report
52,003	Certican®	01/23/2008	PHHO2007IT9720 (PS)	678		Safety Report
52,003	Certican®	01/23/2008	PHHO2007JP19109 FOLLOW-UP (PS)	679		Safety Report
52,003	Certican®	01/22/2008	PHHO2007FR12501 FOLLOW-UP (PS)	675		Safety Report
52,003	Certican®	01/22/2008	PHHO2007FR11090 FOLLOW-UP (PS)	676		Safety Report
52,003	Certican®	01/21/2008	PHHO2007US17617 FOLLOW-UP (PS)	674		Safety Report
52,003	Certican®	01/16/2008	PHHO2007US20875 (PS)	673		Safety Report
52,003	Certican®	01/09/2008	Annual Report covering the period November 15, 2006 to November 14, 2007. (PS)	672		Annual Report
52,003	Certican®	01/04/2008	PHHO2007US21124 (PS)	670		Safety Update
52,003	Certican®	01/04/2008	PHHO2007JP17929 FOLLOW-UP (PS)	671		Safety Report
52,003	Certican®	01/02/2008	PHHO2007JP19109 FOLLOW-UP (PS)	666		Safety Report
52,003	Certican®	01/02/2008	PHHO2007DE20351 FOLLOW-UP (PS)	667		Safety Report
52,003	Certican®	01/02/2008	PHHO2007FR18943 FOLLOW-UP (PS)	668		Safety Report
52,003	Certican®	01/02/2008	PHHO2007FR11090 FOLLOW-UP (PS)	669		Safety Report
52,003	Certican®	12/27/2007	PHHO2007FR19560 Follow-up. (PS)	665		Safety Report
52,003	Certican®	12/27/2007	PHHO2007US20563. (PS)	664		Safety Report
52,003	Certican®	12/24/2007	PHHO2007US13764 Follow-up. (PS)	662		Safety Report
52,003	Certican®	12/24/2007	PHHO2007FR20512. (PS)	663		Safety Report
52,003	Certican®	12/24/2007	PHHO2007DE20351. (PS)	661		Safety Report
52,003	Certican®	12/20/2007	PHHO2007FR19560 Follow-up. (PS)	660		Safety Report
52,003	Certican®	12/20/2007	PHHO2007DE20052 Follow-up. (PS)	659		Safety Report
52,003	Certican®	12/19/2007	Novartis is submitting a IND Amendment to provide update CMC information for the drug substance RAD001-stabilized with BHT (everolimus) and drug product. (PS)	658		CMC Amendment

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	12/18/2007	PHHO2007FR18943 Follow-up. (PS)	656		Safety Report
52,003	Certican®	12/18/2007	PHHO2007DE20052. (PS)	657		Safety Report
52,003	Certican®	12/18/2007	PHHO2007CA19062 Follow-up. (PS)	655		Safety Report
52,003	Certican®	12/17/2007	PHHO2007US06570. (PS)	654		Safety Report
52,003	Certican®	12/13/2007	PHHO2007JP19109 Follow-up. (PS)	653		Safety Report
52,003	Certican®	12/13/2007	PHHO2007US17944 Follow-up. (PS)	652		Safety Report
52,003	Certican®	12/12/2007	PHBS2007TR02235. (PS)	651		Safety Report
52,003	Certican®	12/11/2007	PHHO2007FR19043 Follow-up. (PS)	650		Safety Report
52,003	Certican®	12/11/2007	PHHO2007JP17929 Follow-up. (PS)	649		Safety Report
52,003	Certican®	12/10/2007	PHHO2007FR19560. (PS)	648		Safety Report
52,003	Certican®	12/10/2007	PHHO2007FR18940. (PS)	647		Safety Report
52,003	Certican®	12/07/2007	PHHO2007FR17914 Follow-up. (PS)	646		Safety Report
52,003	Certican®	12/06/2007	PHHO2007JP17929 Follow-up. (PS)	644		Safety Report
52,003	Certican®	12/06/2007	PHHO2007NO19319. (PS)	643		Safety Report
52,003	Certican®	12/06/2007	PHHO2007FR18497 Follow-up. (PS)	642		Safety Report
52,003	Certican®	12/06/2007	PHHO2007FR11090 Follow-up. (PS)	645		Safety Report
52,003	Certican®	12/05/2007	PHHO2007CA19062 Follow-up. (PS)	639		Safety Report
52,003	Certican®	12/05/2007	PHHO200NO08769 Follow-up. (PS)	640		Safety Report
52,003	Certican®	12/05/2007	PHHO2007FR18943. (PS)	641		Safety Report
52,003	Certican®	12/04/2007	PHHO2007JP19109. (PS)	638		Safety Report
52,003	Certican®	11/30/2007	PHHO2007TW16075. (PS)	637		Safety Report
52,003	Certican®	11/30/2007	PHHO2007CA19062 Follow-up. (PS)	636		Safety Report
52,003	Certican®	11/29/2007	PHHO2006US22078 FOLLOW-UP (PS)	635		Safety Report
52,003	Certican®	11/28/2007	PHHO2007FR17369 FOLLOW-UP (PS)	632		Safety Report
52,003	Certican®	11/28/2007	PHHO2007US17617 FOLLOW-UP (PS)	633		Safety Report
52,003	Certican®	11/28/2007	PHHO2007FR19043 (PS)	634		Safety Report
52,003	Certican®	11/27/2007	PHHO2007CA19062 (PS)	631		Safety Report
52,003	Certican®	11/21/2007	PHHO2007FR11090. (PS)	630		Safety Report
52,003	Certican®	11/21/2007	PHHO2007FR18497. (PS)	629		Safety Report
52,003	Certican®	11/21/2007	PHHO2007FR17914 Follow-up. (PS)	628		Safety Report
52,003	Certican®	11/20/2007	PHHO2007FR03202 Follow-up. (PS)	627		Safety Report
52,003	Certican®	11/15/2007	PHHO2007ES08365 Follow-up. (PS)	626		Safety Report
52,003	Certican®	11/12/2007	PHHO2007JP17793 Follow-up. (PS)	625		Safety Report

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52,003	Certican®	11/09/2007	PHHO2007JP17929. (PS)	624		Safety Report
52,003	Certican®	11/09/2007	PHHO2007FR17914 Follow-up. (PS)	623		Safety Report
52,003	Certican®	11/08/2007	PHHO2007US17944. (PS)	622		Safety Report
52,003	Certican®	11/08/2007	PHHO2007AU14332. Follow-up (PS)	621		Safety Report
52,003	Certican®	11/07/2007	PHHO2007CA15784 Follow-up. (PS)	620		Safety Report
52,003	Certican®	11/05/2007	PHHO2007US17617 (PS)	619		Safety Report
52,003	Certican®	11/05/2007	PHHO2007ES08365 Follow-up (PS)	618		Safety Report
52,003	Certican®	11/02/2007	PHHO2007US12809 Follow-up (PS)	617		Safety Report
52,003	Certican®	11/01/2007	PHHO2007SE15401. Follow-up (PS)	616		Safety Report
52,003	Certican®	10/30/2007	PHHO2007FR17369 (PS)	615		Safety Report
52,003	Certican®	10/30/2007	PHHO2007JP17793 (PS)	614		Safety Report
52,003	Certican®	10/29/2007	PHHO2007US12809 follow-up (PS)	613		Safety Report
52,003	Certican®	10/24/2007	PHHO2007CA17142. (PS)	612		Safety Report
52,003	Certican®	10/24/2007	PHHO2007FR03202 Follow-up (PS)	611		Safety Report
52,003	Certican®	10/18/2007	PHHO2007FR03202 Follow-up. (PS)	610		Safety Report
52,003	Certican®	10/17/2007	PHHO2007US13977 Follow-up. (PS)	609		Safety Report
52,003	Certican®	10/16/2007	PHHO2007US12809 Follow-up. (PS)	607		Safety Report
52,003	Certican®	10/16/2007	The regulatory purpose of this study is to support additional Phase 3 development and approval for use of Certican (everolimus) in liver transplantation. (PS)	608		Clinical Information Amendr
52,003	Certican®	10/15/2007	PHHO2007CA15784 Follow-up. (PS)	606		Safety Report
52,003	Certican®	10/12/2007	PHHO2007FRO3202 Follow-up. (PS)	605		Safety Report
52,003	Certican®	10/12/2007	PHHO2007US16146. (PS)	604		Safety Report
52,003	Certican®	10/10/2007	PHHO2007FR03202 Follow-up. (PS)	603		Safety Report
52,003	Certican®	10/09/2007	PHHO2007DE15860. (PS)	602		Safety Report
52,003	Certican®	10/08/2007	PHHO2007US15872 Follow-up. (PS)	600		Safety Report
52,003	Certican®	10/08/2007	PHHO2007US13977. (PS)	601		Safety Report
52,003	Certican®	10/05/2007	PHHO2007US13764. (PS)	599		Safety Report
52,003	Certican®	10/04/2007	PHHO2007CA15784. (PS)	598		Safety Report
52,003	Certican®	10/04/2007	PHHO2007US15872. (PS)	597		Safety Report
52,003	Certican®	10/03/2007	PHHO2007US12809. (PS)	596		Safety Report
52,003	Certican®	09/28/2007	PHHO2004BE07879 Follow-up. (PS)	595		Safety Report
52,003	Certican®	09/27/2007	TC with Diana Daly/HGS DRA re FDA comments. (PS)			Memo of Record (telephone report)
52,003	Certican®	09/27/2007	PHHO2007FR03202. Follow-up (PS)	594		Safety Report

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52,003	Certican®	09/25/2007	PHHO2007SE15401. (PS)	592		Safety Report
52,003	Certican®	09/25/2007	PHHO2007AU14332 Follow-up. (PS)	593		Safety Report
52,003	Certican®	09/24/2007	New Investigator to Study No. CRAD001A2309 and Study No. CRAD001A2401. (PS)	581		New Investigator
52,003	Certican®	09/21/2007	PHHO2007AU11574 Follow-up. (PS)	591		Safety Update
52,003	Certican®	09/20/2007	PHHO2007US07788 Follow-up. (PS)	589		Safety Report
52,003	Certican®	09/20/2007	PHHO2007AU11574 Follow-up. (PS)	590		Safety Report
52,003	Certican®	09/19/2007	PHHO2007ES08365 Follow-up. (PS)	588		Safety Report
52,003	Certican®	09/18/2007	PHHO2007FR14001 Follow-up. (PS)	586		Safety Report
52,003	Certican®	09/18/2007	PHHO2007FR14620. (PS)	587		Safety Report
52,003	Certican®	09/13/2007	PHHO2004BE07879 Follow-up. (PS)	585		Safety Report
52,003	Certican®	09/12/2007	CRAD001D2201 report. This report is provided for use in regulatory submissions and Investigator Brochure. (PS)			Other
52,003	Certican®	09/11/2007	PHHO2007FR14001 Follow-up. (PS)	584		Safety Report
52,003	Certican®	09/10/2007	PHHO2004US12965 Follow-up. (PS)	583		Safety Report
52,003	Certican®	09/07/2007	PHHO2004BE07879 Follow-up. (PS)	582		Safety Report
52,003	Certican®	09/06/2007	PHHO2007BE13048 Follow-up. (PS)	579		Safety Report
52,003	Certican®	09/06/2007	PHHO2007BE12170 Follow-up. (PS)	580		Safety Report
52,003	Certican®	09/05/2007	PHHO2007FR14001. (PS)	578		Safety Report
52,003	Certican®	08/31/2007	PHHO2007US11543 Follow-up. (PS)	577		Safety Report
52,003	Certican®	08/30/2007	PHHO2004BE07879 Follow-up. (PS)	576		Safety Report
52,003	Certican®	08/28/2007	PHHO2007FR10519 Follow-up. (PS)	575		Safety Report
52,003	Certican®	08/27/2007	PHHO2007US11397. Follow-up (PS)	574		Safety Report
52,003	Certican®	08/23/2007	PHHO2007BE13048. Follow-up (PS)	573		Safety Report
52,003	Certican®	08/23/2007	PHHO2007FR10519. Follow-up (PS)	572		Safety Report
52,003	Certican®	08/21/2007	PHHO2007FR09520 Follow-up. (PS)	571		Safety Report
52,003	Certican®	08/20/2007	PHHO2007BE12170 Follow-up. (PS)	570		Safety Report
52,003	Certican®	08/17/2007	PHHO2007AU11574;Follow-Up (PS)	569		Safety Report
52,003	Certican®	08/17/2007	PHHO2007FR09520;Follow-Up (PS)	568		Safety Report
52,003	Certican®	08/17/2007	PHHO2007BE13048;Follow-Up (PS)	567		Safety Report
52,003	Certican®	08/16/2007	PHHO2007FR12501;Follow-Up (PS)	566		Safety Report
52,003	Certican®	08/15/2007	Fax to FDA 7-Day IND Safety Report. (PS)			Safety Report
52,003	Certican®	08/15/2007	PHHO2007IT12077 Follow-up (PS)	565		Safety Report
52,003	Certican®	08/15/2007	PHHO2007US09880 Follow-up. (PS)	564		Safety Report

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52,003	Certican®	08/15/2007	PHHO2007FR10519. (PS)	563		Safety Report
52,003	Certican®	08/14/2007	Fax to FDA 7-Day IND Safety Report. (PS)			Safety Report
52,003	Certican®	08/10/2007	PHHO2004BE07879. Follow-up (PS)	562		Safety Report
52,003	Certican®	08/10/2007	PHHO2007FR12501. (PS)	561		Safety Report
52,003	Certican®	08/08/2007	The purpose of this submission is to provide response with supporting documentation to address the FDA statistical comments requesting additional justification for the 10% non-inferiority margin for the composite efficacy endpoint (graft lost, death or lost to follow-up) at 12 months post transplant. (PS)	560		Clinical Information Amendr
52,003	Certican®	08/07/2007	PHHO2007BE12170;Follow-Up (PS)	559		Safety Report
52,003	Certican®	08/03/2007	PHHO2007FR09520;Follow-Up (PS)	558		Safety Report
52,003	Certican®	08/02/2007	PHHO2007US11543;Follow-Up (PS)	557		Safety Report
52,003	Certican®	08/01/2007	PHHO2007FR03202; Follow- Up (PS)	556		Safety Report
52,003	Certican®	07/31/2007	PHHO2007PL06777;Follow- Up (PS)	553		Safety Report
52,003	Certican®	07/31/2007	PHHO2007US04089;Follow-Up (PS)	555		Safety Report
52,003	Certican®	07/31/2007	PHHO2007IT12077;Follow-Up (PS)	554		Safety Report
52,003	Certican®	07/31/2007	Fax to FDA 7-Day Safety Report. (PS)			Other
52,003	Certican®	07/26/2007	New Investigator to Study No. CRAD001A2310. (PS)	551		New Investigator
52,003	Certican®	07/26/2007	PHHO2007US07788;Follow-Up (PS)	552		Safety Report
52,003	Certican®	07/24/2007	PHHO2007US11543;Follow-Up (PS)	549		Safety Report
52,003	Certican®	07/24/2007	PHHO2007US07788;Follow-Up (PS)	550		Safety Report
52,003	Certican®	07/20/2007	PHHO2007US11397; Follow-Up (PS)	548		Safety Report
52,003	Certican®	07/18/2007	Fax to FDA 7-Day IND Safety Report (PH02007US11397) (PS)			Safety Report
52,003	Certican®	07/17/2007	PHHO2007US11397;Follow-Up (PS)	547		Safety Report
52,003	Certican®	07/13/2007	The purpose of this submission is to support additional discussions with the Division on the regulatory value of Study A2411 in support of the Certican cardiac transplant NDA (No. 21-628) review. (PS)	546		Clinical Information Amendr
52,003	Certican®	07/11/2007	Clarification regarding Liver Protocol Comments. (PS)			Other
52,003	Certican®	07/11/2007	PHRM2007FR01778;Follow-Up (PS)	545		Safety Report
52,003	Certican®	07/09/2007	PHHO2007ES08365 Follow-up (PS)	544		Safety Report
52,003	Certican®	07/09/2007	PHHO2007PL06777 Follow-up (PS)	543		Safety Report
52,003	Certican®	07/03/2007	PHHO2005US14500. (PS)	542		Safety Report
52,003	Certican®	06/26/2007	Fax from FDA regarding Liver Protocol Comments. (PS)			Other
52,003	Certican®	06/25/2007	PHHO2007US09880 (PS)	541		Safety Report
52,003	Certican®	06/21/2007	PHHO2007PL06777 Follow-up (PS)	540		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	06/21/2007	PHHO2007FR07389 Follow-up (PS)	539		Safety Report
52,003	Certican®	06/19/2007	New Investigator to Study No. CRAD001A2309. (PS)	538		New Investigator
52,003	Certican®	06/19/2007	PHBS2007BE07399 Follow-up (PS)	537		Safety Report
52,003	Certican®	06/13/2007	PHHO2007FR07389 Follow-up (PS)	536		Safety Report
52,003	Certican®	06/07/2007	PHHO2006US22078;Follow-Up (PS)	535		Safety Report
52,003	Certican®	06/06/2007	PHHO2007PL06777;Follow-Up (PS)	534		Safety Report
52,003	Certican®	06/05/2007	PHHO2006US22078;Follow-Up (PS)	533		Safety Report
52,003	Certican®	06/05/2007	PHBS2007BE07399;Follow-Up (PS)	532		Safety Report
52,003	Certican®	05/31/2007	Fax from FDA Liver transplantation comments. (PS)			Other
52,003	Certican®	05/30/2007	PHHO2007ES08365 (PS)	531		Safety Report
52,003	Certican®	05/25/2007	PHHO2007PL06777; Follow-Up (PS)	530		Safety Report
52,003	Certican®	05/23/2007	This submission provides description of the Data Monitoring Committee (DMC) Charter for the studies of Certican (everolimus). (PS)	529		Clinical Information Amendr
52,003	Certican®	05/23/2007	PHBS2007BE07399. Follow-up (PS)	528		Safety Report
52,003	Certican®	05/23/2007	Certican Liver tx protocol/FDA comments ongoing review/written comments expected 1-2 weeks. (PS)			Other
52,003	Certican®	05/22/2007	PHHO2007PL06777. Follow-up (PS)	527		Safety Report
52,003	Certican®	05/18/2007	PHBS2007BE07399. Follow-up (PS)	524		Safety Report
52,003	Certican®	05/18/2007	PHRM2007FR01407 (PS)	525		Safety Report
52,003	Certican®	05/18/2007	PHHO2007FR07389. Follow-up (PS)	526		Safety Report
52,003	Certican®	05/16/2007	PHHO2006US11747. Follow-up (PS)	523		Safety Report
52,003	Certican®	05/15/2007	PHBS2007BE07399 (PS)	522		Safety Report
52,003	Certican®	05/09/2007	PHHO2007FR07389 (PS)	521		Safety Report
52,003	Certican®	05/09/2007	Fax to FDA. (7-Day Safety Report). (PS)			Safety Report
52,003	Certican®	05/08/2007	PHHO2007DE07018. (PS)	520		Safety Report
52,003	Certican®	05/03/2007	PHHO2007PL06777. (PS)	519		Safety Report
52,003	Certican®	04/30/2007	This Annual Report covers the period November 15, 2005 through November 14, 2006. (PS)	518		Annual Report
52,003	Certican®	04/23/2007	PHHO2007DE03665 Follow-up. (PS)	517		Safety Report
52,003	Certican®	04/11/2007	PHHO2007US00556. Follow-up (PS)	516		Safety Report
52,003	Certican®	04/03/2007	PHHO2007US04089. Follow-up (PS)	515		Safety Report
52,003	Certican®	03/30/2007	PHHO2007US05182 (PS)	513		Safety Report
52,003	Certican®	03/15/2007	PHHO2007US04089. Follow-up (PS)	510		Safety Report
52,003	Certican®	03/15/2007	PHHO2007CA002219. Follow-up	511		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	03/14/2007	PHHO2007US04215 (PS)	509		Safety Report
52,003	Certican®	03/13/2007	PHHO2007US04089 (PS)	508		Safety Report
52,003	Certican®	03/08/2007	The purpose of the communication is to provide a letter of cross reference granting permission to the FDA Division of Special Pathogen and Transplant Products/HFD-590 to allow representatives from the CDRH Interventional Cardiology Devices Branch (ICDB) to review and discuss those parts of our documents relevant for Abbott Vascular's and Novartis.	506		Other
52,003	Certican®	03/08/2007	New Investigator to Study No. CRAD001A2309 and Study No. CRAD001A2310. (PS)	507		New Investigator
52,003	Certican®	03/07/2007	PHHO2007DE03665. (PS)	505		Safety Report
52,003	Certican®	02/23/2007	The purpuse of this communication is to submit a request for teleconference to discuss the draft study protocol with statistical justifications for a pivotal study in liver transplantation. We also providing a response to the FDA request for information made during teleconference on November 15, 2006. (PS)	504		Response to FDA Request
52,003	Certican®	02/22/2007	PHHO2007CA02219 Follow-up	503		Safety Report
52,003	Certican®	02/15/2007	PHBS2006AT07989 Follow-up. (PS)	502		Safety Report
52,003	Certican®	02/09/2007	PHHO2007CA02219 Follow-up. (PS)	501		Safety Report
52,003	Certican®	02/08/2007	PHHO2007CA02219 Follow-up. (PS)	500		Safety Report
52,003	Certican®	02/07/2007	Novartis is submitting IND amendment to provide updated information on the manufacturing sites and stability programs. The summary of changes and the updated IND sections are included in submission. (ES)	498		CMC Amendment
52,003	Certican®	02/07/2007	PHHO2007CA02219 (PS)	499		Safety Report
52,003	Certican®	02/05/2007	PHBS2007BE07399 FOLLOW-UP (PS)	687		Safety Report
52,003	Certican®	02/01/2007	PHHO2005BE07879 (PS)	497		Safety Report
52,003	Certican®	01/29/2007	Fax from FDA. November 15, 2006 Meeting Minutes. (ES)			Other
52,003	Certican®	01/26/2007	PHHO2006US22076 Follow-up. (PS)	496		Safety Report
52,003	Certican®	01/25/2007	PHHO2007US00556. (PS)	495		Safety Report
52,003	Certican®	01/19/2007	PHHO2006US22076. (PS)	494		Safety Report
52,003	Certican®	01/18/2007	PHHO2007US00556. (PS)	493		Safety Report
52,003	Certican®	12/28/2006	PHHO2006FR20729 Follow-up.	492		Safety Report
52,003	Certican®	12/22/2006	PHHO2005DE16006 Follow-up#2. (PS)	491		Safety Report
52,003	Certican®	12/22/2006	New Investigator to Study No. CRAD001A2309. (ES)	490	2309	New Investigator
52,003	Certican®	12/21/2006	PHHO2006FR20729. (PS)	489		Safety Report
52,003	Certican®	12/21/2006	PHBS2006ES19166. (PS)	488		Safety Report
52,003	Certican®	12/21/2006	PHBS2006ES19190. (PS)	487		Safety Report
52,003	Certican®	12/18/2006	PHHO2006IT15311 Follow-up.	486		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	12/18/2006	PHHO2006FR20566. (PS)	485		Safety Report
52,003	Certican®	12/12/2006	PHHO2006US17466. Follow-up	484		Safety Report
52,003	Certican®	12/08/2006	PHHO2006IT15311. Follow-up	483		Safety Report
52,003	Certican®	12/06/2006	PHHO2006US11747 Follow-up. (PS)	482		Safety Report
52,003	Certican®	11/14/2006	Liver Transplantation Questions and Comments. (ES)			Other
52,003	Certican®	11/09/2006	PHHO2004US12965 Follow-up. (PS)	481		Safety Report
52,003	Certican®	11/07/2006	PHHO2006US17466 Follow-up. (PS)	480		Safety Report
52,003	Certican®	10/31/2006	PHHO2006US17466. (PS)	479		Safety Report
52,003	Certican®	10/24/2006	PHBS2006ES15520. Follow-up (PS)	478		Safety Report
52,003	Certican®	10/23/2006	PHHO2006US11747. Follow-up (PS)	477		Safety Report
52,003	Certican®	10/18/2006	New Investigator to Study No. CRAD001A2310. (ES)	469	2310	New Investigator
52,003	Certican®	10/18/2006	FDA has postponed the TC discussion for liver transplant on 23 Oct (2-3pm). (PS)			Other
52,003	Certican®	10/17/2006	PHBS2006ES15520. (PS)	476		Safety Report
52,003	Certican®	10/13/2006	The purpose of this submission is to provide additional information to support the discussions. (PS)	475		Response to FDA Request
52,003	Certican®	10/10/2006	This amendment describes the procedure to discontinue the study and allows for minimal data collection for the final visit to be conducted at Month 12 or on the date of last contact with the patient. (PS)	474	B253	Change In Protocol
52,003	Certican®	10/06/2006	The purpose of this submission is to provide a point response to the Division's comments. (PS)	472		Response to FDA Request
52,003	Certican®	10/06/2006	PHHO2006IT15311 Follow-up. (PS)	473		Safety Report
52,003	Certican®	10/03/2006	PHHO2006IT15311. (PS)	471		Safety Report
52,003	Certican®	09/29/2006	PHHO2006IT09039 Follow-up. (PS)	468		Safety Report
52,003	Certican®	09/26/2006	Fax to FDA. (7-Day Safety Report).			Safety Report
52,003	Certican®	09/14/2006	New Investigator to Study No. CRAD001A2309. Study No. CRAD001A2310 and Study No. CRAD001A2401. (PS)	461	2309 2310 2401	New Investigator
52,003	Certican®	08/31/2006	Fax from FDA. 10/23/06 Teleconference Grant Letter. (ES)			Other
52,003	Certican®	08/31/2006	FDA Letter. Type B meeting is scheduled October 23, 2006 to discuss general clinical disign issues and regulatory requirements to support the approval of Certican in liver transplantation. (PS)			General Correspondence
52,003	Certican®	08/31/2006	PHHO2006US02640 (PS)	467		Safety Report
52,003	Certican®	08/28/2006	PHHO2006US02640. (PS)	466		Safety Report
52,003	Certican®	08/21/2006	The purpose of this submission is to request a teleconference to discuus general clinical study design issues and requirements to support the approval of Certican in liver transplantation. (ES)	465		Other
52,003	Certican®	08/18/2006	PHHO2006US11747 Follow-up. (PS)	464		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	08/18/2006	PHHO2006BE00473 Follow-up. (PS)	463		Safety Report
52,003	Certican®	08/18/2006	PHHO2006DE09301 Follow-up. (PS)	462		Safety Report
52,003	Certican®	08/17/2006	PHHO2006US11747 Follow-up. (PS)	460		Safety Report
52,003	Certican®	08/16/2006	PHHO2006BE00473. (PS)	459		Safety Report
52,003	Certican®	08/15/2006	PHHO2006US11747. (PS)	458		Safety Report
52,003	Certican®	07/28/2006	PHHO2006DE09652 Follow-up. (PS)	457		Safety Report
52,003	Certican®	07/26/2006	PHHO2006CA03486 Follow-up. (PS)	456		Safety Report
52,003	Certican®	07/25/2006	PHHO2006DE09859 Follow-up. (PS)	455		Safety Report
52,003	Certican®	07/21/2006	PHHO2006DE09652 Follow-up.	454		Safety Report
52,003	Certican®	07/20/2006	PHHO2006DE09652 Follow-up. (PS)	451		Safety Report
52,003	Certican®	07/20/2006	PHHO2006IT09039 Follow-up. (PS)	452		Safety Report
52,003	Certican®	07/20/2006	PHHO2006DE09301 Follow-up. (PS)	453		Safety Report
52,003	Certican®	07/19/2006	PHHO2006DE09652 Follow-Up.	450		Safety Report
52,003	Certican®	07/19/2006	New Investigator to Study No. CRAD001A2309, Study No. CRAD001A2310, Study No. CRAD001A2401. (PS)	449		New Investigator
52,003	Certican®	07/17/2006	PHHO2006IT09039 Follow-Up.	448		Safety Report
52,003	Certican®	07/07/2006	PHHO2006DE09652.	447		Safety Report
52,003	Certican®	07/05/2006	PHBS2006AT07989 Follow-Up.	446		Safety Report
52,003	Certican®	06/27/2006	Comments pertaining to the statistical analysis plan for study 2411 provided in submission number 434.			
52,003	Certican®	06/27/2006	PHHO2006DE09859.	443		Safety Report
52,003	Certican®	06/27/2006	PHBS2006AT07989.	442		Safety Report
52,003	Certican®	06/27/2006	PHNU2006DE02164.	444		Safety Report
52,003	Certican®	06/27/2006	PHHO2006FR09362 Follow-Up.	325		Safety Report
52,003	Certican®	06/27/2006	PHHO2006FR05415 Follow-Up.	324		Safety Report
52,003	Certican®	06/24/2006	PHHO2008CA00612 (PS)	752		Safety Report
52,003	Certican®	06/21/2006	PHHO2006DE09301 Follow-Up.	441		Safety Report
52,003	Certican®	06/16/2006	PHHO2006IT09039.	440		Safety Report
52,003	Certican®	06/15/2006	PHHO2006DE09301.	439		Safety Report
52,003	Certican®	06/14/2006	PHHO2006IT07069 Follow-Up.	438		Safety Report
52,003	Certican®	06/14/2006	Fax to FDA. 7-Day IND Safety Report - (PHHO2006DE09301). (PS)			Safety Report
52,003	Certican®	06/13/2006	Fax to FDA. 7-Day IND Safety Report.			Safety Report
52,003	Certican®	06/06/2006	PHHO2008US06493 (PS)	743		Safety Report
52,003	Certican®	05/23/2006	PHBS2006ES06880. (PS)	437		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	05/19/2006	PHHO2006IT07069 Follow-up.	436		Safety Report
52,003	Certican®	05/11/2006	FDA request on January 31, 2006 Submitted a copy of the statistical analysis plan for the ongoing European heart study A2411.	434	A2411	Response to FDA Request
52,003	Certican®	05/11/2006	PHHO2006IT07069.	435		Safety Report
52,003	Certican®	05/02/2006	Working protocol for RAD001A2309 including Amendment 1 and Amendment 2.	433	A2309	Response to FDA Request
52,003	Certican®	05/01/2006	Amendment 1 to Study No. CRAD001A2310.	432		Change In Protocol
52,003	Certican®	04/17/2006	New Investigator to Study No. CRAD001A2309. New Investigator to Study No. CRAD001A2310. New Investigator to Study No. CRAD001A2401.	431		New Investigator
52,003	Certican®	04/11/2006	E-mail. Re: FDA TC on May 3, 2006 to discuss the everolimus transplant data proposal and requirements for pediatric data exclusivity (2nd Written Request). PS			Other
52,003	Certican®	03/17/2006	To discuss the eligibility requirements for Certican (enerolimus) to obtain pediatric data exclusivity.	428		General Correspondence
52,003	Certican®	03/15/2006	PHNR2006AU00570	427		Safety Report
52,003	Certican®	03/14/2006	PHHO2005US19658	426		Safety Report
52,003	Certican®	03/14/2006	New Investigator to Study No. CRAD001A2309.	425	2309	New Investigator
52,003	Certican®	03/13/2006	Amendment No. 2 to Protocol CRAD001A2309.	424		Change In Protocol
52,003	Certican®	03/08/2006	PHHO2006CA03486	423		Safety Report
52,003	Certican®	02/24/2006	Extension E-02 top Study No. CRAD001 B351.	422	B351	Change In Protocol
52,003	Certican®	02/23/2006	Amendment No. 1 to Study No. CRAD001A2309.	421	2309	Change In Protocol
52,003	Certican®	02/23/2006	Dr. George Demetri: Malignant neoplasm progression, ascites, cholelithiasis, pleural effusion, dyspnoea; Follow-up#3.	420	2206	Safety Report
52,003	Certican®	02/06/2006	[FRANCE] Dr. Jean-Charles Soria: Mental disorder, back pain, delusional disorder, persecutory type, myalgia; Follow-up#2.	419	2235	Safety Report
52,003	Certican®	02/01/2006	[FRANCE] Dr. Jacques Dantal: Respiratory tract infection, lung disorder, fluid overload: Follow-up#1	418	2420	Safety Report
52,003	Certican®	01/27/2006	This Annual Report covers the period November 15, 2004 through November 14, 2005. Includes clinical study information, preclinical study information and Foreign marketing developments.	417		Annual Report
52,003	Certican®	01/24/2006	[FRANCE] Dr. Jacques Dantal: Lung disorder.	416	2420	Safety Report
52,003	Certican®	01/19/2006	New Investigator to Study No. 2310: Drs. G. Ewald, S. D. Lick, N. Pereira, J. Boehmer, D. F. Pauly. Study No. 2309: Dr. S. Mulgaonkar. Study No. 2401: M. A. Hardy.	415	2310 2309 2401	New Investigator
52,003	Certican®	01/18/2006	[FRANCE] Dr. Jean-Charles Soria: Back pain, mental disorder, delusional disorder, persecutory type, myalgia; Follow-up#1.	413	2235	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	01/18/2006	This clinical information amendment contains Study CRAD001A2403 to support the discussions of January 31, 2006 between NVS and FDA regarding the next steps for Certican for the prophylaxis of organ rejection in heart transplant recipients.	414		Clinical Information Amendr
52,003	Certican®	01/11/2006	Dr. Howard Sher: Muscular weakness, myopathy steroid, hydrocephalus, cognitive deterioration, general physical health deterioration, mood altered, depression, cardiovascular disorder, fall; Follow-up#2.	412	2408	Safety Report
52,003	Certican®	01/04/2006	This submission contains documentation (Study No. CRAD001A2411) to support the discussions with the Agency for the January 31, 2006 meeting regarding next steps for Certican for the prophylaxis of organ rejection in heart transplant recipients.	411		Clinical Information Amendr Response to FDA Request
52,003	Certican®	01/03/2006	[BELGIUM] Dr. Van Oosterom: Gastritis haemorrhagic, right ventricular failure, pulmonary hypertension, anaemia, haematochezia, general physical health deterioration; Follow-up#3.	410	2206	Safety Report
52,003	Certican®	12/30/2005	[FRANCE] Dr. Jean-Charles Soria: Back pain, mental disorder, delusional disorder, persecutory type, myalgia.	409	C2235	Safety Report
52,003	Certican®	12/23/2005	Michelle Roos: Hyponatraemia, vomiting, diarrhoea, viral infection, dehydration.	408	AUS15	Safety Report
52,003	Certican®	12/22/2005	Dr. Howard Sher: Muscular weakness, myopathy steroid, hydrocephalus, fall; Fallow-up#1.	407	C2408	Safety Report
52,003	Certican®	12/20/2005	Dr. Alex Adjei: Pulmonary embolism, malignant neoplasm progression, chest pain, dyspnoea, respiratory failure, productive cough; Follow-up#2.	405	AUS15	Safety Report
52,003	Certican®	12/20/2005	New Investigator to Study No. A2310: Dr. Dale. G. Renlund, MD.	406	A2310	New Investigator
52,003	Certican®	12/19/2005	Dr. Howard Sher: Muscular weakness, fall.	404	2408	Safety Report
52,003	Certican®	12/19/2005	New Investigator to Study No. A2309: Dr. Adrian Cotterell, MD.	403	A2309	New Investigator
52,003	Certican®	12/13/2005	New Investigator to Study No. A2309: Drs. J. Leone, S. R. Abul-Ezz, M. L. Aaronson, B. Mistry. Study No. A2401: Dr. J. D. Scandling.	402	A2309 A2401	New Investigator
52,003	Certican®	12/07/2005	New Investigator to Study No. A2309: Drs. C. Franklin, H. Shidban, D. Y. Kim, T. D. Johnston. Study No. A2401: Dr. A. J. Tector.	401	A2309 A2401	New Investigator
52,003	Certican®	12/05/2005	New Investigator to Study No. A2309: Drs. B. Kahan, T. O'Connor, F. Shihab, T. Pruett. Study No. A2401: Drs. S. Bunnapradist, R. Ettenger. Study No. A2403: Dr. L. Czer.	400	A2309 A2401 A2403	New Investigator
52,003	Certican®	11/22/2005	Richard Stone. MD: Pneumonitis, dyspnoea, hypoxia, pleural effusion, performance status decreased, cough, pulmonary fibrosis, fatigue, productive cough, respiratory distress; Follow-up#4.	399	2207	Safety Report
52,003	Certican®	11/17/2005	[GERMANY] Prof. Struber: Renal impairment, immunosuppressant drug level increased, blood creatinine increased, drug interaction; Follow-up#1.	398	DE06	Safety Report
52,003	Certican®	11/14/2005	Dr. Judith Wolf: hyponatraemia, condition aggravated, anorexia, nausea, asthenia, muscle spasms, hypotension.	397	2409	Safety Report
52,003	Certican®	11/11/2005	Dr. Lauren Abrey: International normalised ratio increased, haematuria, drug interaction; Follow-up#1.	396	C2408	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	11/01/2005	Dr. Lauren Abrey: International normalised ratio increased, haematuria.	395	C2408	Safety Report
52,003	Certican®	10/21/2005	The purpose of this submission is to provide a point-by-point response to the Division's comments for study CRAD001A2310.	394		Clinical Information Amendr Response to FDA Request
52,003	Certican®	10/14/2005	[GERMANY] Prof. Struber: Renal impairment, drug interaction, immunosuppressant drug level increased, blood creatinine increased.	393	ADE06	Safety Report
52,003	Certican®	10/04/2005	Dr. Alex Adjei: Pulmonary embolism, chest pain, dyspnoea, respiratory failure, productive cough; Follow-up#1.	392	AUS15	Safety Report
52,003	Certican®	09/30/2005	FDA FAX containing statistical team comments pertaining to Study A2310, submitted 8/29/2005. FDA requested a copy of the final Statistical Analysis Plan and DSMB for Study A2310 prior to the primary data analysis.		A2310	Other
52,003	Certican®	09/28/2005	Dr. Alex Adjei: pulmonary embolism, chest pain, dyspnoea, respiratory failure, productive cough.	391	AUS15	Safety Report
52,003	Certican®	09/26/2005	Richard Stone, MD: Pneumonitis, nausea, dyspnoea, hypoxia, pleural effusion, performance status decreased, cough, pulmonary fibrosis, fatigue, productive cough, respiratory distress; Follow-up#3.	390	2207	Safety Report
52,003	Certican®	09/23/2005	Richard Stone: Pneumonia bacterial, diarrhoea, supraventricular tachycardia, hypokalaemia, pleural effusion, hypoxia, dyspnoea, crackles lung, troponin increased; Follow-up#2.	389	2207	Safety Report
52,003	Certican®	09/23/2005	E-MAILS to/from FDA regarding draft protocol A2310 submitted to the Division on September 6, 2005 (SN 387). In addition, NVS responded to FDA request for the location of IVUS Data Analysis Results for Heart B253 for NDA 21-628 update #2.		A2310	Response to FDA Request
52,003	Certican®	09/22/2005	Fax to FDA (7-Day Safety Report).			Safety Report
52,003	Certican®	09/16/2005	Amendment No. 1 to Study No. RAD001 B253 E3.	388	B253	Change In Protocol
52,003	Certican®	09/06/2005	New Protocol to Study No. A2310 entitled, "A 24-month, multicenter, randomized, open-label noninferiority study of efficacy and safety comparing two exposures of concentration-controlled Certican with reduced neoral versua 3.0 g MMF with standard dose Neoral in de novo heart transplant recipients.	387	A2310	New Protocol
52,003	Certican®	08/25/2005	Richard Stone MD: Pneumonitis, nausea, drug interaction potentiation, dyspnoea, hypoxia, pleural effusion, performance status decreased, cough, pulmonary fibrosis; Follow-up#2.	386	2207	Safety Report
52,003	Certican®	08/23/2005	Dr. Diane Cibrik: Nephropathy toxic, drug interaction, renal tubular necrosis, blood creatinine increased.	385	US09	Safety Report
52,003	Certican®	08/19/2005	New Investigator to Study No. CRAD001A2401: Drs. S. Greenstein, J. D. Mahan, J. R. Thistlethwaite, M. Cooper, D. Laskow, P. Morrissey, L. Chan, C. A. Shadur, O. Pankewycz. Study No. CRAD001A2403: Drs. M. W. Weston, M. J. Zucker, D. Mancini.	384	2401 2403	New Investigator
52,003	Certican®	08/09/2005	Dr. Francis Giles: Leukocytociastic vasculitis, hyperglycaemia, oedema peripheral, calcinosis, pain, erythema, rash, eschar; Follow-up#1.	383	2406	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	08/09/2005	TELECON confirming meeting scheduled with FDA for August 22, 2005, to discuss protocol A2310 with modeling simulations.			Memo of Record (telephone report)
52,003	Certican®	08/05/2005	[GREAT BRITAIN] Dr. Ian Judson: Gastrointestinal haemorrhage, bone marrow depression, cardiac arrest, malignant neoplasm progression, melaena, vomiting, haemoglobin decreased, platelet count decreased, dyspnoea, abdominal pain, loss of consciousness; Follow-up#3	382	2101	Safety Report
52,003	Certican®	08/05/2005	[AUSTRALIA] Dr. Dan Chambers: Vasculitis gastrointestinal, laukocytoclastic vasculitis, dermatitis allergic, neutropenia, white blood cell countdecreased, diarrhoea, vomiting, intestinal ischaemia, biopsy colon abnormal, petechiae, biopsy skin abnormal: Follow-up#1	381		Safety Report
52,003	Certican®	08/03/2005	[AUSTRALIA] Dr. Dan Chambers: Vasculitis gastrointestinal, leukocytoclastic vasculitis, dermatitis allergic, neutropenia, white blood cell count decreased, diarrhoea, vomiting, intestinal ischaemia, biopsy intestine abnormal, biopsy colon abnormal, petechiae, biopsy skin abnormal.	380		Safety Report
52,003	Certican®	08/02/2005	FDA FAX containing minutes from telecon of July 21, 2005. FDA also addressed NVS request for a follow-up teleconference to discuss the heart protocol (A2310).			FDA/Novartis Meeting Minu
52,003	Certican®	07/06/2005	Dr. Judith Wolf: Hyperglycaemia; Follow-up#1.	378	C2409	Safety Report
52,003	Certican®	07/01/2005	Dr. L. Miller: Cardiac tamponade, anastomotic leak, unresponsive to verbal stimuli, fall, cardiac arrest, accelerated idioventricular rhythm; Follow-up#5	377	A2403	Safety Report
52,003	Certican®	06/30/2005	[GREAT BRITAIN] Prof. Ian Judson: Cryptogenic organizing pneumonia, lung infiltration, dyspnoea, dyspnoea exertional; Follow-up#1	376	2101	Safety Report
52,003	Certican®	06/27/2005	This submission provides a point-by-point response to the Division's comments for study CRAD001A2310 submitted February 4, 2005.	375		Clinical Information Amendr
52,003	Certican®	06/22/2005	New Protocol to Study No. CRAD001 A2309 entitled, "A 24-Month, multicenter, randomized, open-label non-inferiority study of efficacy and safety comparing concentration-controlled Certican in two doses (1.5 and 3.0 mg/day starting doses) with reduced Neoral versus 1.44 g Myfortic with standard dose of Neoral in de novo renal transplant patients.	374	A2309	New Protocol
52,003	Certican®	06/21/2005	[AUSTRALIA] Dr. Josette Eris: Drug exposure during pregnancy, premature rupture of membranes, normal delivery, hypertension; Follow-up#1.	373	A2307	Safety Report
52,003	Certican®	06/08/2005	Howard Burris, MD: Mental status changes, anaemia.	372	2101	Safety Report
52,003	Certican®	06/03/2005	TELECON with FDA in order to schedule a telecon on 21-Jul-2005 to discuss protocol A2310 (heart) statistical model and simulations for exposures. The Division will also respond to NVS proposals on A2309 (kidney) at the same time.			Memo of Record (telephone report)
52,003	Certican®	06/02/2005	Dr. L. Miller: Cardiac tamponade, anastomotic leak, unresponsive to verbal stimuli, fall, cardiac arrest, accelerated idioventricular rhythm; Follow-up#4.	371	A2403	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	06/02/2005	[GREAT BRITAIN] Dr. Ian Judson: Gastrointestinal haemorrhage, bone marrow depression, circulatory collapse, cardiac arrest, malignant neoplasm progression, melaena, vomiting, haemoglobin decreased, platelet count decreased, dyspnoea, abdominal pain, loss of consciousness; Follow-up#2.	370	2101	Safety Report
52,003	Certican®	06/01/2005	[AUSTRALIA] Dr. Steve Chadban: Drug exposure during pregnancy, cerebral ventricle dilatation, renal disorder, umbilical cord vascular disorder.	369	2307E1	Safety Report
52,003	Certican®	06/01/2005	[AUSTRALIA] Dr. Josette Eris: Drug exposure during pregnancy, premature rupture of membranes, normal delivery, hypertension.	368	A2307	Safety Report
52,003	Certican®	05/31/2005	[GREAT BRITAIN] Dr. Ian Judson: Gastrointestinal haemorrhage, bone marrow depression, circulatory collapse, cardiac arrest, malignant neoplasm progression, melaena, vomiting, haemoglobin decreased, platelet count decreased, dyspnoea, abdominal pain, loss of consciousness; Follow-up#1.	367	2101	Safety Report
52,003	Certican®	05/26/2005	[SWITZERLAND] Dr. D. Uehlinger: Eye haemorrhage, Retinal detachment, eye operation; Follow-up#1.	366	A2307	Safety Report
52,003	Certican®	05/20/2005	Response to request to provide questions for discussion on study CRAD001A2301.	365		Response to FDA Request
52,003	Certican®	05/19/2005	This Annual Report covers the period November 15, 2003 through November 14, 2004. Includes clinical study information, preclinical study information, Fareign marketing developments and outstanding regulatory business.	364		Annual Report
52,003	Certican®	05/16/2005	Dr. L. Miller: Cardiac tamponade, anastomotic leak, unresponsive to verbal stimuli, fall, cardiac arrest, accelerated idioventricular rhythm; Follow-up#3.	363	2403	Safety Report
52,003	Certican®	05/13/2005	Point-by-point response to the Division's comments for Study CRAD001A2309.	362		Response to FDA Request
52,003	Certican®	05/12/2005	Richard Stone. MD: Interstitial lung disease, pneumonitis, nausea, drug interaction potentiation, dyspnoea, hypoxia, pleural effusion, performance status decreased, cough, pulmonary fibrosis; Follow-up#1.	361	2207	Safety Report
52,003	Certican®	05/12/2005	Amendment No. 4 to Study No. CRAD001AUS09.	360	US09	Change in Protocol
52,003	Certican®	05/11/2005	Richard Stone. MD: Pneumonia, diarrhoea, dyspnoea, hypoxia, pleural effusion, crackles lung; Follow-up#1	359	2207	Safety Report
52,003	Certican®	05/06/2005	[SWITZERLAND] Dr. D. Uehlinger: Eye haemorrhage, retinal detachment, eye operation.	358	2307E1	Safety Report
52,003	Certican®	05/06/2005	Richard Stone: Pneumonia, hypoxia, diarrhoea, pleural effusion, dyspnoea, crackles lung.	357	2207	Safety Report
52,003	Certican®	05/05/2005	Dr. L. Miller: Cardiac tamponade, anastomotic leak, unresponsive to verbal stimuli, fall, cardiac arrest, accelerated idioventricular rhythm; Follow-up#2.	356	A2403	Safety Report
52,003	Certican®	05/05/2005	TELECON with FDA regarding Advisory Committee meeting date and the teleconference to be scheduled for the new heart study A2310 regarding modeling and simulations.			Memo of Record (telephone report)
52,003	Certican®	05/04/2005	Richard Stone, MD: Interstitial lung disease, pneumonitis, nausea, dyspnoea, hypoxia, pleural effusion, performance status decreased, cough, pulmonary fibrosis.	355	2207	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	05/03/2005	Dr. L. Miller: Cardiac tamponade, anastomotic leak, unresponsive to verbal stimuli, fall, cardiac arrest, accelerated idioventricular rhythm; Follow-up#1	354	2403	Safety Report
52,003	Certican®	04/28/2005	Dr. L. Miller: Cardiac tamponade, anastomic leak, unresponsive to verbal stimuli, fall.	353	2403	Safety Report
52,003	Certican®	04/27/2005	[GREAT BRITAIN] Prof. Ian Judson: Cryptogenic organizing pneumonia, lung infiltration, dyspnoea, dyspnoea exertional.	352	2101	Safety Report
52,003	Certican®	04/24/2005	[GERMANY] Peter Reichardt: Neoplasm progression, tumour haemorrhage, haemoglobin decreased, blood lactate dehydrogenase increased, blood potassium increased, blood uric acid increased, hyperbilirubinaemia, blood creatinine increased; Follow-up#1.	350	2206	Safety Report
52,003	Certican®	04/19/2005	New Investigator to Study No. CRAD001A2401: Drs. M. Koerner, E. Hartmann, H. Shidban, J. D. Whelchel, J. Leone, G. Basadonna. Study No. CRAD001A2403: Drs. D. Mancini, L. R. Goldberg.	349	A2401 A2403	New Investigator
52,003	Certican®	04/18/2005	[GERMANY] Peter Reichardt: Tumour lysis syndrome, tumour haemorrhage, haemoglobin decreased, blood lactate dehydrogenase increased, blood potassium increased, blood uric acid increased, hyperbilirubinaemia, blood creatinine increased.	348	2206	Safety Report
52,003	Certican®	04/08/2005	James Yao: Hypoglycaemia, feeling abnormal, confusional state.	347	BUS52	Safety Report
52,003	Certican®	04/06/2005	[GERMANY] Dr. Kaltenhaeuser: Septic shock, peripheral occlusive disease, vasculitis, drug level decreased, skin ulcer, haemoglobin decreased, C-reactive protein increased.	346		Safety Report
52,003	Certican®	04/04/2005	TELECON with FDA regarding CIOMS VI recommendations and investigator notifications from transplant and oncology indications.			Memo of Record (telephone report)
52,003	Certican®	03/28/2005	FAX from FDA containing questions on Serial Number 339, 341 and 342.			
52,003	Certican®	03/15/2005	[SWITZERLAND] Malabsorption, acne, drug interaction, drug level decreased.	345		Safety Report
52,003	Certican®	03/09/2005	New Investigator to Study No. CRAD001A2401: Drs. L. Goldberg, A. H. Wilkinson, R. Peddi, C. A. Shadur.	344	A2401	New Investigator
52,003	Certican®	03/02/2005	[CANADA] DR. Cole: Diffuse alveolar damage, cryptogenic organizing pneumonia, obliterative bronchiolitis, lung transplant rejection, cardiac arrest, pneumonia, viral infection, respiratory tract infection, pulmonary oedema, pulmonary fibrosis, respiratory disorder, haemodynamic instability, dyspnoea, hypoxia, myalgia, pyrexia, productive cough, respiratory failure, circulatory collapse.	343	A2401	Safety Report
52,003	Certican®	02/16/2005	Submission of replacement pages for the draft clinical protocol (Study CRAD001A2310) submitted February 4, 2005 (Serial No. 339).	342		Clinical Information Amendr
52,003	Certican®	02/07/2005	New Investigator to Study No. CRAD001A2405: Drs. Randall C. Starling, John M. Herre.	340	2405	New Investigator
52,003	Certican®	02/04/2005	This submission provides a point-by-point response to the Division's comments dated December 3, 2004, and contains the revised complete protocols for review and comment.			Clinical Information Amendr Response to FDA Request

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	01/25/2005	Letter of cross reference granting permission to the Division of Special Pathogen and Immunologic Drug Products to allow representatives from other branches of the FDA to discuss those parts of our documents relevant for Guidant's Drug Eluting Stent Investigational Device Exemptions.	338		General Correspondence
52,003	Certican®	01/14/2005	This letter authorizes the FDA to refer to this IND (and NDA 21-560 and 21-628) in support of an IND that will be filed by W. H. Tang, MD.	337		General Correspondence
52,003	Certican®	12/22/2004	New Investigator to Study No. CRAD001A2403: Dr. Leslie Miller, MD.	336	A2403	New Investigator
52,003	Certican®	12/14/2004	New Investigator to Study No. CRAD001AUS09: Dr. Oleh Pankewycz, MD. Study No. CRAD001A2401: Dr. Randall Starling.	335	US09 A2401	New Investigator
52,003	Certican®	12/09/2004	[CANADA] Dr. Cole: Diffuse alveolar damage, cryptogenic organizing pneumonia, obliterative bronchiolitis, lung transplant rejection, cardiac arrest, pneumonia, viral infection, respiratory tract infection, pulmonary oedema, pulmonary fibrosis, respiratory disorder, haemodynamic instability, dyspnoea, hypoxia, myalgia, pyrexia, productive cough; Follow-up#2.	334	2401	Safety Report
52,003	Certican®	12/03/2004	New Investigator to Study No. CRAD001A2401: Drs. P. J. Hauptman, A. Guasch, R. M. Ferguson. Study No. CRAD001A2403: Dr. G. M. Felker. Study No. CRAD001A2405: Dr. J. Kobashigawa.	333	2401 2403 2405	New Investigator
52,003	Certican®	11/05/2004	New Investigator to Study No. CRAD001US09: Drs. D. Cibrik, M. Hardy; Study No. CRAD001A2401: Drs. J. Butler, F. Wright, G. Klintmalm, K. Butt, J. A. Hill; Study No. CRAD001 A2403: Drs. B. Raybum, F. W. Smart; Study No. CRAD001 A2405: Dr. L. Miller.	332	US09 A2401 A2403 A2405	Annual Report
52,003	Certican®	11/02/2004	Dr. Meir Wetzer. MD: Cardiac failure congestive, asthma, dyspnoea, oedema peripheral, eyelid oedema, weight increased, dilatation atrial, ventricular hypertrophy; Follow-up#1	331	2207	Safety Report
52,003	Certican®	10/29/2004	[CANADA] Dr. Cole: Lung transplant rejection, cardiac arrest, pneumonia, viral infection, respiratory tract infection, respiratory disorder, haemodynamic instability, dyspnoea, hypoxia, myalgia, productive cough; Follow-up#1	330	2401	Safety Report
52,003	Certican®	10/26/2004	New Investigator to Study No. CRAD001A2401: Drs. D. Hricik, V. G. Valentine, H. J. Eisen, T. Pruett, R. Benza, J. Curtis, P. R. Rajagopalan. Study No. CRAD001A2403: Dr. A. J. Tector.	329	A2401 A2403	New Investigator
52,003	Certican®	10/19/2004	[SPAIN] Dr. Tabernero: Malignant neoplasm progression, stomatitis, drug ineffective, enterocolitis, abdominal pain, anorexia, vomiting, constipation, skin lesion, metastases to peritoneum, performance status decreased, respiratory disorder, hypoalbuminaemia, generalised oedema; Follow-up#1.	328	C2107	Safety Report
52,003	Certican®	10/15/2004	[CANADA] Dr. Cole: Lung transplant rejection, cardiac arrest, pneumonia, respiratory tract infection, viral infection, respiratory disorder, haemodynamic instability, dyspnoea, hypoxia, myalgia, pyrexia, productive cough.	327	2401	Safety Report
52,003	Certican®	10/12/2004	Dr. Meir Wetzler. MD: Cardiac failure congestive, dyspnoea, oedema peripheral, eyelid oedema, weight increased, dilatation atrial, ventricular hypertrophy.	326	2207	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	10/01/2004	New Investigator to Study No. CRAD001A2401: Drs. B. Kahan, J. E. Loyd, A. Frost, D. J. Conti, J. M. Hare. Study No. CRAD001US09: Drs. M. T. Sellers, M. Cooper, S. Bunnapradist, V. R. Peddi, E. Hartmann, D. Norman.	325	A2401 US09	New Investigator
52,003	Certican®	09/27/2004	Dr. Francis Giles: Leucocytoclastic vasculitis, hyperglycaemia, oedema peripheral, calcinosis, deep vein thrombosis, pain, erythema, rash, eschar.	324	2406	Safety Report
52,003	Certican®	09/24/2004	New Investigator to Study No. US09; Drs. S. Mulgonkar, M. I. Lorber, E. Elkhammas, R. B. Love, D. G. Wombolt; Study No.2403; Dr. H.J. Eisen; Study No. 2405; Dr. S. F. Davis.	323	US09 2403 2405	New Investigator
52,003	Certican®	09/23/2004	[SPAIN] Dr. Tabernero: Enterocolitis, stomatitis, abdominal pain, anorexia, vomiting, constipation.	322	C2107	Safety Report
52,003	Certican®	09/20/2004	New Investigator to Study No. CRAD001A2401: Drs. S. Mulgonkar, M. I. Lorber, E. Elkhammas, R. B. Love, D. G. Wombolt: Study No. CRAD001US09: Drs. J. Ortiz, S. Greenstein, M. I. Abecassis, G. Francos, R. Stephan.	321	A2401 US09	New Investigator
52,003	Certican®	09/08/2004	Dr. Judith Wolf: Hyperglycaemia.	320	2409	Safety Report
52,003	Certican®	09/03/2004	New protocol to Study No. CRAD001 A2403 entitled, "A six-Month, multicenter, randomized, Open-label Study of the Safety, Tolerability and Efficacy of two Neoral doses in addition to Certican and Steroids in de novo Heart Transplant Recipients". Investigator: Howard Eisen, MD.	319	A2403	New Protocol
52,003	Certican®	08/27/2004	Vincent Valentine. MD: Renal failure acute, renal insufficiency, thrombocytopenia, lung transplant rejection, hyperglycaemia, blood creatinine increased, blood urea increased, fatigue, malaise, graft loss: Follow-up#1	318	B152	Safety Report
52,003	Certican®	08/20/2004	New protocol to Study No. CRAD001 A2405 entitled, "A Six-Month, Multicenter, Open-Label, single arm, pilot study of the renal safety of Everolimus in addition to Neoral in cardiac transplant recipients with established Allograft Vasculopathy". Also, Amendment 1 to Protocol CRAD001 A2405. New Investigator: Howard Eisen, MD. And Information Amendment: New Concept design for De Novo Heart Study.	317	A2405	New Protocol
52,003	Certican®	08/18/2004	Vincent Valentine. MD; Lung transplant rejection, renal failure acute, renal insufficiency, thrombocytopenia, hyperglycaemia, fatigue, malaise, graft loss, blood creatinine increased, blood urea increased.	316	B152E1	Safety Report
52,003	Certican®	08/12/2004	[SWITZERLAND] Prof. W. Kiowski: Pyrexia, C-reactive protein increased, red blood cell sedimentation rate increased; Follow-up#2	315	B253	Safety Report
52,003	Certican®	07/08/2004	Dr. George Demetri: Ascites, disease progression, drug interaction, dyspnoea; Follow-up#2	314	2206	Safety Report
52,003	Certican®	07/02/2004	Dr. George Demetri: Ascites, disease progression, dyspnoea; Follow-up#1	313	2206	Safety Report
52,003	Certican®	06/28/2004	Dr. George Demetri: Dyspnoea, ascites, disease progression, drug ineffective.	312	2206	Safety Report
52,003	Certican®	06/16/2004	[BELGIUM] Dr. Van Oosterom: Gastritis haemorrhagic, right ventricular failure, pulmonary hypertension, anaemia, blood in stool, general physical health deterioration: Follow-up#2	311	2206	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	06/14/2004	[BELGIUM] Dr. Van Oosterom: Gastritis haemorrhagic, right ventricular failure, pulmonary hypertension, anaemia, blood in stool, general physical health deterioration; Follow-up#1	310	2206	Safety Report
52,003	Certican®	06/10/2004	This Annual Report covers the period November 15, 2002 through November 14, 2003. Includes clinical/preclinical information and Foreign marketing developments.	309		Annual Report
52,003	Certican®	06/10/2004	[BELGIUM] Dr. Van Oosterom: Gastritis haemorrhagic, right ventricular failure, pulmonary hypertension, anaemia, blood in stool, general physical health deterioration.	308	2206	Safety Report
52,003	Certican®	06/03/2004	Howard A. Burris, III, MD; Epistaxis, platelet count decreased, bleeding time prolonged; Follow-up#1	307	2101	Safety Report
52,003	Certican®	05/24/2004	[SWITZERLAND] Prof. W. Kiowski: Pyrexia, C-reactive protein increased, red blood cell sedimentation rate increased; Follow-up#1	306	B253	Safety Report
52,003	Certican®	05/03/2004	Howard A. Burris, III, MD: Epistaxis, platelet count decreased, bleeding time prolonged.	305	2101	Safety Report
52,003	Certican®	04/07/2004	FAX from FDA containing comments from the reviewing medical officer, statistician and clinical pharmacologist on the February 27, 2004 protocol for Study A2411.			
52,003	Certican®	04/06/2004	[BELGIUM] Dr. Van Oosterom: Gastritis haemorrhageic, thrombocytopenia, anaemia, nausea, vomiting, melaena.	304	2206	Safety Report
52,003	Certican®	03/17/2004	Amendment No.1 and Amendmen No. 2 to Study No. RAD001 A2410.	303	A2410	Change In Protocol
52,003	Certican®	03/17/2004	Amendment No. 1 and Amendment No. 2 to Study No. RAD001 A2409.	302	A2409	Change In Protocol
52,003	Certican®	03/17/2004	Amendment No.1 and Amendment No. 2 to Study No. RAD001 A2408.	301	A2408	Change In Protocol
52,003	Certican®	03/15/2004	New protocol to Study No. A2409 entitled, "Open-label, two-period, single-sequence, crossover study to evaluate the influence of ketoconazole on the pharmacokinetics of everolimus in healthy subjects. Investigator: Dr. Magdy Shenouda, MD.	300	A2409	New Investigator New Protocol
52,003	Certican®	03/12/2004	New protocol to Study No. A2410 entitled, "A open-label, two-period, single-sequence, crossover study to evaluate the influence of verapamil on the pharmacokinetics of everolimus in healthy subjects. New investigator: Mark.J. Allison, MD.	299	A2410	New Investigator New Protocol
52,003	Certican®	03/11/2004	New protocol to Study No. A 2408 entitled, "Open-label, two-period, single-sequence, crossover study to evaluate the influence of erythromycin on the pharmacokinetics of everolimus in healthy subjects. Investigator: Dr. Magdy Shenouda, MD.	298	A2408	New Investigator New Protocol
52,003	Certican®	03/10/2004	FAX from FDA containing comments on the drug-drug interaction protocols submitted February 18, 2004, Serial No. 294)			
52,003	Certican®	03/05/2004	New Investigator to Study No. A 2401: Dr. Jeffrey Punch, MD.	297	A2401	New Investigator

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	02/27/2004	[FRANCE] Alexandre Karras; Histiocytosis haematophagic, human herpesvirus 6 infection, graft loss, lymphadenopathy, neurological symptom, gastrointestinal disorder, weight decreased, pyrexia, anaemia, haemoglobin decreased, white blood cell count decreased, platelet count decreased, liver function test abnormal, blood lactate dehydrogenase increased, blood triglycerides increased, serum ferritin increased, hyponatraemia, nephrectomy.	296		Safety Report
52,003	Certican®	02/27/2004	In response to the approvable letter for NDA 21-628 and subsequent interactions with the Division, this submission contains a revised study summary and protocol for a de novo heart transplantation study for review and comment prior to initiation.	295	A2411	Clinical Information Amendr Response to FDA Request
52,003	Certican®	02/18/2004	In response to a recommendation from the Division at the January 6, 2004 teleconference for drug interaction studies, this submission contains final protocols for each drug interaction study and a request for timely review comments.	294		
52,003	Certican®	02/13/2004	FAX from FDA containing comments on the protocol synopses for three drug-drug interaction studies submitted February 6, 2004.			
52,003	Certican®	02/03/2004	In response to a recommendation from the Division at the January 6, 2004 teleconference for drug interaction studies, this submission contains a study summary and assessment schedule for each drug interaction study	293		Response to FDA Request
52,003	Certican®	12/08/2003	This letter authorizes FDA to refer to this IND in support of an IND that will be filed by B. Kahan, MD.	291		General Correspondence
52,003	Certican®	11/03/2003	New protocol: Study No. CRAD001AUS09 entitled, "A prospective, multicenter, open label, randomized study of the safety, tolerability and efficacy of Certican (RAD001) with Simulect, corticosteroids and lower levels versus higher levels of tacrolimus in de novo renal transplant recipients.	290	US09	New Protocol
52,003	Certican®	10/01/2003	[SWEDEN] Gunnar Martensson: Respiratory failure, cardiac failure NOS, pneumonitis NOS, acute respiratory distress syndrome, coagulopathy, bronchial obstruction, asthma nos, hypoxia, lung infiltration NOS, alveolitis NOS, pulmonary haemorrhage, pulmonary oedema NOS, hypoperfusion, atelectasis, lung consolidation, dyspnoea, eosinophilia; Follow-up#4	289	B159	Safety Report
52,003	Certican®	09/26/2003	[SWEDEN] Gunnar Martensson: Respiratory failure, cardiac failure NOS, pneumonitis NOS, lung disorder NOS, coagulopathy, bronchial obstruction, asthma NOS, hypoxia, lung infiltration NOS, alveolitis NOS, pulmonary haemorrhage, lung consolidation, dyspnoea, eosinophilia; Follow-up#3.	288	B159	Safety Report
52,003	Certican®	09/15/2003	[AUSTRALIA] Dr. Scott Campbell; Optic neuropathy NOS, nuclear magnetic resonance imaging brain abnormal, vision blurred, visual acuity reduced; Follow-up#3	287	A2307	Safety Report
52,003	Certican®	09/12/2003	Minutes of the September 11 and 12, 2003, meeting to discuss the Pediatric Written Request.			FDA/Novartis Meeting Minu
52,003	Certican®	09/11/2003	TELECON with FDA to discuss Novartis' Request for a Type A Meeting on the Written Request and data exclusivity.			Memo of Record (telephone report)
52,003	Certican®	09/05/2003	FDA LETTER responding to the request for a meeting to discuss the pediatric Written Request.			
52,003	Certican®	08/21/2003	Request a Type A meeting to discuss the Written Request prior to the NDA action date of October 20, 2203 (NDAs 21-560 and 21-628).	286		Request for FDA Meeting

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	08/07/2003	TELECON with FDA regarding 24 month statistical analysis plan for Study No. B159 (Submitted July 9, 2003, Serial No. 285)			Memo of Record (telephone report)
52,003	Certican®	08/01/2003	TELECON with FDA to discuss the statistical proposals found acceptable for Study B159 24-month data analysis.			Memo of Record (telephone report)
52,003	Certican®	07/10/2003	In reference to the Pre-NDA meeting held on May 1, 2003, this amendment to Study B159 provides for a detailed statistical methodology for the 24-month data analysis.	285	B159	Change In Protocol
52,003	Certican®	05/27/2003	Submission of slides presented at pre-NDA meeting held on May 1, 2003, to discuss the use of Certican in lung transplantation.	284		General Correspondence
52,003	Certican®	05/05/2003	FAX from FDA containing attendence sheets for May 1, 2003 pre-NDA meeting.			
52,003	Certican®	05/01/2003	FDA minutes of the May 1, 2003 pre-NDA/Type B meeting. The purpose of the meeting was to obtain feedback from the Agency concerning the proposed NDA in lung transplantation.			FDA/Novartis Meeting Minu
52,003	Certican®	04/29/2003	FAX from FDA containing comments concerning pre-NDA background package (Serial No. 281)			
52,003	Certican®	04/25/2003	FAX from FDA containing comments concerning pre-NDA background package (Serial No. 281)			
52,003	Certican®	04/07/2003	FDA LETTER containing details of the Type B meeting scheduled for May 1, 2003, requested March 21, 2003.			
52,003	Certican®	04/03/2003	This Annual Report covers the period November 15, 2001 through November 14, 2002. Includes clinical and preclinical study/safety information.	283		Annual Report
52,003	Certican®	04/01/2003	Submission of additional desk copies of the Briefing Book dated March 21, 2003.	282		Response to FDA Request
52,003	Certican®	03/21/2003	This Briefing Book is being submitted in preparation for a pre-NDA (Type B) meeting scheduled May 1, 2003, to discuss submission proposals to support the use of Certican in lung transplantation. This Briefing Book replaces submission dated March 4, 2003 (Serial No. 279)	281		Briefing Book
52,003	Certican®	03/19/2003	[SWEDEN] Gunnar Martensson; Respiratory failure, cardiac failure NOS, pneumonitis NOS, bronchial obstruction, asthma NOS, hypoxia, lung infiltration NOS, alveolitis NOS, pulmonary haemorrhage, lung consolidation, dyspnoea NOS, eosinophilia; Follow-up#2	280	B159	Safety Report
52,003	Certican®	03/04/2003	Request for pre-NDA meeting (Type B) to discuss submission proposals in support of an NDA for the use of Certican in lung transplantation.	279		
52,003	Certican®	02/19/2003	[SWEDEN] Gunnar Martensson; Respiratory failure, cardiac failure NOS, pneumonitis NOS, bronchial obstruction, asthma NOS, hypoxia, lung infiltration NOS, alveolitis NOS, lung consolidation, dyspnoea NOS, eosinophilia; Follow-up#1	278	B159	Safety Report
52,003	Certican®	01/03/2003	[AUSTRALIA] Dr. Scott Campbell; Optic neuropathy NOS, nuclear magnetic resonance imaging brain abnormal, vision blurred, visual acuity reduced; Follow-up#2	277	2307	Safety Report
52,003	Certican®	12/24/2002	[AUSTRALIA] Dr. Scott Cambell; Optic neuropathy NOS, nuclear magnetic resonance imaging brain abnormal, vision blurred, visual acuity reduces; Follow-up#1	276	2307	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	11/19/2002	TELECON with FDA on November 18 and 19, 2002 to discuss tradename potential for similarity between Certican and Foradil Certihaler.			Memo of Record (telephone report)
52,003	Certican®	10/29/2002	TELECON with FDA regarding the SAS data transfer.			Memo of Record (telephone report)
52,003	Certican®	10/25/2002	Minutes of the October 25, 2003 meeting to discuss plans for submitting the statistical datasets for the upcoming NDAs.			FDA/Novartis Meeting Minu
52,003	Certican®	10/21/2002	FDA LETTER asking Novartis to determine if the new protocol submitted August 6, 2002, Serial No. 268, meets the requirements for listing in the Clinical Trials Data Bank.			
52,003	Certican®	10/17/2002	[Sweden] Gunnar Martensson; Pneumonitis NOS, bronchial obstruction, asthma NOS, Hypoxia, alveolitis NOS, respiratory failure, lungconsolidation, dyspnoea NOS, eosinophilia	274	B159	Safety Report
52,003	Certican®	10/15/2002	[France] Prof Bourbigot; Protocol No. CRAD001 A2307; renal impairment NOS, hepatitis acute, concomitant disease progression, blood creatinine increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, alanine aminotransferase increased; follow-up# 2	273	A2307	Safety Report
52,003	Certican®	09/20/2002	[Australia] Dr Scott Campbell; Optic neuropathy NOS, vision blurred, visual acuity reduced	272	A2307	Safety Report
52,003	Certican®	09/05/2002	TELECON from FDA assigning NDA Numbers and User Fee ID#.			Memo of Record (telephone report)
52,003	Certican®	09/04/2002	TELECON with FDA to discuss the submission of a new Oncology IND for RAD.			Memo of Record (telephone report)
52,003	Certican®	09/04/2002	A telecon is being requested to discuss a proposal for the transfer of SAS datasets and programs for Division review.	271		General Correspondence
52,003	Certican®	08/15/2002	This submission provides a copy of the communication received from the Data Safety Monitoring Board (DSMB) dated July 23, 2002 and the Novartis written notification to Study B253 investigators, dated July 26, 2002.	270		Clinical Information Amendr
52,003	Certican®	08/08/2002	n reference to a telephone conversation on August 5, 2002, regarding a GCP audit, this correspondence provides written notification to the file with a copy of the letter submitted on August 6, 2002, to the Division of Scientific Investigations.	269		General Correspondence
52,003	Certican®	08/06/2002	New protocol: Study No. US08 entitled, "Single center, prospective, single-arm, open-label trial of rapid steroid withdrawal in combination with Certican (RAD), Simulect, and Neoral for the prevention of acute rejection in de novo renal transplant recipients". Investigator: R. M. Ferguson, MD	268	US08	New Protocol
52,003	Certican®	08/05/2002	TELECON with FDA regarding the UCLA GCP audit findings and Novartis' intent to inform DSI.			Memo of Record (telephone report)
52,003	Certican®	08/05/2002	This letter authorizes FDA to refer to this IND in support of an IND filed by B. J. Hering, MD (BB-IND 8919).	267		General Correspondence
52,003	Certican®	07/17/2002	New investigator to Study No. 2307: M. L. Lorber, MD	266	2307	New Investigator
52,003	Certican®	07/12/2002	In reference to the pre-NDA meeting held on March 25, 2002, and to the FDA Meeting Minutes, this correspondence requests clarification on several issues raised in the minutes and contains revision to those minutes.	265		

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	07/11/2002	[France] Prof Bourbigot; Protocol No. CRAD001 A2307; renal impairment NOS, hepatitis acute, concomitant disease progression, blood creatinine increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, alanine aminotransferase increased; follow-up	264	A2307	Safety Report
52,003	Certican®	07/02/2002	FDA LETTER referencing the "Best Pharmaceuticals for Children Act" (BPCA) and serving as notification that the Written Request, originally issued on April 25, 2000, is considered to be reissued as of the date of this letter.			
52,003	Certican®	06/03/2002	Barry Donald Kahan, MD; Protocol No. FTY A2202; anassarca, disease progression NOS, oedema NOS, dyspnoea exertional, weight increased, blood creatinine increased	261	A2202	Safety Report
52,003	Certican®	05/29/2002	New investigators: Study No. 2306: Drs. J. Magee, P. Morissey; Study No. 2307: Drs. D. Norman, J. D. Scandling	260	2306 2307	New Investigator
52,003	Certican®	05/15/2002	New investigator to Study No. 2307: F. H. Wright, MD	259	2307	New Investigator
52,003	Certican®	05/01/2002	This Annual Report covers the period November 15, 2000, through November 14, 2001. Includes preclinical and clinical study/safety information, CMC changes, and a revised Investigator's Brochure dated June 29, 2001.	258		Annual Report
52,003	Certican®	04/30/2002	New investigators to Study No. 2306: D. Wombolt, MD; Study No. 2307: K. M. H. Butt, MD	257	2306,2307	New Investigator
52,003	Certican®	03/25/2002	FDA minutes of the pre-NDA/Type B meeting held March 25, 2002. regarding the renal and heart transplantation indications.			FDA/Novartis Meeting Minu
52,003	Certican®	03/22/2002	New investigator to Study No. 2306: T. Pruett, MD	255	2306	New Investigator
52,003	Certican®	03/21/2002	This submission is in response to an FDA request to provide additional summary documentation (B201/B251 6 month amendments) to support the Division's review and proposals for the use of Certican in renal transplantation.	254		Response to FDA Request
52,003	Certican®	03/07/2002	FDA LETTER containing a meeting date in response to the February 14, 2002, correspondence requesting a meeting to discuss the proposal to submit a single NDA for two separate indications.			
52,003	Certican®	02/28/2002	TELECON with FDA to discuss pre-NDA meeting logistics and format.			Memo of Record (telephone report)
52,003	Certican®	02/22/2002	New investigators: Study No. 2306: Drs. P. R. Rajagopalan, T. R. Srinivas; Study No. 2307: Drs. J. D. Whelchel, J. Leone	250	2306 2307	New Investigator
52,003	Certican®	02/14/2002	This Briefing Book is being submitted in preparation for the pre-NDA being requested in this correspondence. The purpose of this meeting is to obtain FDA feedback and agreement on our proposal for submission of a single NDA containing two separate indications for use of Certican in heart and renal transplantation.	249		Briefing Book Request for FDA Meeting
52,003	Certican®	02/12/2002	TELECON with FDA to discuss the scheduling of the pre-NDA meeting.			Memo of Record (telephone report)
52,003	Certican®	12/21/2001	New investigators to Study No. A2202: Drs. L. Toselli, H. Tedesco, P. Neuhaus, R. J. Hene, S. Flechner	248		General Correspondence
52,003	Certican®	12/20/2001	Dr. Joshua Hare; Pulmonary fibrosis, cardiac failure congestive; Follow-up#2	247	B253	Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	12/11/2001	Dr. Vincent Valentine; Rhabdomyolysis, renal failure acute, renal failure chronic, hyperkalaemia, fluid overload, metabolic acidosis NOS, bradycardia NOS, liver function tests NOS abnormal; Follow-up#2	246	B159	Safety Report
52,003	Certican®	12/10/2001	New investigator to Study No. 2306: H. Shidban, MD	245	2306	New Investigator
52,003	Certican®	11/21/2001	Amendment No. 3 to Study No. B156; Amendment No. 2 to Study No. B157-E-01; Amendment No. 7 to Study No. B152	244	B156 B157-E-01 B152	Change In Protocol
52,003	Certican®	11/15/2001	New investigators to Study No. A2202: Drs. S. J. Tomlanovich, A. N. Langnas	243		General Correspondence
52,003	Certican®	10/31/2001	Amendment No. 4 to Study No. B251.	242	B251	Change In Protocol
52,003	Certican®	10/31/2001	TELECON to FDA regarding the delay in the NDA submission from November 2001 to June 2002. FDA also acknowledged that multiple indications can be submitted in the same application.			Memo of Record (telephone report)
52,003	Certican®	10/18/2001	Dr. Joshua Hare; Protocol No. CRAD0001 B253; pulmonary fibrosis; follow-up	241	B253	Safety Report
52,003	Certican®	10/15/2001	Extension 1 to Protocol No. A2202 titled, "Two-year extension of a one-year, multicenter, prospective, open-label study of the safety, tolerability and preliminary efficacy of oral FTY720 and RAD001 in de novo adult renal transplant recipients at increased risk of delayed graft function".	240		General Correspondence
52,003	Certican®	10/12/2001	Dr. Hall; Protocol No. CRAD0001 B253; pulmonary fibrosis	239	B253	Safety Report
52,003	Certican®	10/09/2001	New investigator to Study No. A2202: A. Humar, MD	238	A2202	New Investigator
52,003	Certican®	09/25/2001	This submission contains a draft protocol of a nonclinical study titled, "An oral neonatal and juvenile development study in rats with 13- and 26-week recovery period".	237		Preclinical Amendment
52,003	Certican®	09/13/2001	FAX from FDA containing comments from the reviewing statistician on protocols for Studies No. 2306 and 2307 (August 9, 2001).			
52,003	Certican®	09/05/2001	This Annual Report covers the period November 15, 1999 through November 14, 2000. Includes preclinical and clinical study information and CMC changes.	235		Annual Report
52,003	Certican®	09/05/2001	New investiatgor to Study A2202: R. Mendez, MD	236	A2202	New Investigator
52,003	Certican®	08/31/2001	This Annual Report covers the period November 15, 1998 to November 14, 1999. Includes preclinical and clinical study information, CMC changes, and an investigator's brochure dated November 26, 1999.	234		Annual Report
52,003	Certican®	08/16/2001	FAX from FDA containing comments from the reviewing clinical pharmacologist on the submission dated August 7, 2001, Serial No. 228.			
52,003	Certican®	08/15/2001	Dr. Vincent Valentine; Protocol No. B159. Rhabdomyolysis, renal failure acute, renal failure chronic, hyperkalaemia, fluid overload, metabolic acidosis NOS, bradycardia NOS, liver function tests NOS abnormal; follow-up	232	B159	Safety Report
52,003	Certican®	08/09/2001	New protocol: Study No. 2307 entitled, "A 1 year multicenter, randomized, open label, parallel group study of the safety, tolerability and efficacy of two doses (1.5 and 3 mg/day) of Certican (RAD001) with Simulect, corticosteroids and optimized administration of Neoral in de novo renal transplant recipients".	231	2307	New Protocol

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	08/09/2001	New protocol: Study No. 2306 entitled, "A 1 year multicenter, randomized, open label, parallel group study of the safety, tolerability and efficacy of two doses (1.5 and 3 mg/day) of Certican (RAD001) with steroids and optimized administration of Neoral in de novo renal transplant recipients".	230	2306	New Protocol
52,003	Certican®	08/09/2001	General correspondence. New investigator to FTY 720 Study No. A2202: P. R. Rajagopalan, MD	229	A2202	General Correspondence
52,003	Certican®	08/07/2001	This submission contains a list of proposed additional dissolution experiments to be performed on the 0.25 and 1 mg tablet.	228		CMC Amendment
52,003	Certican®	08/06/2001	[Canada] Dr. H. Ross; compassionate need patient; heart transplant rejection, drug ineffective, disease progression NOS, ventricular extrasystoles; follow-up	227		Safety Report
52,003	Certican®	08/03/2001	TELECON to FDA regarding the everolimus starting material, rapamycin, in reference to the upcoming submission of the NDA.			Memo of Record (telephone report)
52,003	Certican®	08/02/2001	Joseph P. Lynch, MD; Protocol No. B159; hypersensitivity NOS, throat oedema, dyspnoea NOS, hypertension NOS, face oedema	226	B159	Safety Report
52,003	Certican®	07/31/2001	TELECON with FDA to discuss the endocrine findings and proposals for study amendment in the clinical program.			Memo of Record (telephone report)
52,003	Certican®	07/30/2001	[Canada] Dr. H. Ross; compassionate need patient; heart transplant rejection, ventricular extrasystoles	225		Safety Report
52,003	Certican®	07/23/2001	FAX from FDA containing comments on amendments to Study No. 2407, Serial No. 219.		2407	
52,003	Certican®	07/19/2001	TELECON with FDA to discuss the April 17, 2001, fax from FDA that contained several questions regarding the justification of the dissolution method submitted December 21, 2000.			Memo of Record (telephone report)
52,003	Certican®	07/19/2001	TELECON with FDA to discuss the dissolution profile for the RAD001 tablets and Novartis' memorandum of April 17, 2001.			Memo of Record (telephone report)
52,003	Certican®	07/13/2001	Vincent Valentine, MD; Protocol No. AD001 B159; rhabdomyolysis, pyrexia, myalgia, weakness, liver function tests NOS abnormal; follow-up	224	B159	Safety Report
52,003	Certican®	07/12/2001	FDA LETTER indicating that the teleconference requested to discuss dissolution methodology for the dosage forms is a meeting type C. The date, time and CDER participants are given.			
52,003	Certican®	07/11/2001	TELECON to FDA regarding Novartis' reporting obligations for the close-out of a study site for GCP related issues.			Memo of Record (telephone report)
52,003	Certican®	07/10/2001	Dr. Vincent Valentine; Center 16. Rhabdomyolysis, renal failure acute, renal failure chronic, hyperkalaemia, fluid overload, metabolic acidosis NOS, bradycardia NOS, liver function tests NOS abnormal.	223	B159	Safety Report
52,003	Certican®	07/02/2001	This submission contains endocrine findings in specific clinical trials, overviews of preclinical safety findings, summaries of our discussions with endocrine consultants and proposals for FDA feedback. A list of tentative dates and participants for a meeting is also provided.	222		Clinical Information Amendr Request for FDA Meeting
52,003	Certican®	06/29/2001	Protocol A2202, Amendment No. 3.	221	A2202	Change In Protocol

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	06/28/2001	This correspondence notifies the FDA of Novartis' intent to import the material listed for further processing into a drug that will be exported from the US.			
52,003	Certican®	06/25/2001	TELECON FROM FDA requesting an overview of the planned submission of the endocrine package based on the recent endocrine findings from adult kidney studies and in view of the Rapamune FDA preclinical toxicology reviews. Discussed were contents/timelines and communication to NIH.			Memo of Record (telephone report)
52,003	Certican®	06/21/2001	TELECON TO FDA notifying the agency that a package is being prepared for submission to FDA containing endocrine findings based on results from adult kidney studies. Novartis would request a teleconference and provide tentative dates.			Memo of Record (telephone report)
52,003	Certican®	06/14/2001	FAX FROM FDA providing review comments on Protocol A2414 submitted on May 29, 2001 to NDA 50-716.		A2414	
52,003	Certican®	06/08/2001	Response to the medical review comments and requests regarding Amendment # 3 for Study B251, Serail # 211. Additional information is provided on the monitoring and timely review of acture rejection episodes in de novo renal transplant studies B201 and B251.	220		Response to FDA Request
52,003	Certican®	06/05/2001	As per the FDA April 17, 2001 FAX which included additional questions concerning the proposed dissolution methodology for the dosage form, Novartis is requesting a telephone conference between FDA clinical pharmacology representatives including the reviewing chemist and Novartis US and Basle representatives.	218		CMC Amendment General Correspondence
52,003	Certican®	06/05/2001	Vincent Valentine, MD. Rhabdomyolysis.	217	B159	Safety Report
52,003	Certican®	05/15/2001	Protocol A2202, Amendment 2.	216	A2202	Change In Protocol
52,003	Certican®	05/09/2001	Point-by-point response to FDA communication dated April 19, 2001 which provided medical review comments and requests for additional information on Amendment # 3 for Study B251, serial no. 211.	215	B251	Response to FDA Request
52,003	Certican®	04/17/2001	FDA FAX providing the comments from the reviewing clinical pharmacologist regarding CMC information amendments Serial Nos. 200 and 208.			
52,003	Certican®	03/23/2001	[Italy] Dr. Francis Cardelli. Center 18. Leukopenia NOS.	213	AIT01	Safety Report
52,003	Certican®	03/21/2001	TELECON WITH FDA regarding FDA's acceptance of cross referencing the new IND in oncology to IND 52,003. In order to avoid redundancy on all supporting documents intended for the submission of the NDA later in the year, Novartis made proposal as outlined. Acceptance of these proposals will be confirmed by the Medical Officers.			Memo of Record (telephone report)
52,003	Certican®	03/21/2001	New investigators to Protocol A2202: Drs. Douglas Norman, Clarence Foster.	212	A2202	New Investigator
52,003	Certican®	03/19/2001	Protocol B251, Amendment No. 3.	211	B251	Change In Protocol
52,003	Certican®	03/15/2001	New investigator to Protocol A2202: Ron Shapiro, MD.	210	A2202	New Investigator

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	03/12/2001	TELECON FROM FDA in response to a voice message left on March 9, 2001 by the Oncology TA . The Agency confirmed that it was acceptable for Novartis to cross-reference the upcoming RAD oncology IND to the transplant IND submitted earlier. The upcoming IND will be submitted to the Division of Oncologic Drug Products to support an indication in sold tumors. The agency re-confirmed that it was acceptable to cross-reference the CMC and toxicology section of the IND to the transplant			Memo of Record (telephone report)
52,003	Certican®	03/07/2001	[Spain] Dr. L. Pulpon. Centre 128. Rhabdomyolysis, renal failure acute, weakness, pain in limb, nausea.	209	B253	Safety Report
52,003	Certican®	03/05/2001	FDA FAX providing the minutes of the February 6, 2001 pe-NDA meeting (Type B) to reach FDA consensus on the NDA submission requirements for the 120-day safety update and to inform the agency of the major efficacy and safety results from the Phase III program.			FDA/Novartis Meeting Minu
52,003	Certican®	02/22/2001	At the request of the FDA, provided a legible replacement copy of CMC document - Drug product in vitro dissolution rate: justification of method, 15-Dec-00, which was included in the December 21, 2000 correspondence (serial no. 200).	208		CMC Amendment
52,003	Certican®	02/15/2001	Correspondence to document the Division's acceptance of Novartis' proposals included in the January 12, 2001 correspondence which provided statistical proposals to facilitate the timely and efficient transfer of SAS programs for the NDA reviewers. The proposals were accepted during a February 6, 2001 conversation with the FDA.	205		General Correspondence
52,003	Certican®	02/15/2001	New investigator for Protocol B253-E01: O.H. Frazier, MD.	207	B253-E01	New Investigator
52,003	Certican®	02/15/2001	New investigator for Protocol A2202: Marc I. Lorber, MD.	206	A2202	New Investigator
52,003	Certican®	02/06/2001	FDA FAX providing the attendance list for the pre-NDA meeting scheduled for February 6. 2001 and informing Novartis that the TELECON scheduled for February 7, 2001 is not needed.			
52,003	Certican®	01/23/2001	FDA LETTER referring to Novartis' December 13, 2000 correspondence requesting a meeting to discuss the final requirements for NDA submission. The meeting which the agency considers to be a type B, has been rescheduled for February 6, 2001.			
52,003	Certican®	01/23/2001	FDA FAX which provides comments from the reviewing medical officer and the statistician regarding the submission dated December 6, 2000, serial no. 191.			
52,003	Certican®	01/22/2001	Provided point-by-point response to medical/clinical pharmacology comments provided in FDA's communication dated January 9, 2001.	204		Response to FDA Request
52,003	Certican®	01/18/2001	Extension E-01 to Study B253, "A two-year extension of the two-year randomized, multicenter, double-blind study of the efficacy and safety of SDZ RAD versus azathioprine as part of a triple immunosuppressive therapy regimen in de novo heart transplant recipients". New investigators: Drs. Howard J. Eisen, James A. Hill, Paul J. Hauptman, Robert B. Love.	203	B253-E01	Clinical Information Amendr New Investigator
52,003	Certican®	01/17/2001	TELECON FROM FDA informing Novartis that the Division will have to reschedule the January 31 meeting. The new date is February 6, 2001. Novartis indicated that the cancellation is an inconvenience for the team but that the team members will be requested to confirm the new date.			Memo of Record (telephone report)

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	01/12/2001	Requested a teleconference with the FDA to facilitate the timely transfer of SAS programs for Division review. Included are Novartis' proposals for discussion with the statistical reviewers.	202		Request for FDA Meeting
52,003	Certican®	01/09/2001	FDA FAX which includes review comments from the medical officer and the clinical pharmacologist relating to the December 18, submission, serial no. 195.			
52,003	Certican®	01/08/2001	Submitted Novartis' proposals for the NDA 120-Day Safety Update. The proposals and related NDA issues will be discussed in a meeting on January 31, 2001.	201		General Correspondence
52,003	Certican®	12/22/2000	New investigators to Protocol A2202: Drs. Deise De boni Monteiro De Carvalho, Helio Tedesco Silva Junior (non-US investigators) , Hans Sollinger (US investigator), Barry Kahan and Stephen Katz, (co investigators).	198	A2202	New Investigator
52,003	Certican®	12/22/2000	FDA LETTER noting that based on Novartis December 6, 2000 meeting request, the agency has determined that the meeting is a type B and it is scheduled for January 31, 2001.			
52,003	Certican®	12/21/2000	Provided a CD-ROM which contains a demonstration of the electronic submission in accordance with the FDA Guidance for industry for providing regulatory submissions in electronic format. Also provided is an NDA table of contents that itemizes contents available for paper and electronic archive.	199		
52,003	Certican®	12/21/2000	In response to FDA telefax dated June 27, 2000 expressing concern regarding the dissolution method used for Certican tablets, provided document entitled," In vitro dissolution rate: Justification of method".	200		CMC Amendment
52,003	Certican®	12/20/2000	TELECON FROM FDA indicating that the agency will be ready to have a teleconference with Novartis on January 3, 2001 to discuss the proposed amendment and a face to face meeting on January 31, 2001 to discuss NDA submission requirements.			Memo of Record (telephone report)
52,003	Certican®	12/20/2000	TELECON TO FDA to confirm delivery of the electronic demo to the FDA Division of Special Pathogens and Immunologic Drug Products.			Memo of Record (telephone report)
52,003	Certican®	12/20/2000	New Protocol A2202, "A one-year, multicenter, prospective, open-label study of the safety, tolerability and preliminary efficacy of oral FTY720 and RAD001 in de novo adult renal transplant recipients at increased risk of delayed graft function". Also included is Amendment 1 to Protocol A2202.	197	A2202	New Protocol
52,003	Certican®	12/19/2000	In accordance with FDA request of October 24, 2000, provided a CD-ROM which contains two carcinogenicity studies: SPM/113, Oncogenicity study by oral gavage administration to rats for 104 weeks, and SPM/118, Oncogenicity study by oral gavage administration to mice for 104 weeks.	196		Response to FDA Request
52,003	Certican®	12/18/2000	Submitted draft Amendment to Study B251 for FDA comment and requesting feedback from the agency before January 4, 2001.	195	B251	
52,003	Certican®	12/15/2000	As requested by the FDA, provided additional summary statistics for creatinine clearance by Nankivell formula. This information is considered an amendment to the Briefing Book, Section 5.2, submitted December 6, 2000.	194		Response to FDA Request

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	12/12/2000	[Russian Federation] Dr. Alexander Sokolsky. Center 88. Cerebrovascular accident NOS, hypertension NOS, infection NOS, pyrexia, weakness, dyspnea NOS, hyperglycemia NOS, hypotension NOS, heart rate increased, hypoglycemia NOS, convulsions NOS, depressed level of consciousness, apnea, memory impairment, confusion, urinary incontinence, cerebral atrophy.	193	B201	Safety Report
52,003	Certican®	12/08/2000	FDA FAX providing statistical analysis issues relating to the April 17, 2000 submission, serial no. 154.			
52,003	Certican®	12/08/2000	TELECON TO FDA to reach agreement on the documentation to be submitted to both FTY720 and RAD001 INDs to support the clinical program which uses both investigational drugs (Protocol 2202, FTY 720). It was agreed that routine regulatory submissions would be made only to IND 57,293 with only a copy of the cover letter submitted to the RAD 001 IND indicating that attachments would be found in the FTY720 IND. The Division would like to see Novartis' proposals for safety reporting in writing.			Memo of Record (telephone report)
52,003	Certican®	12/07/2000	Provided information on an additional 0.75 mg tablet which is dose proportional to the current 0.5 and 1.0 mg dosage strengths. The following documents are included: composition, batch formula and method of preparation, drug product stability data/report, RAD001 0.75 mg tablets (KN 3749223.00.002 and 003) dated 23-Aug-2000.	192		CMC Amendment
52,003	Certican®	12/06/2000	Request for FDA teleconference/meeting in mid January 2001 to discuss the final requirements for the NDA submission. Also included is requested additional information on renal data from the ongoing Phase 3 kidney transplant studies.	191		Request for FDA Meeting
52,003	Certican®	11/17/2000	[Norway] Dr. S. Simonsen. Center 146. Alveolar proteinosis, dyspnoea NOS. Follow-up # 1.	190	B253	Safety Report
52,003	Certican®	11/08/2000	[Norway] Dr. S. Simonsen. Center 146. Alveolar proteinosis, dyspnoea NOS.	189	CRAD001B2	Safety Report
52,003	Certican®	11/08/2000	New Investigator to Protocol IA06: Francis H. Wright, Jr., MD.	188	IA06	New Investigator
52,003	Certican®	10/05/2000	Dr. Paul Hauptman. Study CRAD001B253. Renal failure acute, thromboembolism NOS, pleural effusion, renal tubular necrosis, pericardial effusion. Follow-up # 2. The initial and first follow-up reports were submitted under case No. CRAD001/B253/0/16/6/1/USA.	186	CRAD001B2	Safety Report
52,003	Certican®	10/05/2000	Dr. Shamkant Mulgaonkar; Study CRAD001B251, Center 12. Hemolytic uremic syndrome, graft rejection, graft loss, drug ineffective, nephrectomy.	185	CRAD001B2	Safety Report
52,003	Certican®	10/02/2000	Provided information on new clinical materials consisting of 0.1 and 0.25 mg fast dispersible tablets differentiated by their appearance as they have an engraving on both sides. Included are the following documents: Drug product composition, site of manufacture, packaging and control, RAD001, 0.1 and 0.25, fast dispersible tablets, KN 374962.00.005 and KN 3745403.00.015, date 7-Mar 2000; Stability Report, 2U99 1895, date 16-Apr-1999.	184		CMC Amendment
52,003	Certican®	09/26/2000	Submitted first interpretable results for Studies B251 and 2304.	183	B251 2304	Clinical Information Amendr

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	09/21/2000	Request for a teleconference with the Division to discuss the summary findings from Novartis' pivotal trials in kidney transplantation. Included proposed agenda and list of Novartis participants.	182		
52,003	Certican®	09/18/2000	New investigators to conduct the following Protocols: Drs. Mark D. Pescovitz, Donald Hricik, John J. Curtis Study US01. Robert Naraghi, MD, Study IA06. Alan H. Wilkinson, MD, Studies IA11 and IA01.	181	US01 IA06 IA11 IA01	New Investigator
52,003	Certican®	08/24/2000	As requested during the pre-NDA meeting on December 3, 1999, provided 6 month first interpretable results for Studies CRAD B251 and CRAD B201. Additional analyses on creatinine values for each study is also included.	180		Response to FDA Request
52,003	Certican®	08/22/2000	Provided revised Chemistry Manufacturing and Controls information in support of a new clinical trial formulation consisting of 0.25, 0.5 and 1 mg tablets. The following documents are provided: drug product composition, manufacturing formula, stability data/report, date 7-Jun-2000	179		CMC Amendment
52,003	Certican®	08/17/2000	In reference to FDA communication of May 11, 2000 which requested Novartis to provide information regarding interaction between everolimus (formerly RAD001) and St. John's Wort, it is anticipated that everolimus will be recognized as a drug with a potential for interaction with St. John's Wort based on Novartis' evaluation of the potential for drug-drug interactions in the firm's Phase 3 renal transplant program. Accordingly, St. John's Wort will be mentioned in the proposed labeling. Also included for	178		Response to FDA Request
52,003	Certican®	08/15/2000	Provided for the followig new investigators: Dr. Stephen J. Tomlanovich for Protocol CRAD001 IA01 and IA11; Drs. John J. Curtis and Donald E. Hricik for Protocol CRAD001A US01; Dr. Robert Naraghi for Protocol CRAD001 IA06.	177	IA01 IA11 US01 IA06	New Investigator
52,003	Certican®	07/24/2000	FDA FAX providing the comments from the reviewing clinical pharmacologist regarding Point # 3 in Novartis' correspondence (Serial No. 159) responding to FDA's March 22, 2000 memorandum.			
52,003	Certican®	07/14/2000	New investigators for Protocol CRAD001 B351: Drs. Jacques Lemire, John D. Mahan, Robert Ettenger.	176	B351	New Investigator
52,003	Certican®	07/06/2000	Requested FDA approval for the use of the term "dispersible" for the drug product tablet and remove all references to speed at which the drug product disintegrates when placed in water. At the present time, there is a "normal" immediate release tablet and a "fast dispersible" tablet.	175		CMC Amendment General Correspondence
52,003	Certican®	07/06/2000	Nghiem, Dai Dao, MD. Arthralgia.	174	CRAD001B2	Safety Report
52,003	Certican®	06/30/2000	Amendment No. 1 to Protocol B351.	173	B351	Change In Protocol
52,003	Certican®	06/29/2000	[Italy] Dr. Fabio Vistoli. Hepatic failure, death.	172	CRAD001IA(	Safety Report
52,003	Certican®	06/29/2000	In response to the April 5, 2000 FDA request, provided an electronic copy of two carcinogenicity studies in rats and mice, SPM/113 and SPM/118, initially submitted on February 24, 2000 as paper copies, Serial No. 133.	171		Preclinical Amendment Response to FDA Request
52,003	Certican®	06/28/2000	FDA FAX providing the comments of the reviewing Clinical Pharmacologist regarding response 1, 3, 4, 5 from the April 20, 2000 submission, serial no. 156, Study B258 (Protocol comment).		B258	

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	06/28/2000	Correspondence to document the June 29, 2000 telephone conversation with the FDA at which time the Regulatory Manager informed Novartis that the Office of Postmarketing Drug Risk Assessment has made a tentative decision to accept Novartis' proposed trademark Certican for IND 52,003.	170		General Correspondence
52,003	Certican®	06/27/2000	FDA FAX providing the comments of the Clinical Pharmacologist regarding response 1, 3, 4, 5 from the March 30, 2000 submission, serial no. 146 (dissolution issues).			
52,003	Certican®	06/27/2000	FDA FAX providing comments from the reviewing Clinical Pharmacologist regarding response 5 from the April 17 2000, submission , serial no. 152 (Protocol comment).			
52,003	Certican®	06/26/2000	New investigators for Protocol IA01: Drs. Janet L. Karlix and Richard Howard (co-principal) Allan M. Roza, Oleh Pankewycz, Jonathan Bromberg. New investigators for Prot. IA06: Drs. George Burke III, Jon Odorico. New investigators for Prot. IA11: Drs.Allan Roza, Jonathan Bromberg. New investigator for Prot. B159 : Dr. Joseph P. Lynch.	169	IA01 IA06 IA11 B159	New Investigator
52,003	Certican®	06/26/2000	As requested by the FDA in the April 25, 2000 telex, provided clarification to clinical investigators participating in Study 258 regarding points in the Informed Consent form for the trial. Additionally, as requested by the Division, included is a letter informing the clinical trial investigators that Neoral is available free of charge to patients in the RAD clinical program.	168		Response to FDA Request
52,003	Certican®	06/21/2000	TELECON FROM FDA informing Novartis that the FDA Office of Postmarketing Drug Risk Assessment has tentatively approved the proposed trademark Certican for the drug product. A final decision on the trademark approval will be made after the NDA submission.			Memo of Record (telephone report)
52,003	Certican®	06/15/2000	Submitted revised CMC information to support the Fast Dispersible Tablet dosage form. Included are the following drug product documentation: Composition, manufacturing formula, specifications and control procedures, RAD001 01 and 0.25 mg fast dispersible tablets, KN 3749462.00.007, KN 3745403.00.018, dated May 8, 2000 and Stability Report for development batches, SR1895A, release date March 23, 2000.	167		CMC Amendment
52,003	Certican®	06/02/2000	New investigators: Luigi Bonomini, MD, for Protocol IA06; Jeffrey D. Hosenpud, MD, for Protocol B253; Steven Lobritto, MD, for Protocol B258.	165	IA06 B253 B258	New Investigator
52,003	Certican®	05/30/2000	As proposed in the teleconference of May 25, 2000 with the FDA, Novartis provided a summary of the clinical issues for discussion at the teleconference scheduled for June 2, 2000. The synopsis for Study B153 and the supporting literature is also included in this correspondence.	164	B153	Clinical Information Amendr
52,003	Certican®	05/25/2000	FDA LETTER which includes the comments from the reviewing clinical pharmacologist relating to Protocol US01 submitted on April 17, 2000, serial no. 153.			
52,003	Certican®	05/22/2000	Novartis provided its assessment of efficacy and contingency plans for the scenario of simultaneous equivalence and inferiority of RAD to MMF. FDA requested this information at the December 3, 1999 pre-NDA meeting . Novartis also clarified for the FDA the definition of rejection episodes discussed in Studies B251 and B201.	163		Clinical Information Amendr Response to Clinical Hold

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	05/19/2000	In response to FDA request of April 5, 2000, provided the following toxicology studies that evaluated the combination of RAD and cyclosporine: Report 203-461, "Toxicity study by oral gavage administration to Hanlbm Wistar rats for 4 weeks followed by a 2 week reversibility period". Report 203-080, "Combination of Sandimmun-Neoral and SDZ RAD 4-week oral (gavage) toxicity study in Cynomolgus monkeys". Complete submission in 5 vols.	161		Preclinical Amendment Response to FDA Request
52,003	Certican®	05/18/2000	Provided Study CRAD001 B257, Appendix 8.2, Pharmacokinetic evaluation, to support Novartis' position that the current (original protocol Study B258) blood-sampling schedule is appropriate for the study objectives.	162		Clinical Information Amendr
52,003	Certican®	05/18/2000	[France] Dr. Saliba; sudden death.	160	CRAD001B1	Safety Report
52,003	Certican®	05/12/2000	Provided a point-by-point response to FDA comments dated March 22, 2000 regarding Study IA04, serial no. 116.	159		Response to FDA Request
52,003	Certican®	05/08/2000	FDA LETTER which contains the review comments from the clinical pharmacologist concerning Protocol A2304, Serial No. 150. .		A2304	
52,003	Certican®	05/08/2000	FDA LETTER providing the recommendations of the reviewing clinical pharmacologist regarding Protocol A2303, Serial No. 149.		A2303	
52,003	Certican®	05/02/2000	TELECON TO the FDA reviewing chemist concerning the status of the proposed stability protocols (RSP1870A and 2RSP99-1895) submitted on March 30, 2000. The agency has determined that the protocols are acceptable. Regarding the "name" (fast dispersible, etc.) issue for the dosage form, the FDA suggested that Novartis propose a list of "names" to the FDA for approval.			CMC Amendment Memo of Record (telephone report)
52,003	Certican®	04/26/2000	New investigator to Protocol B258: Jeffrey D. Punch, MD.	158	B258	New Investigator
52,003	Certican®	04/25/2000	FDA LETTER in reference to Novartis' proposed Pediatric Study Request submitted on October 29, 1999. To obtain needed pediatric information on the active moiety everolimus, FDA is making a formal Written Request for information from studies as listed. Included in the letter are agency recommendations regarding Novartis' request.			
52,003	Certican®	04/24/2000	FDA FAX providing requirements regarding the informed consent document that was received by the FDA on March 29, 2000 for Study B258 , serial no. 134. .			
52,003	Certican®	04/20/2000	Point-by-point response to FDA review comments communicated via facsimile on March 31, 2000 regarding Study B258.	156	B258	Response to FDA Request
52,003	Certican®	04/19/2000	FDA's minutes of the January 27, 2000 meeting with Novartis to discuss CMC issues related to the RAD001 development program which were not covered by the pre-NDA meeting of December 3, 1999.			CMC Amendment
52,003	Certican®	04/17/2000	Request for a Type B meeting to discuss Novartis' Phase 3 clinical program for the use of RAD001 in de novo liver transplantation. Supporting documentation and protocol summary for Study B252 is included.	155		Request for FDA Meeting
52,003	Certican®	04/17/2000	In response to FDA request for Division review communicated in the December 3, 1999 pre-NDA meeting, provided Novartis' proposal entitled, "Protocol analyses - Renal Indication".	154		Clinical Information Amendr

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	04/17/2000	New Protocol CRAD001A US01 entitled, "A multicenter, open-label, single-arm, exploratory study to assess the safety and tolerability of reduced-dose tacrolimus with RAD in maintenance renal transplant recipients with renal insufficiency". Study US01 will replace draft protocol for Study IA04 submitted on December 15, 1999 (serial no. 116). Also noted that Novartis is preparing a point-by-point response to the Division's clinical pharmacology review comments of March 22, 2000.	153	US01	New Protocol
52,003	Certican®	04/17/2000	Point-by-point response to the Division's facsimile communication of March 10, 2000 which provided medical and clinical pharmacology review comments on Study B351.	152	B351	
52,003	Certican®	04/17/2000	In response to FDA request of April 11, 2000, provided information to support Novartis' position that the data of Study B257 are considered acceptable for robust statistical evaluation and conclusions.	157		Response to FDA Request
52,003	Certican®	04/11/2000	[Germany] Dr. B. Nonnast-Daniel; Neuropathy, gout. Follow-up # 3.	151	CRAD001B2	Safety Report
52,003	Certican®	04/11/2000	TELECON FROM FDA requesting patient information enrolled in Pediatric Study B257. A formal recommendation will be made by the FDA after more information is received on patient enrollment in the study.			Memo of Record (telephone report)
52,003	Certican®	04/06/2000	New Protocol CRAD001A2304 entitled, "Determination of the effect of two cyclosporine formulations on the pharmacokinetics of single oral doses of RAD001 in healthy subjects using a randomized, two period, four sequence, crossover study design.	150	A2304	New Protocol
52,003	Certican®	04/06/2000	New Protocol CRAD001A2303 entitled, "An open-label, single-dose, case-control study to compare the pharmacokinetics of RAD001 in subjects with moderate hepatic impairment to matched healthy control subjects". New investigator, Kenneth C. Lasseter, MD.	149	A2303	New Investigator New Protocol
52,003	Certican®	04/06/2000	Pursuant to the agency's March 24, 2000 communication which provided clinical pharmacology comments regarding bioequivalence issues for RAD001, provided a summary synopsis and assessment schedule for Study A2301 entitled, "A randomized, open-label, four-way crossover study to evaluate the bioequivalence of a single 1mg dose of RAD001 administered as a 0.25mg market formulation (MF) tablet, a 0.5 mg (MF) tablet, a 0.25mg Final Market image (MFI) tablet and a 1 mg FMI tablet to healthy	148	A2301	Clinical Information Amendr
52,003	Certican®	04/03/2000	As per the request that was made during the pre-NDA meeting between FDA and Novartis, an example of the packaged (CR-blister) placebo for RAD001 Tablets is provided to the reviewing chemist.			CMC Amendment
52,003	Certican®	04/03/2000	New investigator, Protocol B258: Harvey L. Sharp, MD.	147	B258	New Investigator
52,003	Certican®	03/31/2000	FDA LETTER providing the comments from the reviewing medical officer and the clinical pharmacologist concerning Protocol B258, Serial No. 134.			
52,003	Certican®	03/30/2000	As requested by the agency during the January 27, 2000 pre-NDA meeting, Novartis provided information concerning stability issues discussed at the meeting. Additionally, as requested in the February 3, 2000 telefax, information is provided regarding dissolution questions outlined in the telefax. Included: RAD001 0.1, 0.25 mg Fast Dispersible Tablets, 2U99 1895 Stability Report dated 16-Apr-99.	146		CMC Amendment Response to FDA Request

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	03/28/2000	[Germany] Dr. Kehle; edema legs. Follow-up # 2.	145	CRAD001B2	Safety Report
52,003	Certican®	03/24/2000	[Germany] Dr. Nonnast-Daniel; neuropathy, gout. Follow-up # 2.	144	CRAD001B2	Safety Report
52,003	Certican®	03/24/2000	[Germany] Dr. Kehle; edema legs. Follow-up # 1.	143	CRAD001B2	Safety Report
52,003	Certican®	03/24/2000	TELECON from FDA requesting information to address the reviewing clinical pharmacologist's comments regarding bioequivalence issues, bio-link between market formulation and final market image tablets.			Memo of Record (telephone report)
52,003	Certican®	03/22/2000	FDA LETTER providing the comments of the reviewing clinical pharmacologist with regard to Study IA04, Serial No. 116. .		IA04	
52,003	Certican®	03/20/2000	Submitted the following two new protocols: Study IA01 entitled, "A 1 year multicenter, randomized, open label, parallel group pilot study of the efficacy and safety of RAD with early versus possibly delayed initiation of Neoral in de novo renal transplant recipients at increased risk of delayed graft function". Study IA11 entitled, "A 1 year multicenter, single arm, open label, pilot study of the efficacy and safety of RAD in de novo renal transplant recipients at immunological high risk of rejection".	142	IA01/IA11	New Protocol
52,003	Certican®	03/13/2000	New investigator to Protocol B351: Mark I. Menster, MD.	141	B351	New Investigator
52,003	Certican®	03/10/2000	FDA LETTER responding to Novartis' February 1, 2000 correspondence which requested a teleconference to discuss the impact of different cyclosporine products on the RAD development program. The agency categorized the meeting to be a type C and scheduled it for March 15, 2000.			
52,003	Certican®	03/10/2000	FDA FAX providing comments from the clinical pharmacologist and the reviewing medical officer regarding Study B351.		B351	
52,003	Certican®	03/10/2000	TELECON FROM FDA providing comments on Pediatric Protocol B351. Novartis' suggestion that the response to the requests might be best addressed in the final reports was acceptable by the agency.		B351	Memo of Record (telephone report)
52,003	Certican®	03/10/2000	FDA FAX providing the minutes of the pre-NDA meeting with Novartis held on December 3, 1999.			FDA/Novartis Meeting Minu
52,003	Certican®	03/10/2000	New investigator to Protocol IA06: Gary A. Wilson, MD.	140	IA06	New Investigator
52,003	Certican®	03/06/2000	[Belgium] Dr. Maimone; hepatitis cholestatic, hepatic function abnormal, fever, asthenia, follow-up # 3.	139	CRAD001B2	Safety Report
52,003	Certican®	03/06/2000	In follow-up to a telephone conversation on March 1, 2000 regarding Study B351, provided additional comments on dose justification and pharmacokinetic data availability to support initiation of the trial.	138	B351	Clinical Information Amendr
52,003	Certican®	03/01/2000	TELECON WITH FDA soliciting FDA comment on the pediatric de novo kidney protocol B351, submitted on February 4, 2000. The protocol is still in the process of being discussed by the Division and a decision to request a teleconference has not yet been made. Novartis will obtain additional information to address the Clinical Pharmacology reviewer's comments on the study communicated to Novartis during the teleconference.			Memo of Record (telephone report)
52,003	Certican®	02/28/2000	Point by point response to FDA comments communicated to Novartis on February 16, 2000 relating to Study IA06.	137	IA06	Response to FDA Request

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	02/28/2000	TELECON WITH FDA to confirm Novartis' request for a teleconference to discuss an amendment to RAD transplant studies to avoid confusing results in cases where patients are switched to an alternate cylosporine product during the RAD registration program. The FDA suggested a teleconference on March 15, 2000.			Memo of Record (telephone report)
52,003	Certican®	02/25/2000	[Australia]; Dr. R. Rigby; hemolysis. Follow-up # 2.	136	CRAD001B2	Safety Report
52,003	Certican®	02/24/2000	Provided the FDA with Novartis' minutes of the pre-NDA Chemistry Manufacturing and Controls meeting that took place on January 27, 2000 with the FDA.	135		FDA/Novartis Meeting Minu
52,003	Certican®	02/24/2000	New Protocol, Study B258 entitled, "Multicenter, open-label, single oral dose pharmacokinetic, safety and tolerability study of RAD001 in pediatric stable liver transplant patients". New investigator: Estella M. Alonso, MD.	134	B258	New Investigator New Protocol
52,003	Certican®	02/24/2000	In response to the Pharmacology-Toxicology reviewer's questions with regard to the dose selection for the RAD carcinogenicity studies in rats and mice, provided the following documents: Summary discussion on dose justification; Report 973228, "SDZ RAD-Oncogenicity study by oral gavage administration to Hanibm Wistar rats for 104 weeks"; Report 973229, "SDZ RAD-Oncogenicity study by oral gavage administration to CD-1 mice for 104 weeks". Complete submission in 12 volumes.	133		Preclinical Amendment
52,003	Certican®	02/16/2000	[Spain]; Dr. Segovia; renal failure acute, follow-up # 2. .	132	CRAD001B2	Safety Report
52,003	Certican®	02/16/2000	FAX FROM FDA providing comments relating to Study IA06, Serial No. 118.		IA06	
52,003	Certican®	02/10/2000	In response to FDA request to obtain information to evaluate interethnic variability regarding pharmacokinetics in the Hispanic population of Study B251, Novartis requested the study coordinators to confirm the ethnicity of Hispanic patients in Study B251.	131		Clinical Information Amendr
52,003	Certican®	02/07/2000	Point-by-point response to FDA facsimile dated December 16, 1999 which contained requests from the clinical pharmacologist. The response provided information on synopsis for Study W301 and PK data and information on RAD food effect to be evaluated in Study W302 and B201.	130		Response to FDA Request
52,003	Certican®	02/07/2000	Amendment 1 to Protocol CRAD001 0101. Additionally, included is available information to provide justification for the participation of liver transplant patients in Study 0101	129	0101	Change In Protocol
52,003	Certican®	02/07/2000	FDA FAX which includes the names of the Novartis and FDA representatives who will attend the January 27, 2000 meeting to discuss the stability protocols for RAD001.			
52,003	Certican®	02/06/2000	TELECON FROM FDA in follow-up to Novartis' request for authorization to use the trademark Certican for RAD. The agency outlined the current FDA process for nomenclature review and approval.			Memo of Record (telephone report)
52,003	Certican®	02/04/2000	New Protocol, Study CRAD001 B351, "Multicenter, open-label, single-arm, safety, tolerability, efficacy and pharmacokinetic study of RAD001 in pediatric de novo renal transplant patients". Also included is Study CRAD001 B257, "Multicenter, open-label, single-oral dose pharmacokinetic, safety and tolerability study of RAD001 in pediatric stable renal transplant patients", Interim pharmacokinetic report. Additionally, requested is a written response to Novartis' submission of October 29,	128	B351B257	New Protocol

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	02/03/2000	FAX from FDA requesting information relating to the dissolution data submitted in the pre-NDA briefing package of November 1, 1999, Serial No. 104.			
52,003	Certican®	02/01/2000	In follow-up to the Division's concerns regarding interactions between RAD and different cyclosporine formulations expressed during the December 3, 1999 pre-NDA meeting, Novartis requested a teleconference with the Division to agree on the necessary protocol amendments to ensure that the RAD registration database and FDA's review of it are not compromised if multiple cylcosporine products with different bioavailability profiles are co-administered with RAD during the clinical program.	127		
52,003	Certican®	02/01/2000	[Belgium]; Dr. Maimone; hepatitis cholestatic, hepatic function abnormal, fever, anemia, follow-up #2	126	CRAD001B2	Safety Report
52,003	Certican®	01/31/2000	Provided additional information requested by the FDA for review of Novartis' request for confirmation for the use of the proprietary tradename Certican. A letter from the European Agency for the Evaluation of Medicinal Products authorizing the use of the proposed tradename Certican is also included in the submission. .	125		Response to FDA Request
52,003	Certican®	01/27/2000	Minutes from the January 27, 2000 CMC pre-NDA meeting with the FDA.			FDA/Novartis Meeting Minu
52,003	Certican®	01/19/2000	[CANADA]; hepatic function abnormal, follow-up 3.	124	CRAD001B2	Safety Report
52,003	Certican®	01/18/2000	Documentation which provides for a new process for the stabilization of RAD 001 drug substance. This submission also provides information on new clinical materials of RAD 001, 0.25, 0.5 and 1 mg tablets. Updated documents include: drug product composition, manufacturing formula and method of preparation and stability data, dated 8-Jun-99.	123		CMC Amendment
52,003	Certican®	01/14/2000	New investigator to Protocol 251: James R. Thistlethwaite, Jr. MD, PhD. Also delete Dr. E Steve Woodle, principal investigator for Protocol 251.	121	B251	New Investigator
52,003	Certican®	01/14/2000	[GERMANY]; Neuropathy, follow-up 1.	122	CRAD001B2	Safety Report
52,003	Certican®	01/12/2000	Novartis requested confirmation from the Division regarding the acceptance for use of the proprietary tradename Certican. Also included in the correspondence is an acknowledgment letter from the director, USAN Program, indicating that the USAN Council adopted "everolimus" as the US Adopted Name (USAN) for Novartis' immunosuppressant RAD001.	120		
52,003	Certican®	01/10/2000	Briefing book provided to the FDA in preparation for the meeting scheduled for 27-Jan-2000 to discuss CMC issues.	119		Briefing Book
52,003	Certican®	01/07/2000	New Protocol IA06 entitled, " A multi-center, open label, exploratory study to assess the safety and tolerability of Simulect, Neoral, RAD and steroids for the prevention of acute rejection in diabetic patients undergoing simultaneous pancreas-kidney transplantation".	118	IA06	New Protocol
52,003	Certican®	12/23/99	Novartis' minutes of the 12/3/99 pre-NDA meeting with the FDA for RAD001 for the indication of prevention of rejection in solid organ transplantation.	117		General Correspondence
52,003	Certican®	12/21/99	TELECON WITH FDA to discuss the RAD compassionate need protocol 0101 (ser. no. 108). The agency expressed concerns with the inclusion criteria and the dose justification for liver patients. Additional information is requested.			Memo of Record (telephone report)

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	12/16/99	TELECON FROM FDA requesting Novartis' availability for a meeting on January 27, 2000 to discuss the stability program and protocol for RAD. Novartis would like to discuss additional CMC questions at the meeting.			Memo of Record (telephone report)
52,003	Certican®	12/16/99	FDA FAX which includes requests from the reviewing clinical pharmacologist related to the December 3, 1999 pre-NDA meeting for RAD001.			
52,003	Certican®	12/15/99	Requested a teleconference with the FDA to discuss the following new protocol, Study CRAD001 IA04, "A multi-center, open label, single arm, exploratory study to assess the safety and tolerability of reduced-dose tacrolimus with RAD001 in maintenance renal transplant recipients with renal insufficiency".	116	IA04	
52,003	Certican®	12/03/99	[Belgium] Dr. Maimone; hepatitis cholestatic, hepatic function abnormal, fever, asthenia, follow-up.	115	CRAD001B2	Safety Report
52,003	Certican®	12/02/99	[Spain] Dr. Javier Segovia; renal failure acute, follow-up.	114	CRAD001B2	Safety Report
52,003	Certican®	11/30/99	Novartis provided an alternate proposal for discussion at the pre-NDA meeting scheduled for December 3, 1999.	113		Other
52,003	Certican®	11/23/99	[Canada] Site 84; hepatic function abnormal, follow-up.	111	CRAD001B2	Safety Report
52,003	Certican®	11/23/99	[Germany] Dr. B. Nonnast-Daniel; neuropathy.	112	CRAD001B2	Safety Report
52,003	Certican®	11/17/99	Submitted the following new investigator to Protocol No. 159; Kenneth R. McCurry, MD.	110	159	New Investigator
52,003	Certican®	11/12/99	New Protocol CRAD001 0101 entitled, "Compassionate use of RAD prior to regsitration in heart, kidney, liver and lung transplant patients".	108	0101	New Protocol
52,003	Certican®	11/12/99	[Belgium] Dr. Maimone; hepatitis cholestatic, hepatic function abnormal, fever, asthenia.	109		Safety Report
52,003	Certican®	11/12/99	[Canada] Site 84; hepatic functional abnormal, follow-up.	107		Safety Report
52,003	Certican®	11/12/99	Baz, Maher, MD; haemolysis, follow-up.	106		Safety Report
52,003	Certican®	11/03/99	[Canada] Site 84; hepatic function abnormal.	105		Safety Report
52,003	Certican®	11/01/99	As requested in the FDA letter dated 10/12/99 acknowledging Novartis' pre-NDA meeting request, provided pre-NDA briefing book which contains background information included in 2 volumes.	104		Briefing Book
52,003	Certican®	10/29/99	Submitted documentation to provide a Proposed Pediatric Study Request for RAD001 and to request the issuance of a Written Request. The enclosed information consists of proposed pediatric program, study synopses and examples of formatted reports.	103		
52,003	Certican®	10/28/99	[Canada] Houde, Isabelle, MD; NPN increased, drug-drug interaction (symptom specified), epididymitis, drug level increased, follow-up.	102		Safety Report
52,003	Certican®	10/21/99	Valantine, Hannah, MD; hepatic function abnormal, hyperlipaemia, drug level increased, graft rejection, cardiac failure left.	101		Safety Report
52,003	Certican®	10/12/99	[Argentina] Kaplinsky, Edgardo, MD; hepatic function abnormal, renal failure acute, tremor, follow-up.	100		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	10/12/99	FDA LETTER responding to Novartis' 9/27/99 correspondence requesting a pre-NDA meeting. The FDA indicated that the meeting has been scheduled for December 3, 1999. If the background information for this meeting is not received by the agency one month prior to the meeting, rescheduling of the meeting may be necessary.			
52,003	Certican®	10/07/99	TELECON from FDA informing Novartis that the Pre-NDA meeting will be held on December 3, 1999. It was also noted that a separate meeting for the CMC issues might be requested.			Memo of Record (telephone report)
52,003	Certican®	10/06/99	[Australia] Dr. Josette Eris; hepatic function abnromal.	099		Safety Report
52,003	Certican®	10/04/99	A point by point response is provided to the Division on additional information requested for Serial No. 048 (15-day report for CRAD001/B158/0/102/2/1/D).	098		
52,003	Certican®	10/01/99	Gonwa, Thomas, MD; purpura thrombocytopenic, graft rejection, renal tubular necrosis, hypertension, glomerulonephritis.	097		Safety Report
52,003	Certican®	09/27/99	Burdick, James, MD; cardiomyopathy, cardiac failure, oedema generalised, pleural effusion, myocardial ischaemia, hepatic function abnormal, follow-up.	096		Safety Report
52,003	Certican®	09/27/99	This submission requests a Pre-NDA meeting to discuss the content and format requirements for the RAD001 Tablet NDA. A table of contents from the briefing book currently in preparation is included.	095		Request for FDA Meeting
52,003	Certican®	09/21/99	FAX from FDA containing comments from the reviewing clinical pharmacologist on amendment to protocol B257 (Serial No. 077).		B257	
52,003	Certican®	09/20/99	[Germany] Prof. Neubaus; face oedema, follow-up.	094		Safety Report
52,003	Certican®	09/17/99	[Germany] Dr. Budde; renal failure acute, nephropathy toxic.	093		Safety Report
52,003	Certican®	09/15/99	Langas, Alan, DO; chest pain, hypertension pulmonary, renal failure acute, anaemia haemolytic,emphyema, pleural effusion, atrial flutter, cardiac arrest.	091		Safety Report
52,003	Certican®	09/14/99	[Spain] Dr. Javier Segovia; renal failure acute.	090		Safety Report
52,003	Certican®	09/14/99	[Canada] Houde, Isabelle, MD; NPN increased, drug-drug interaction (symptom specified), epididymitis, drug level increased, follow-up.	089		Safety Report
52,003	Certican®	09/14/99	[Canada] Houde, Isabelle, MD; NPN increased, drug-drug interaction (symptom specified), epididymitis, drug level increased, follow-up.	088		
52,003	Certican®	09/10/99	Baz, Maher, MD; haemolysis.	087		Safety Report
52,003	Certican®	09/08/99	New investigator for Protocol 156: Alan H. Wilkinson, MD. Also provided for Charlotte M. McKee, new investigator for Protocol 159, and for Drs. Roberts Ettenger and Jacques Lemire, new investigators for Protocol 257.	086	156/159/257	New Investigator
52,003	Certican®	09/02/99	Rajagopalan, P.R., MD; gastritis, thrombocytopenia, weight decrease, follow-up.	085		Safety Report
52,003	Certican®	09/02/99	[Argentina] Kaplinski, Edgardo, MD; hepatic finctional abnormal, renal failure acute, tremor.	084		Safety Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	09/02/99	[Canada] Houde, Isabelle, MD; NPN increased, drug-drug interaction (symptom specified), epididymitis, drug level increased, follow-up (MedWatch).			Safety Report
52,003	Certican®	09/01/99	[Germany] Prof. Neubas; face oedema.	083		Safety Report
52,003	Certican®	08/27/99	[Australia] hepatic functional abnormal, follow-up.	082		Safety Report
52,003	Certican®	08/24/99	[France] Thubanroyn Danielen; haemolytis, follow-up.	081		Safety Report
52,003	Certican®	08/17/99	[France] Thubanroyn Danielen; haemolysis, follow-up.	080		Safety Report
52,003	Certican®	08/12/99	[France] Thubanroyn Danielen; haemolysis.	079		Safety Report
52,003	Certican®	08/12/99	[Canada] Houde, Isabelle, MD; NPN increased, drug-drug interaction (sypmtom speceified), epididymitis, Drug level increased.	078		Safety Report
52,003	Certican®	08/12/99	Submitted change to Protocol B257 entitled: Amendment No.1.	077	B257	Change In Protocol
52,003	Certican®	08/11/99	[Australia] Dr. Josette Eris; hepatic functional abnormal.	076		Safety Report
52,003	Certican®	08/10/99	New subinvestigators for , Protocol B158 investigator. Also Hans Sollinger, MD, PhD has been added as a new investigator for Protocol B156 and John Mahan, MD has been added as a new investigator for Protocol B257.	074	B158/B156/E	New Investigator
52,003	Certican®	08/10/99	[Australia] Dr. R. Rigby; haemolysis, follow-up.	075		Safety Report
52,003	Certican®	08/05/99	FDA LETTER providing comments of Novartis' response to comment 3 (distribution of patients in each age strata) inclided in FDA fax of 6/25/99 regarding Protocol B257.		B257	
52,003	Certican®	07/22/99	TELECON TO FDA to obtain feedback on Novartis' response dated 7/9/99 to FDA questions faxed6/25/99 regarding pediatric Protocol B257.		B257	Memo of Record (telephone report)
52,003	Certican®	07/19/99	Hauptman, Paul, MD; renal failure acute, renal tubular necrosis, embolism - blood clot, pericardial effusion, pleural effusion, follow-up.	073		Safety Report
52,003	Certican®	07/16/99	New Investigators: P. R. Rajagopalan, MD; for Protocol B156; S. Forrest Dodson, MD; and Russell Wiesner, MD for Protocol B158; Stacy F. Davis for Protocol B253.	072	156/158/253	New Investigator
52,003	Certican®	07/15/99	Point by point response to the 5/24/99 teleconference minutes provided in the FDA communication dated 6/21/99. Novartis also requested written comments from the FDA on proposals for study B159.	071	B159	
52,003	Certican®	07/09/99	Point by point response to the FDA review comments to Protocol B257 included in the 6/25/99 communication.	070	B257	
52,003	Certican®	07/07/99	[Germany] Dr. Kehle; lymphoedema, oedema legs.	068		Safety Report
52,003	Certican®	07/07/99	[Australia] Dr. R. Rigby; haemolysis.	069	B257	Safety Report
52,003	Certican®	07/06/99	[France] Prof. Nourad; haemolysis, nephropathy toxic.	067		Safety Report
52,003	Certican®	07/01/99	Annual report covering the period from 15-Nov-97 through 14-Nov-98. Includes Precilincal, Clinical, CMC, information as well as a new General Investigational Plan For THe Coming Year.	066		Annual Report

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	06/30/99	Valentine, V.; sepsis, renal failure acute, respiratory insufficiency, dyspnoea, thrombocytopenia, GI Haemmorrhage, drug level increased, hyperglycaemia, death, follow-up.	065		Safety Report
52,003	Certican®	06/23/99	Also provided new investigator Barry D. Kahan, MD to Protocol 156.	064	156	New Investigator
52,003	Certican®	06/21/99	Valentine, V.; respiratory insufficiency, dyspnoea, renal failure acute, thrombocytopenia, GI haemorrhage, nephropathy toxic.	063		Safety Report
52,003	Certican®	06/17/99	In response toFDA request communicated in the 6/1/99 teleconference, provided additional clarification to the submission of Amendment 1 for study 156, Serial No. 052.	062	156	Other
52,003	Certican®	06/03/99	In response to FDA request of 6/2/99, provided desk copies of Protocol B257, submission dated 5/24/99.	060	B257	Other
52,003	Certican®	06/03/99	TELECON FROM FDA requesting additional copies of pediatric protocol 257.			Memo of Record (telephone report)
52,003	Certican®	06/02/99	Registration Stability Protocol RAD001A (SDZ RAD) 0.25mg, 0.5mg, 1mg tablets, 1RSP98 1870, 9-Nov-98.	058		CMC Amendment
52,003	Certican®	05/24/99	Study CRAD001 B257 new protocol. Also includes CMC information amendment providing information on the new RAD001 0.1 and 0.25mg fast dispersible tablets-pediatric formulation. (PS)	056		CMC Amendment New Protocol
52,003	Certican®	05/21/99	Initial report CRAD001B158010221D (PS)	055		Safety Report
52,003	Certican®	05/14/99	Response to FDA request for copies of published literature cited in our submission dated April 14, 1999 SN049. (PS)	054		Response to FDA Request
52,003	Certican®	05/13/99	Studies RADB 152, RADB 253 new investigator (PS).	053		New Investigator
52,003	Certican®	04/29/99	Study RADB 156 change in protocol, amendment 1. (PS)	052		Change in Protocol
52,003	Certican®	04/26/99	Novartis requests confirmation from FDA regarding the acceptance for use of the trademark Certican. (PS)	051		Other
52,003	Certican®	04/23/99	Amendment 1 to Protocol RADB 251.	050	251	Clinical Information Amendr
52,003	Certican®	04/14/99	Response to FDA correspondence dated 11/24/98 which raised several medical and statistical issues regarding Study B 159.	049	B 159	Clinical Information Amendr
52,003	Certican®	04/09/99	Also provided for Dr. Nghiem.	047	B 251	New Investigator
52,003	Certican®	04/09/99	Also provided for Dr. Freeman, new investigator for Protocol RADB 158.	047	B 158	New Investigator
52,003	Certican®	04/09/99	Also provided for Dr. McCurry.	047	B 253	New Investigator
52,003	Certican®	04/09/99	Also provided for Dr. Kinkhabwala.	047	B 251	New Investigator
52,003	Certican®	04/09/99	Also provided for Dr. Kaplan, new investigator for Protocol RADB 156.	047	B 156	New Investigator
52,003	Certican®	04/09/99	Submitted the following new investigators to Protocol RADB 251: Drs. Cohen, Nghiem and Kinkhabwala.	047	B 251	New Investigator
52,003	Certican®	04/09/99	Also submitted the following new investigators to Protocol RADB 253: Dr. Kobashigawa and McCurry.	047	B253	New Investigator
52,003	Certican®	04/05/99	Point by point response to FDA letter dated 1/20/98 which raised several statistical issues regarding Study RADB 156.	046	B 156	Clinical Information Amendr

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Cerlican®	03/30/99	Burdick, J,; cardiomyopathy, cardiac failure, pleural effusion, oedema generalised, hepatic function abnormal, myocardial ischaemia.	045	B251	Safety Report
52,003	Cerlican®	03/11/99	Study RADB 158 change in protocol, amendment 1. Study RADB 159 change in protocol, amendment 1. Studhy RADB253 change in protocol amendment 1 and 2. (PS)	044		Change In Protocol
52,003	Cerlican®	03/08/99	Submitted the following new investigator to Protocol RADB 159: Dr. Lawrence.	043	RADB159	New Investigator
52,003	Cerlican®	03/04/99	Submitted the following new investigator to Protocol RADB 159: Dr. Davis.	042	RADB159	New Investigator
52,003	Cerlican®	03/04/99	Also submitted the following new investigators to Protocol RADB 251: Drs. Leichtman, Harland, Thompson and Johnson.	042	RADB251	New Investigator
52,003	Cerlican®	03/04/99	Also provided for Dr. Johnson.	042	RADB251	New Investigator
52,003	Cerlican®	03/04/99	Also provided for Dr. Thompson.	042	RADB251	New Investigator
52,003	Cerlican®	03/04/99	Also submitted the following new investigator to Protocol RADB 253: Dr. Hill.	042	RADB253	New Investigator
52,003	Cerlican®	03/02/99	Submitted the following technical documentation: Drug product manufacture, MANU_CP_967_1 and Drug product composition and container, COMP_CP_967_1, dated 9-Apr-98: KN 3845403.00.005, 0.25 mg tablets; KN 3749215.00.002, 0.5 mg tablets; KN 3745411.00.005, 1 mg tablets.	041		CMC Amendment
52,003	Cerlican®	03/02/99	Also included Stability Report SDZ RAD solid dispersion, 5U97 1769, dated 7-Jan-98. **SDZ RAD 0.25mg, 0.5mg, 1mg, 5mg, 10mg and placebo tablets, Stability Report for development batches, 5U98 1800, dated 24-Apr-98.	041		CMC Amendment
52,003	Cerlican®	02/10/99	Submitted the following co-investigators for Protocol RADB 251: Wilkinson and Danovitch.	039	B251	New Investigator
52,003	Cerlican®	02/10/99	Also provided for Dr. Danovitch.	039	B251	New Investigator
52,003	Cerlican®	02/10/99	Also provided for Dr. Orens.	040	B 159	New Investigator
52,003	Cerlican®	02/10/99	Also provided for Drs. Woodle and Neylan, Protocol B251 investigators.	040	B 251	New Investigator
52,003	Cerlican®	02/10/99	Also provided for Dr. Neylan.	040	B 251	New Investigator
52,003	Cerlican®	02/10/99	Also provided for Drs. Andrew L. Smith and Lindenfeld, Protocol B253 investigators.	040	B 253	New Investigator
52,003	Cerlican®	02/10/99	New investigator for Protocol RADB 158: Dr. Abecassis.	040	B 158	New Investigator
52,003	Cerlican®	02/10/99	Also provided for Drs. Valentine and Orens, new investigators for Protocol B159.	040	B 159	New Investigator
52,003	Cerlican®	02/10/99	Also provided for Dr. Lindenfeld.	040	B 253	New Investigator
52,003	Cerlican®	01/14/99	Submitted the following new investigators to Protocol RADB 159: Drs. Rosengard and Loyd.	038	RADB 159	New Investigator
52,003	Cerlican®	01/14/99	Also submitted the following new investigator to Protocol RADB 253: Dr. Hare.	038	RADB 253	New Investigator
52,003	Cerlican®	01/14/99	Also provided for Dr. Loyd.	038	RADB 159	New Investigator

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	12/14/98	New protocol RADB 156, "A 3 year, multicenter, randomized, open label, parallel group study of the efficacy and safety of RAD tablets given in conjunction with Simulect, corticosteroids and either full or reduced dose Neoral in de novo renal transplant recipients". Also provided for Dr. Curtis.	036	B156	Clinical Information Amendr New Investigator New Protocol
52,003	Certican®	11/20/98	Also provided for Dr. Van Buren.	035	251	New Investigator
52,003	Certican®	11/20/98	Also provided for Dr. Hauptman.	035	253	New Investigator
52,003	Certican®	11/20/98	Also provided for Dr. Miller.	035	253	New Investigator
52,003	Certican®	11/20/98	Also provided for Dr. Aris.	035	159	New Investigator
52,003	Certican®	11/20/98	Also submitted the following new investigators to Protocol RADB 253: Drs. Frazier, Hauptman, Miller.	035	253	New Investigator
52,003	Certican®	11/20/98	Submitted the following new investigators to Protocol RADB 159: Drs. Frost, Mullett, Aris.	035	159	New Investigator
52,003	Certican®	10/27/98	Also provided for Dr. Wombolt.	034	251	New Investigator
52,003	Certican®	10/27/98	Also provided for Dr. Lorber.	034	251	New Investigator
52,003	Certican®	10/27/98	Also provided for Dr. Ouseph (co-investigator).	034	251	New Investigator
52,003	Certican®	10/27/98	Also provided for Dr. Burrows.	034	251	New Investigator
52,003	Certican®	10/27/98	Also submitted the following new investigator for Protocol RADB 159: Dr. Maurer.	034	159	New Investigator
52,003	Certican®	10/27/98	Also provided for Dr. Mancini.	034	253	New Investigator
52,003	Certican®	10/27/98	Also provided for Dr. Hricik.	034	251	New Investigator
52,003	Certican®	10/27/98	Also provided for Dr. Renlund.	034	253	New Investigator
52,003	Certican®	10/27/98	Submitted the following new investigator to Protocol RADB 157: Dr. Min (who replaces Dr. Elkhammas).	034	157	New Investigator
52,003	Certican®	10/27/98	Also submitted the following investigators to Protocol RADB 251: Drs. Farney, Hricik, Lorber, Burrows, Wombolt, and Jones and Ouseph (co-investigators).	034	251	New Investigator
52,003	Certican®	10/13/98	Also submitted the following new investigators to Protocol RADB 159: Drs. Garrity, McGiffin (co- investigator), and Young (co-investigator).	033	159	New Investigator
52,003	Certican®	10/13/98	Also provided for Dr. Matas.	033	251	New Investigator
52,003	Certican®	10/13/98	Also provided for Dr. Starling.	033	253	New Investigator
52,003	Certican®	10/13/98	Also submitted the following new investigators to Protocol RADB 251: Drs. Dunn, Matas.	033	251	New Investigator
52,003	Certican®	10/13/98	Also provided for Dr. Young.	033	159	New Investigator
52,003	Certican®	10/13/98	Submitted the following new investigator to Protocol RADB 152: Dr. Rosengard.	033	152	New Investigator
52,003	Certican®	09/25/98	Annual Report covering the period November 15, 1996 to November 14, 1997 (PS).	031		Annual Report
52,003	Certican®	09/25/98	Also submitted the following new investigators to Protocol RADB 158: Drs. Langnas, Merion.	032	158	New Investigator
52,003	Certican®	09/25/98	Also provided for Dr. Trulock.	032	159	New Investigator

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	09/25/98	Also provided for Dr. Merlon.	032	158	New Investigator
52,003	Certican®	09/25/98	Also provided for Dr. Pruett.	032	251	New Investigator
52,003	Certican®	09/25/98	Also provided for Dr. Doyle.	032	159	New Investigator
52,003	Certican®	09/25/98	Also submitted the following new investigators to Protocol RADB 251: Drs. Barone, Conti, Elkhammas, Pollack, Pruett, Burdick, Kahan.	032	251	New Investigator
52,003	Certican®	09/25/98	Also provided for Dr. Conti.	032	251	New Investigator
52,003	Certican®	09/25/98	Also provided for Dr. Elkhammas.	032	251	New Investigator
52,003	Certican®	09/25/98	Also provided for Dr. Baz.	032	159	New Investigator
52,003	Certican®	09/25/98	Also provided for Dr. Kahan.	032	251	New Investigator
52,003	Certican®	09/25/98	Also submitted the following new investigators to Protocol RADB 159: Drs. Hertz, Doyle, Trulock, Baz.	032	159	New Investigator
52,003	Certican®	09/25/98	Submitted the following new investigator to Protocol RADB 152: Dr. McCurry.	032	152	New Investigator
52,003	Certican®	09/10/98	Fax from Dr. Self, UK, providing DRA with a copy of the MCA CTX approval letters for studies RADB 201-E-00 and 159.			
52,003	Certican®	08/27/98	Studies RADB151, RADB152, RADB157, RADB159, RADB251 new investigator (PS).	030		New Investigator
52,003	Certican®	08/27/98	Novartis telecon meeting minutes from meeting held with FDA on August 25, 1998 to discuss points of clarification to the FDA communication dated August 20, 1998. (PS)	030		FDA/Novartis Meeting Minu
52,003	Certican®	08/25/98	Studies RADB151, RADB152, RADB157, RADB159, RADB251 new investigator (PS).	029		New Investigator
52,003	Certican®	08/19/98	Study RADB 253 new protocol (PS).	028		New Protocol
52,003	Certican®	08/12/98	Study RADB158 new protocol. (PS)	027		New Protocol
52,003	Certican®	08/09/98	Study RADB 251 new protocol (PS)	023		New Protocol
52,003	Certican®	08/04/98	Communication to FDA regarding 52-week oral (gavage) toxicity study 1463-045 in the cynomolgus monkey. (PS)	026		Preclinical Amendment
52,003	Certican®	07/24/98	Study RADB 159 new protocol (PS).	025		New Protocol
52,003	Certican®	07/09/98	Also submitted the following new investigator to Protocol RADB 157: Dr. Tomlanovich.	024	157	New Investigator
52,003	Certican®	07/09/98	Also provided for Dr. Davis.	024	152	New Investigator
52,003	Certican®	07/09/98	Submitted the following new investigators to Protocol RADB 152: Drs. Garrity, Davis.	024	152	New Investigator
52,003	Certican®	07/07/98	Novartis requested the FDA to accept the firm's rationale for the termination of study 1463-045, a 52 week oral (gavage) toxicity study in the cynomolgus monkey, being conducted at Covance Laboratories GmbH, Germany. The study was terminated at week 39 due to the observed tolerability problems in several dose groups.			Preclinical Amendment
52,003	Certican®	06/08/98	Submitted an overview of safety reporting in Phase 2-3 RAD trials per request by the Division at a March 11, 1998 meeting.	022		Clinical Information Amendr

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	05/20/98	Study RADB 152, RADB 157 new investigator (PS)	020		New Investigator
52,003	Certican®	05/01/98	Submitted per request at the 3/11/98 meeting with the FDA the following carcinogenicity protocols for review: SDZ RAD: Oncogenicity Study By Oral Gavage Administration To Hanibm Wistar Rats for 104 Weeks (Doc. No. 203-069) and Amendments 1-9 and SDZ RAD: Oncogenicity Study By Oral Gavage Administration to CD-1 Mice for 90 Weeks (Doc. No. 203-082) and Amendments 1-7.	019		Preclinical Amendment
52,003	Certican®	04/22/98	Document 203-082 range finding toxicity study by oral gavage administration to CD-1 mice for 13 weeks. (PS)	018		Preclinical Amendment
52,003	Certican®	04/17/98	Study RADB 152 new investigator (PS)	017		New Investigator
52,003	Certican®	03/27/98	Submitted a summary of the discussion and agreements of the meeting held on March 11, 1998 between Novartis, consultants and the FDA to discuss the clinical development program for RAD.			Clinical Information Amendr
52,003	Certican®	03/02/98	FDA FAX: Review of the End-of-Phase 2 Meeting Request Package and comments and recommendations that the Division would like Novartis to be prepared to discuss at the March 11, 1998 meeting.			
52,003	Certican®	02/18/98	Study RADB 157 change in protocol. (PS)	015		Change In Protocol
52,003	Certican®	02/18/98	New Protocol RADB 152 entitled "A One Year Randomized, Multicenter, Open-Label, Parallel, Group Study of the Efficacy and Safety of SDZ RAD Tablets Versus Antilymphocyte Globulin and Azathioprine in Lung or Heart/Lung Transplant Receipients with Bronchiolitis Obliterans Syndrome." Also submitted Amendment Nos. 1 and 2.	016	RADB 152	Clinical Information Amendr New Protocol
52,003	Certican®	02/02/98	Letter requesting an End-of-Phase 2 meeting to present the clinical development program. Also submitted was a comprehensive Briefing Book.	014		Briefing Book Request for FDA Meeting
52,003	Certican®	01/26/98	An Information Amendment submitting complete reproductive toxicology reports (please note that an '*' is placed prior to the submissions that contain full reports, all other studies are summary reports). Document Nos.: *203-069, *203-072, *203-077, *203-074, *203-073, *203-076, 203-068, 203-070, 203-461, 203-071, 203-062, 203-063, 203-067, 203-037, 203-036, 203-078, 203-075.	013		Preclinical Amendment
52,003	Certican®	01/20/98	FDA FAX providing the statisticians review comments on Protocol for Study RADB 156.			
52,003	Certican®	01/16/98	Submitted new protocol: Protocol RADB 157-E-00, A One-Year, Multicenter, Randomized, Double-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability and Pharmacokinetics of SDZ RAD in De Novo Renal Transplant Recipients.	012	RADB157-E-	Clinical Information Amendr New Protocol
52,003	Certican®	01/16/98	Also submitted Amendment No. 1 to Protocol RADB 157. Also the following new investigator: Dr. Elkhammas.	012	RADB 157	Clinical Information Amendr New Investigator
52,003	Certican®	01/16/98	Also included the following stability reports: RAD Solid Dispersion, Stability Report 3U96 1769, dated 15-Nov-96. **RAD Tablets, 0.25 mg, 1 mg, 5 mg, 10 mg, Stability Report 1U97 1800, dated 8-Feb-97.	012		CMC Amendment

REF	PRODUC	DATE	DESCRIPTION	SERI	PROTOCOL	SUBMISSION TYPE
52,003	Certican®	01/16/98	Also provided documentation to support the following formulations: Description of the Manufacturing and Packaging: KN3745346.00.001, 2% RAD solid dispersion, KN 3744448.00.002, 9.09% RAD solid dispersion, KN 3745403.00.002, 0.25 mg tablet, KN 3745411.00.002, 1 mg tablet, KN 3745429.00.002, 5 mg tablet, KN 3745437.00.002, 10 mg tablet. Also included placebo drug product information.	012		CMC Amendment
52,003	Certican®	09/25/97	Study RADB 151 new investigator (PS).	011		New Investigator
52,003	Certican®	09/04/97	Follow-up safety report RADW1020641N (PS)	010		Safety Report
52,003	Certican®	03/21/97	Response to FDA correspondence dated February 3, 1997 which provided IND review comments and requests for additional information. (PS)	007		Response to FDA Request
52,003	Certican®	03/03/97	Study RADB 151 new investigator (PS).	006		New Investigator
52,003	Certican®	02/12/97	Change in Company Name To Novartis (PS).	005		Other
52,003	Certican®	01/31/97	Study RADB 202 change in protocol, amendment 1. (PS)	002		Change In Protocol
52,003	Certican®	01/31/97	Study RADB 154 change in protocol, amendment 1. (PS)	003		Change In Protocol
52,003	Certican®	01/31/97	Study RADB 151 change in protocol, amendment 1. (PS)	004		Change In Protocol
52,003	Certican®	01/28/97	Update Form 1572 to add New Clinical Lab Facility for Study B154. (PS)	001		Clinical Information Amendr
52,003	Certican®	11/25/96	Acknowledge receipt of original IND for prophylaxis of organ rejection.			Other
52,003	Certican®	11/15/96	Submission of Original IND for prophylaxis of organ rejection. (PS)	000		Original IND