

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-560s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: Trial RAD001A2309 “A 24-month, multicenter, randomized, open-label noninferiority study of efficacy and safety comparing concentration-controlled Certican™ [everolimus] in two doses (1.5 and 3.0 mg/day starting doses) with reduced Neoral® versus 1.44 g Myfortic® with standard dose Neoral in de novo renal transplant recipients” which contains the 24-month follow-up safety data on all patients enrolled in the trial.

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PMR/PMC Schedule Milestones: Final protocol Submission Date: Completed, trial is ongoing  
Study/Clinical trial Completion Date: 08/18/2009  
Final Report Submission Date: 07/30/2009  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

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 assess a signal of serious risks of wound healing complications, hyperlipidemia, proteinuria, and graft thromboses, and other adverse events.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Trial RAD001A2309 is a 24-month, multicenter, randomized, open-label noninferiority study of efficacy and safety comparing concentration-controlled everolimus in two doses (1.5 and 3.0 mg/day starting doses with target trough concentrations of 3 to 8 ng/mL) with reduced Neoral® (cyclosporine) versus 1.44 g Myfortic® (mycophenolic acid) with standard dose Neoral in de novo renal transplant recipients which contains the 24-month follow-up safety data on all patients enrolled in the trial. The 12-month follow-up safety data on all patients enrolled in the trial was reviewed as a part of the NDA submission and the Division is making the submission of the 24-month data a post marketing requirement in order to obtain longer term safety follow-up on all patients enrolled, particularly on those serious safety risks that led to the Risk Evaluation and Mitigation Strategy (REMS): wound healing complications, hyperlipidemia, proteinuria, and graft thromboses. This trial will not provide new safety information regarding the serious risk of nephrotoxicity when everolimus is administered with standard doses of cyclosporine.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, multi-center, open-label noninferiority study of efficacy and safety comparing concentration-controlled everolimus in two doses (1.5 and 3.0 mg/day starting doses) with reduced doses of Neoral® versus 1.44 g Myfortic® with standard doses of Neoral in de novo renal transplant recipients. The sponsor will be required to submit the full study report that contains 24-month follow-up safety data on all patients enrolled in the trial.

Required

- Observational pharmacoepidemiologic study  
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)  
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
 Pharmacokinetic studies or clinical trials  
 Drug interaction or bioavailability studies or clinical trials  
 Dosing trials  
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Full study report that contains 24-month follow-up safety data on all patients enrolled in the trial RAD001A2309.

- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Ozlem Belen, MD, MPH  
Deputy for Safety, DSPTP

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(signature line for BLAs)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	Zortress (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
04/19/2010

OZLEM A BELEN  
04/19/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 12, 2010

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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**Total no. of pages including cover: 3**

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NDA 21-560

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zortress (everolimus) Tablets, specifically the REMS issues listed below.

Please address and respond to these issues as soon as possible.

1. You need to number the professional societies as you did with the targeted group of healthcare professionals.
2. Add the word "Professional" into the attachment B heading: "ATTACHMENT B. DEAR HEALTHCARE PROFESSIONAL/PROFESSIONAL ASSOCIATION LETTER"
3. Please remove the period in the Proteinuria bullet in attachment B.
4. We ask you that you submit the final and complete REMS document, attachments to the REMS document (Medication Guide and the Letters) and the Supporting Document to the EDR.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
04/12/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 6, 2010

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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NDA 21-560

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zortress (everolimus) Tablets. Please find enclosed two attachments. The first is the package insert (PI) that we consider close to final. If you want to make any changes, please call us to discuss before sending another version of labeling. Our rationale for excluding some of the adverse reactions < 10% is listed below:

- Different terms with equivalent or similar meaning are excluded.
- Non-specific adverse reactions which are very unlikely to be related to the treatment regimen are also excluded.
- Some of the terms related to procedural/technical complications excluded.

The second is the Medication Guide with our request to make one formatting change.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

28 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
04/06/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 2, 2010

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zortress (everolimus) Tablets. Please find attached REMS elements, excluding Medication Guide, as it was addressed with you in a previous communication, Dear Healthcare Professional (DHCP) letter and Dear Pharmacist (DP) letter). We want to ensure that the re-submitted Supporting Document is revised to be entirely consistent with the REMS document as shown below, so we are providing you a revised REMS document in "WORD Track Changes." The re-submitted REMS should include only the REMS, DHCP/Association letter, Pharmacist Letter, and the Supporting Document. Please make additional corrections to the formatting, as appropriate. Please submit the revised REMS by April 9, 2010.

8 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

NDA 21-560

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
04/02/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**TRANSMITTAL SHEET**

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**DATE:** April 1, 2010

<b>To:</b> Mr. Ronald Van Valen	<b>From:</b> Ms. Jacquelyn Smith Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via E-mail	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-7646  Email: ronald.vanvalen@novartis.com	<b>Phone number:</b> 301-796-1600

**Subject:** NDA 21-560-Zortress (everolimus) Tablets- Providing Postmarketing Requirements for NDA 21-560 to Novartis for Final Agreement

**Total no. of pages including cover:** 4

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**Document to be mailed:**                       YES                       NO

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Dear Mr. Van Valen,

In order to assist with the completion of the review of NDA 21-560, please provide your final agreement and concurrence to the information listed below.

We request you submit to the NDA, as an official submission, your stated agreement to the Postmarketing Requirement identified below. We further ask that your agreement identify this Postmarketing Requirement specifically and completely.

Please submit a complete, official response acknowledging that you are in agreement with the below timetable no later than April 6, 2010.

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 assess signals of the serious risks of wound healing complications, hyperlipidemia, proteinuria, and graft thromboses, and other adverse events as described in your proposed labeling.

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 signals of the serious risks of wound healing complications, hyperlipidemia, proteinuria, and graft thromboses.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1. Trial RAD001A2309 “A 24-month, multicenter, randomized, open-label noninferiority 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 Neoral in de novo renal transplant recipients” and submit the 24-month follow-up safety data for patients enrolled in the trial.**

Final protocol submission  
Trial Completion Date:  
Final Report Submission:

Completed; trial is ongoing  
by August 18, 2009  
by July 30, 2010

NDA 21-560

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Jacquelyn Smith, M.A.  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
04/01/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 26, 2010

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zortress (everolimus) Tablets. Please find attached REMS elements, excluding Medication Guide, as it was addressed with you in a previous communication, Dear Healthcare Professional (DHCP) letter and Dear Pharmacist (DP) letter. Please make additional corrections to the formatting, as appropriate. Please submit your revised version of all three documents by April 2, 2010

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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JACQUELYN E SMITH  
03/26/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 16, 2010

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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NDA 21-560

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zortress (everolimus) Tablets. Please find attached the revised package insert (PI) and medication guide (MG). Please make additional corrections to the formatting, as appropriate. Please submit your revised version of both documents by March 23, 2010.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
03/16/2010



NDA 21-560

**ACKNOWLEDGE CLASS 2 RESPONSE**

Novartis Pharmaceuticals Corporation  
Attention: Mr. Ronald G. Van Valen  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

We acknowledge receipt of your January 22, 2010 resubmission to your new drug application for Zortress (everolimus) Tablets.

We consider this a complete, class 2 response to our December 23, 2009 action letter. Therefore, the user fee goal date is July 22, 2010.

If you have any questions, call me at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Jacquelyn Smith, M.A.  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
02/22/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** February 12, 2010

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560 Requests

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Dear Mr. Van Valen:

Please refer to NDA 21-560, Zortress (everolimus) Tablets.

Note that these comments are *preliminary, interim* comments during our on-going review. Additional and/or updated comments will be forthcoming.

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Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
02/12/2010



**Food and Drug Administration Center  
for Drug Evaluation and Research**

**OFFICE OF ANTIMICROBIAL  
PRODUCTS**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** February 1, 2010

**To:** Mr. Ron Van Valen, Director, Drug Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** Container Label and Carton Labeling

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Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zortress (everolimus) tablets.

The Division of Medication Error Prevention and Analysis (DMEPA) has the following recommendations for the container label and carton labeling:

***Blister Labels – Sample and Trade***

1. Relocate the dosage form so that it immediately follows the established name. Revise the presentation of the drug name as follows:

Zortress  
(everolimus) tablet

2. Delete the trailing zero (i.e. 1.0 mg) on 1 mg strength.
3. Black font color is used to differentiate the strength on the 1 mg blister labels. However, on the carton labeling, the 1 mg is highlighted in orange. For consistency purposes, use only one color for the product strength (black or orange) on both the blister label and carton labeling since all other strengths use the same strength color on the respective blister label and carton labeling.
4. Per 203.38(c), “each unit shall bear a label that clearly denotes its status as a drug sample, e.g., “sample,” “not for sale,” “professional courtesy package.” Revise accordingly if space permits.

***Trade Carton Labeling***

1. The blue triangular graphic highlights the net quantity statement, takes up more than 1/3 of the principal display panel and distracts from more relevant information. Remove or minimize the graphic so that it does not highlight the net quantity statement and compete in prominence with the proprietary name, established name, and product strength.
2. Relocate the dosage form so that it immediately follows the established name. Revise the presentation of the drug name as follows:

Zortress  
(everolimus) tablet

3. Delete the trailing zero (i.e. 1.0 mg) on 1 mg strength.
4. Revise the net content statement to more accurately describe the content description (e.g. Carton contains 6 individual blister cards of 10 tablets).

***Sample Carton Labeling***

1. Relocate the dosage form so that it immediately follows the established name. Revise the presentation of the drug name as follows:

Zortress  
(everolimus) tablet

NDA 21-560

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

---

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/s/

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JACQUELYN E SMITH  
02/01/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Drug Marketing, Advertising, and Communications (DDMAC)/Paul Loebach, CSO**

FROM (Name, Office/Division, and Phone Number of Requestor):

**Ms. Jacquelyn Smith, RPM/Dr. Ozlem Belen, DDS  
Division of Special Pathogen and Transplant Products (DSPTP)**

DATE  
**January 27, 2010**

IND NO.

NDA NO.  
**21-560**

TYPE OF DOCUMENT

DATE OF DOCUMENT  
**January 22, 2010**

NAME OF DRUG  
**Zortress (everolimus)**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
**Immunosuppressant**

DESIRED COMPLETION DATE  
**March 22, 2010**

NAME OF FIRM: **Novartis**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** On January 22, 2010, our Division received a resubmission for NDA 21-560, Zortress (everolimus) (seeking indication for the prophylaxis of organ rejection in renal transplantation), in response to the December 23, 2009 complete response (CR) letter. The REMS included in this resubmission has a Medication Guide that needs to be reviewed. For your convenience, the EDR link to access the resubmission is \\CDSESUB1\EVSPROD\NDA021560\0046.

SIGNATURE OF REQUESTOR  
**Jacquelyn Smith, PM**

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
01/27/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Medication Error Prevention and Analysis (DMEPA)/Karen Townsend/PM**

FROM (Name, Office/Division, and Phone Number of Requestor):

**Jacquelyn Smith, PM (DSPTP/Dr. Mark Seggel, OPS/ONDQA/DPA II**

DATE  
**January 27, 2010**

IND NO.

NDA NO.  
**21-560**

TYPE OF DOCUMENT

DATE OF DOCUMENT  
**January 22, 2010**

NAME OF DRUG  
**Zortress (everolimus)**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
**Immunosuppressant**

DESIRED COMPLETION DATE  
**March 22, 2010**

NAME OF FIRM: **Novartis**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** On January 22, 2010, our Division received the resubmission for NDA 21-560, Zortress (everolimus) (seeking indication for the prophylaxis of organ rejection in renal transplantation) in eCTD format via Gateway. This resubmission is in response to the Division's complete response (CR) letter dated December 23, 2009. Although the PDUFA date is July 22, 2010, we are seeking to take an earlier action and are appreciative of your help in accomplishing this.

Dr. Mark Seggel, chemistry reviewer, is requesting a review of the carton and container labeling. For your convenience, the EDR link to this resubmission is \\CDSESUB1\EVSPROD\NDA021560\0046. Thank you.

SIGNATURE OF REQUESTOR  
**Jacquelyn Smith, PM**

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

---

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/s/

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JACQUELYN E SMITH  
01/27/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): OSE/Division of Risk Management  
(DRISK) Dr. Claudia Karwoski, DD/Darrell Jenkins,  
RPM

FROM (Name, Office/Division, and Phone Number of Requestor):  
Ms. Jacquelyn Smith, RPM/Dr. Ozlem Belen, DDS  
Division of Special Pathogen and Transplant Products  
(DSPTP)

DATE  
January 27, 2010

IND NO.

NDA NO.  
21-560

TYPE OF DOCUMENT

DATE OF DOCUMENT  
January 22, 2010

NAME OF DRUG  
Zortress (everolimus)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
Immunosuppressant

DESIRED COMPLETION DATE  
March 22, 2010

NAME OF FIRM: Novartis

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** On January 22, 2010, our Division received the resubmission for NDA 21-560, Zortress (everolimus) (seeking indication for the prophylaxis of organ rejection in renal transplantation) in eCTD format via Gateway. This resubmission is in response to the Division's complete response (CR) letter dated December 23, 2009. Although the PDUFA date is July 22, 2010, we are seeking to take an earlier action and are appreciative of your help in accomplishing this. A revised REMS is included in this resubmission. The elements of the revised REMS include the Medication Guide and a communication plan. For your convenience, the EDR link to access the resubmission is \\CDSESUB1\EVSPROD\NDA021560\0046. Review of the Medication Guide by the patient labeling reviewer will be necessary. Please contact Dr. Belen or me if you have any questions. Thank you.

SIGNATURE OF REQUESTOR  
Jacquelyn Smith, PM

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
01/27/2010



NDA 021560

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Ronald G. Van Valen  
Executive Director, Drug Regulatory Affairs

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) resubmission dated June 30, 2009, received June 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Everolimus Tablets, 0.25 mg, 0.5 mg, 0.75 mg, and 1 mg.

We also refer to your October 19, 2009, correspondence, received October 19, 2009, requesting review of your proposed proprietary name, Zortress. We have completed our review of the proposed proprietary name, Zortress and have concluded that it is acceptable.

The proposed proprietary name, Zortress, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 19, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Jacquelyn Smith at (301) 796-1002.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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CAROL A HOLQUIST  
01/15/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

---

**DATE:** December 4, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560 Requests

---

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**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600 Thank you.**

NDA 21-560

Dear Mr. Van Valen:

Please refer to your Everolimus NDA, 21-560, specifically your bioanalytical assay.

Please provide a summary of the validation of the bioanalytical assay used in Study 2309. In your NDA submission you have provided a "Bioanalytical Data Report" in Appendix 16.2.5, however, it does not include a summary of the results of the validation of the assay. Specifically, we need information to determine the analytical performance of the assay such as Reproducibility/Repeatability, Limits of Quantitation, Linearity, Analyte Recovery, Accuracy, Precision, Freeze/Thaw Stability, etc. In addition to the summary of the validation of the assay, please also include a summary of the performance of the assay during the runs of the clinical samples, i.e., in-process precision and accuracy of the Quality Control (QC) samples. Please refer to FDA Guidance entitled "Bioanalytical Method Validation" for details on the information that is provided in support of a bioanalytical assay validation and performance. We request that you provide this information by close of business on Friday, December 11, 2009.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
12/04/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

---

**DATE:** December 4, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** Draft Package Insert

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NDA 21-560

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for everolimus tablets.

We also refer to your package insert (PI) labeling. While our review of your PI is ongoing, we are providing you with some of our preliminary proposed changes to the following complete sections in the Full Prescribing Information:

- Section 2 Dosage and Administration
- Section 7 Drug Interactions
- Section 12 Clinical Pharmacology – we previously sent Section 12.1 and have no additional changes, but are resending it so you can see the complete section

Please note that additional proposals for other sections of the PI are forthcoming. In addition, we may have further edits to the sections we are sending you today.

In addition, until the Division of Medication Errors and Prevention Analysis (DMEPA) completes its review of your proposed trade name, we will use the name “everolimus” throughout the draft package insert.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Enclosure

8 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
12/04/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 24, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** Proteinuria

---

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600 Thank you.**

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for everolimus tablets.

In the everolimus submission we need clarification on one issue related to proteinuria. Please provide an explanation for the following:

In the protocol for Study A2309 the urine protein to creatinine (UP/UC) ratio was defined as:

- Normal (< 30 mg/g);
- Mild proteinuria (30 to < 300 mg/g);
- Sub-Nephrotic proteinuria (300 - <3000 mg/g);
- Nephrotic proteinuria ( $\geq$ 3000 mg/g).

It appears that the normal range above correlates with the definition of albuminuria (based on a 24-hour excretion) or clinical proteinuria (based on a spot urine dipstick), rather than spot urine protein-to-creatinine ratio, according to the National Kidney Foundation (NKF) definitions of proteinuria and albuminuria.<sup>1</sup>

According to the NKF, the cut-off values for clinical proteinuria based on a spot urine protein-to-creatinine ratio are:

- Normal (< 200 mg/g)
- Clinical Proteinuria (> 200 mg/g)

Can you please explain your rationale in choosing (<30 mg/g) instead of (< 200 mg/g) as the threshold for normal UP/UC ratio and how you determined the ranges for sub-nephrotic and nephrotic proteinuria.

Can you please also clarify if spot urine protein/urine creatinine and/or spot urine albumin/urine creatinine were used in the study? Were results for one used interchangeably with the other?

Please provide an answer by Friday, November 27, 2009.

---

<sup>1</sup> Table 15. Definitions of Proteinuria and Albuminuria:  
[http://www.kidney.org/PROFESSIONALS/kdoqi/guidelines\\_ckd/p4\\_class\\_g1.htm](http://www.kidney.org/PROFESSIONALS/kdoqi/guidelines_ckd/p4_class_g1.htm)

NDA 21-560

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission.

Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
11/24/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 20, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** Draft Package Insert

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authorized. If you have received this document in error, please notify us  
immediately by telephone at 301-796-1600 Thank you.**

NDA 21-560

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for everolimus tablets.

We also refer to your package insert (PI) labeling. While our review of your PI is ongoing, we are providing you with some of our preliminary proposed changes to the following sections in the Full Prescribing Information:

Section 3 (Dosage Forms and Strengths)  
Section 4 (Contraindications)  
Section 8.1 (Pregnancy)  
Section 11 (Description)  
Section 12.1 (Mechanism of Action)  
Section 14 (Clinical Studies)  
Section 16 (How Supplied/Storage and Handling)

Please note that additional proposals for other sections of the PI are forthcoming. In addition, we may have further edits to the sections we are sending you today.

In addition, until the Division of Medication Errors and Prevention Analysis (DMEPA) completes its review of your proposed trade name, we will use the name “everolimus” throughout the draft package insert.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Enclosure

5 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

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JACQUELYN E SMITH  
11/20/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 20, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560/ assay comments

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Dear Mr. Van Valen:

Please refer to NDA, 21-560, specifically the November 18, 2009 teleconference discussion between Novartis, DSPTP and CDRH regarding your Everolimus assays. The teleconference was very informative and clarified many of our questions, but we feel the following comments will help the assay review progress more efficiently. Please respond to us as soon as possible.

1. To facilitate discussion between FDA, Novartis, and their diagnostic partner firm(s), we recommend that each company submit to FDA a letter of authorization allowing FDA to discuss their products and interactions with the other firm(s). These letters should outline the specific limits of the authorization. If, in order to facilitate discussions related to test availability, FDA potentially needs to engage in discussions with Novartis, (b) (4) then FDA will need authorization letters from each firm.
2. Novartis may wish to consider that the most straightforward comparison for any new assay would be for the new assay to measure samples from Novartis Study A2309 and compare their new analytical results with the analytical results obtained during the study. This recommendation assumes the samples are stable over the time period/conditions stored.
3. Tests using different measurement technologies are often not directly comparable. Immunoassays, for example, often have significant cross-reactivity with metabolites that can bias test results. If Novartis is planning to rely on an immunoassay as the commercialized test, we would like a justification of how much cross-reactivity would be acceptable, keeping in mind that cross-reactivity can lead, not only to bias, but also to a higher degree of unexpected variability in test results between samples. We recommend that these discussions be held as soon as possible to facilitate efficient review of test performance.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
11/20/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Medication Error Prevention and Analysis (DMEPA)**

FROM (Name, Office/Division, and Phone Number of Requestor):

**Jacquelyn Smith, PM (DSPTP/Dr. Mark Seggel, OPS/ONDQA/DPA II)**

DATE  
**November 17, 2009**

IND NO.

NDA NO.  
**21-560**

TYPE OF DOCUMENT

DATE OF DOCUMENT  
**June 30, 2009**

NAME OF DRUG  
**Everolimus**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
**Immunosuppressant**

DESIRED COMPLETION DATE  
**December 17, 2009**

NAME OF FIRM: **Novartis**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** DSPTP received the resubmission for NDA 21-560, Everolimus Tablets (seeking indication for the prophylaxis of organ rejection in renal transplantation) in eCTD format via Gateway. The letter and receipt date is June 30, 2009. The PDUFA date is December 30, 2009. There will be Advisory Committee held on December 7, 2009.

Dr. Mark Seggel, chemistry reviewer, is requesting a review of the carton and container labeling. The EDR link to access the carton and container labeling is \\CDSESUB1\EVSPROD\NDA021560\0010. Thank you.

SIGNATURE OF REQUESTOR  
**Jacquelyn Smith, PM**

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
11/17/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**TRANSMITTAL SHEET**

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**DATE:** November 13, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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**Total no. of pages including cover:**

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Dear Mr. Van Valen:

Please refer to your Everolimus NDA, 21-560, specifically GFR data issues. Please respond to our questions no later than Wednesday, November 18, 2009.

1. The Statistical Analysis Plan or SAP (see RAP Module 3 – Detailed Statistical Methodology) defined “re-aligned visit windows” in Table 3-1, page 8. Visit numbers 32 and 42 were the month 12 treatment and study endpoints, respectively. Table 8-2, page 29 of the SAP, also defined imputation methods for month 12 GFR (MDRD) missing values. Methods 1 and 2 corresponded to end of treatment and end of study, respectively. A portion of the table below shows part of Table 6-3 in the Novartis Briefing Book. These calculations appear to have been obtained using the variable “gfr\_m1” from the “renal” analysis dataset but using “revisit=42”, where the “m1” refers to imputation method 1 and the “revisit” variable refers to the re-aligned visit windows. Why do you use “revisit=42” when Table 6-3 should be based on the *last day of treatment* as stated in the first paragraph of section 6.1.2 of the Novartis Briefing Book (page 26)? Should not “revisit=32” be used instead? The lower portion of the table below shows the results when “revisit=32” is used instead of “revisit=42” and there are slight differences between the two.

#### Renal function (MDRD calculated GFR) at 12 months

	Everolimus 1.5 mg	Everolimus 3.0 mg	Myfortic 1.44 g
<b>Table 6-3 in Sponsor Briefing Book Using Revisit=42</b>	<b>n=275</b>	n=278	n=277
Mean (SD)	54.55 (21.68)	51.29 (22.74)	52.18 (26.66)
Median (Range)	55.0 (0.0-140.90)	51.58 (0.0-124.00)	49.70 (0.0-366.40)
Difference in Mean*	2.37	-0.89	
t-test based 95% CI	(-1.69,6.44)	(-5.02,3.24)	
t-test based 97.5% CI	(-2.28,7.03)	(-5.62,3.84)	
p-value, t-test (no difference)	0.251	0.673	
<b>Using Revisit=32</b>	<b>n=274</b>	n=278	<b>n=272</b>
Mean (SD)	54.53 (21.72)	51.29 (22.74)	52.06 (26.51)
Median (Range)	54.95 (0.00-140.90)	51.58 (0.00-124.0)	49.65 (0.00-366.40)
Difference in Mean*	2.47	-0.769	
t-test based 95% CI	(-1.60,6.55)	(-4.90,3.37)	
t-test based 97.5% CI	(-2.19,7.14)	(-5.50,3.96)	
p-value, t-test (no difference)	0.233	0.716	

\* Everolimus-Myfortic;

2. The following illustrates how the original values (variable “gfr\_ov”) were assigned to the variable “gfr\_m1” from the “renal” dataset. The last treatment observation was 63.1 on revisit=7 and is correctly imputed at revisit=32 (treatment endpoint) by LOCF. It is also correctly assigned to the “gfr\_m1” variable.

Obs GFR_M1	SUBJ ID GFR_M2	TRT GFR_M3	REVISIT GFR_M4	GFRM_OV GFR_M5	GFR_M
94	0100_00008	1	1	3.7	3.70
63.1	39.2	.	.	63.1	
95	0100_00008	1	2	12.7	12.70
63.1	39.2	.	.	63.1	
96	0100_00008	1	3	36.6	36.60
63.1	39.2	.	.	63.1	
97	0100_00008	1	4	46.3	48.60
63.1	39.2	.	.	63.1	
98	0100_00008	1	4	50.9	48.60
63.1	39.2	.	.	63.1	
99	0100_00008	1	5	56.4	56.40
63.1	39.2	.	.	63.1	
100	0100_00008	1	6	70.4	70.40
63.1	39.2	.	.	63.1	
101	0100_00008	1	7	63.1	63.10
63.1	39.2	.	.	63.1	
102	0100_00008	1	8	39.2	39.20
63.1	39.2	.	.	63.1	
103	0100_00008	1	32	63.1	63.10
63.1	39.2	.	.	63.1	
104	0100_00008	1	42	39.2	39.20
63.1	39.2	.	.	63.1	

However, for the following patient, revisit=32 is correctly imputed from revisit=9 (the last assessment) for the variable “gfr\_ov” but is not assigned to the variable “gfr\_m1”. Instead the value of revisit=42 (12.7) is assigned to “grf\_m1”.

Obs GFR_M1	SUBJ ID GFR_M2	TRT GFR_M3	REVISIT GFR_M4	GFRM_OV GFR_M5	GFR_M
46	0100_00004	3	1	10.1	10.10
12.7	12.7	12.7	12.7	12.7	
47	0100_00004	3	2	8.3	8.30
12.7	12.7	12.7	12.7	12.7	
48	0100_00004	3	3	4.1	4.10
12.7	12.7	12.7	12.7	12.7	
49	0100_00004	3	4	4.9	4.80
12.7	12.7	12.7	12.7	12.7	
50	0100_00004	3	4	4.7	4.80
12.7	12.7	12.7	12.7	12.7	

51	0100_00004	3	5	6.5	6.50
12.7	12.7	12.7	12.7	12.7	
52	0100_00004	3	6	5.1	5.10
12.7	12.7	12.7	12.7	12.7	
53	0100_00004	3	7	7.2	7.20
12.7	12.7	12.7	12.7	12.7	
54	0100_00004	3	8	13.9	13.90
12.7	12.7	12.7	12.7	12.7	
55	0100_00004	3	9	13.6	18.05
12.7	12.7	12.7	12.7	12.7	
56	0100_00004	3	9	22.5	18.05
12.7	12.7	12.7	12.7	12.7	
57	0100_00004	3	12	25.7	25.70
12.7	12.7	12.7	12.7	12.7	
58	0100_00004	3	13	12.7	12.70
12.7	12.7	12.7	12.7	12.7	
59	0100_00004	3	32	22.5	22.50
12.7	12.7	12.7	12.7	12.7	
60	0100_00004	3	42	12.7	12.70
12.7	12.7	12.7	12.7	12.7	

There appears to be about 184 similar cases (62 in everolimus 1.5 mg, 78 in everolimus 3.0mg and 44 in Myfortic 1.44 g) as the latter. Can you please explain why the variable “gfr\_m1” is assigned values from “gfr\_ov” using revisit=32 and sometimes using revisit=42? Furthermore, when using revisit=42, the values for gfr\_m1 up to gfr\_m5 are all identical. Why is this so?

- The following patient had correctly imputed revisit=32 for the variable “gfr\_ov”. However, the value for revisit=42 is 19.9 instead of 16.8 (revisit=13) which is supposedly the last observation. Moreover, the value at revisit=13 is assigned to the variable “gfr\_m1” instead of revisit=32. Can you please explain this?

Obs	SUBJ ID	TRT	REVISIT	GFRM_OV	GFR_M
GFR_M1	GFR_M2	GFR_M3	GFR_M4	GFR_M5	
203	0101_00004	1	1	5.9	5.90
16.8	16.8	16.8	16.8	16.8	
204	0101_00004	1	3	6.7	6.70
16.8	16.8	16.8	16.8	16.8	
205	0101_00004	1	4	8.9	6.65
16.8	16.8	16.8	16.8	16.8	
206	0101_00004	1	4	4.4	6.65
16.8	16.8	16.8	16.8	16.8	
207	0101_00004	1	5	8.1	8.10
16.8	16.8	16.8	16.8	16.8	
208	0101_00004	1	6	14.2	14.20
16.8	16.8	16.8	16.8	16.8	

209	0101_00004	1	7	26.1	23.00
16.8	16.8	16.8	16.8	16.8	
210	0101_00004	1	7	19.9	23.00
16.8	16.8	16.8	16.8	16.8	
211	0101_00004	1	12	20.5	20.50
16.8	16.8	16.8	16.8	16.8	
212	0101_00004	1	13	16.8	16.80
16.8	16.8	16.8	16.8	16.8	
213	0101_00004	1	32	19.9	19.90
16.8	16.8	16.8	16.8	16.8	
214	0101_00004	1	42	19.9	19.90
16.8	16.8	16.8	16.8	16.8	

The following patients also have similar issues:

Obs GFR_M1	SUBJ ID GFR_M2	TRT GFR_M3	REVISIT GFR_M4	GFRM_OV GFR_M5	GFR_M
458	0111_00008	1	1	12.4	12.4
31.8	31.8	31.8	31.8	31.8	
459	0111_00008	1	3	12.4	12.4
31.8	31.8	31.8	31.8	31.8	
460	0111_00008	1	4	20.3	20.3
31.8	31.8	31.8	31.8	31.8	
461	0111_00008	1	5	30.1	30.1
31.8	31.8	31.8	31.8	31.8	
462	0111_00008	1	6	35.7	35.7
31.8	31.8	31.8	31.8	31.8	
463	0111_00008	1	7	29.9	29.9
31.8	31.8	31.8	31.8	31.8	
464	0111_00008	1	8	31.2	31.2
31.8	31.8	31.8	31.8	31.8	
465	0111_00008	1	9	29.5	29.5
31.8	31.8	31.8	31.8	31.8	
466	0111_00008	1	11	44.3	44.3
31.8	31.8	31.8	31.8	31.8	
467	0111_00008	1	12	30.9	30.9
31.8	31.8	31.8	31.8	31.8	
468	0111_00008	1	13	31.8	31.8
31.8	31.8	31.8	31.8	31.8	
469	0111_00008	1	32	30.9	30.9
31.8	31.8	31.8	31.8	31.8	
470	0111_00008	1	42	30.9	30.9
31.8	31.8	31.8	31.8	31.8	

Obs GFR_M1	SUBJ ID GFR_M2	TRT GFR_M3	REVISIT GFR_M4	GFRM_OV GFR_M5	GFR_M
1042	0115_00022	1	1	7.5	7.5
32.6	32.6	32.6	32.6	32.6	

1043	0115_00022	1	2	8.4	8.4
32.6	32.6	32.6	32.6	32.6	
1044	0115_00022	1	3	12.5	12.5
32.6	32.6	32.6	32.6	32.6	
1045	0115_00022	1	4	20.5	21.9
32.6	32.6	32.6	32.6	32.6	
1046	0115_00022	1	4	23.3	21.9
32.6	32.6	32.6	32.6	32.6	
1047	0115_00022	1	5	30.1	30.1
32.6	32.6	32.6	32.6	32.6	
1048	0115_00022	1	6	27.3	27.3
32.6	32.6	32.6	32.6	32.6	
1049	0115_00022	1	7	27.8	27.8
32.6	32.6	32.6	32.6	32.6	
1050	0115_00022	1	8	27.9	27.9
32.6	32.6	32.6	32.6	32.6	
1051	0115_00022	1	10	27.0	27.0
32.6	32.6	32.6	32.6	32.6	
1052	0115_00022	1	12	32.1	32.1
32.6	32.6	32.6	32.6	32.6	
1053	0115_00022	1	13	32.6	32.6
32.6	32.6	32.6	32.6	32.6	
1054	0115_00022	1	32	27.9	27.9
32.6	32.6	32.6	32.6	32.6	
1055	0115_00022	1	42	32.1	32.1
32.6	32.6	32.6	32.6	32.6	

4. The values in Table 6-1 (Renal Function (MDRD Calculated GFR)), page 25 of the Novartis Briefing Book, appears to be derived by using the variable “gfr\_m” (the mean MDRD GFR). Is this correct?

Page 8 of the SAP states that for multiple measurements post-baseline, the average value (as given by the variable “gfr\_m”) will be presented. However, the following patients do not seem to follow this rule. The blue text shows that “gfr\_m” is the average of values in “gfr\_ov” whereas the red text uses only one of the multiple values. Can you please explain why this is so?

Obs	SUBJ ID	TRT	REVISIT	GFRM_OV	GFR_M
GFR_M1	GFR_M2	GFR_M3	GFR_M4	GFR_M5	
5035	0168_00008	1	1	5.2	5.20
65.0	65.0	65.0	65.0	65.0	
5036	0168_00008	1	2	6.4	6.40
65.0	65.0	65.0	65.0	65.0	
5037	0168_00008	1	3	23.1	23.10
65.0	65.0	65.0	65.0	65.0	

5038	0168_00008	1	4	37.8	39.35
65.0	65.0	65.0	65.0	65.0	
5039	0168_00008	1	4	40.9	39.35
65.0	65.0	65.0	65.0	65.0	
5040	0168_00008	1	5	33.6	33.60
65.0	65.0	65.0	65.0	65.0	
5041	0168_00008	1	5	41.3	33.60
65.0	65.0	65.0	65.0	65.0	
5042	0168_00008	1	6	52.4	52.40
65.0	65.0	65.0	65.0	65.0	
5043	0168_00008	1	6	42.8	52.40
65.0	65.0	65.0	65.0	65.0	
5044	0168_00008	1	6	58.2	52.40
65.0	65.0	65.0	65.0	65.0	
5045	0168_00008	1	6	43.2	52.40
65.0	65.0	65.0	65.0	65.0	
5046	0168_00008	1	7	48.1	48.10
65.0	65.0	65.0	65.0	65.0	
5047	0168_00008	1	7	41.3	48.10
65.0	65.0	65.0	65.0	65.0	
5048	0168_00008	1	8	24.7	24.70
65.0	65.0	65.0	65.0	65.0	
5049	0168_00008	1	8	28.0	24.70
65.0	65.0	65.0	65.0	65.0	
5050	0168_00008	1	9	33.3	49.00
65.0	65.0	65.0	65.0	65.0	
5051	0168_00008	1	9	49.0	49.00
65.0	65.0	65.0	65.0	65.0	
5052	0168_00008	1	9	43.4	49.00
65.0	65.0	65.0	65.0	65.0	
5053	0168_00008	1	9	55.3	49.00
65.0	65.0	65.0	65.0	65.0	
5054	0168_00008	1	9	47.0	49.00
65.0	65.0	65.0	65.0	65.0	
5055	0168_00008	1	10	44.7	33.20
65.0	65.0	65.0	65.0	65.0	
5056	0168_00008	1	10	33.2	33.20
65.0	65.0	65.0	65.0	65.0	
5057	0168_00008	1	11	39.7	39.70
65.0	65.0	65.0	65.0	65.0	
5058	0168_00008	1	12	54.0	54.00
65.0	65.0	65.0	65.0	65.0	
5059	0168_00008	1	12	51.1	54.00
65.0	65.0	65.0	65.0	65.0	
5060	0168_00008	1	13	43.0	65.00
65.0	65.0	65.0	65.0	65.0	
5061	0168_00008	1	13	43.9	65.00
65.0	65.0	65.0	65.0	65.0	
5062	0168_00008	1	13	65.0	65.00
65.0	65.0	65.0	65.0	65.0	
5063	0168_00008	1	32	65.0	65.00
65.0	65.0	65.0	65.0	65.0	
5064	0168_00008	1	42	65.0	65.00
65.0	65.0	65.0	65.0	65.0	

Obs GFR_M1	SUBJ ID GFR_M2	TRT GFR_M3	REVI SIT GFR_M4	GFRM_OV GFR_M5	GFR_M
5790	0187_00014	2	1	6.5	6.50
85.4	85.4	85.4	85.4	85.4	
5791	0187_00014	2	2	11.1	11.10
85.4	85.4	85.4	85.4	85.4	
5792	0187_00014	2	3	28.5	28.50
85.4	85.4	85.4	85.4	85.4	
5793	0187_00014	2	3	41.8	28.50
85.4	85.4	85.4	85.4	85.4	
5794	0187_00014	2	4	56.2	64.45
85.4	85.4	85.4	85.4	85.4	
5795	0187_00014	2	4	72.7	64.45
85.4	85.4	85.4	85.4	85.4	
5796	0187_00014	2	5	74.3	74.30
85.4	85.4	85.4	85.4	85.4	
5797	0187_00014	2	6	71.1	71.10
85.4	85.4	85.4	85.4	85.4	
5798	0187_00014	2	7	63.4	63.40
85.4	85.4	85.4	85.4	85.4	
5799	0187_00014	2	8	56.7	56.70
85.4	85.4	85.4	85.4	85.4	
5800	0187_00014	2	9	68.8	68.80
85.4	85.4	85.4	85.4	85.4	
5801	0187_00014	2	10	67.4	67.40
85.4	85.4	85.4	85.4	85.4	
5802	0187_00014	2	11	78.8	78.80
85.4	85.4	85.4	85.4	85.4	
5803	0187_00014	2	12	75.2	75.20
85.4	85.4	85.4	85.4	85.4	
5804	0187_00014	2	13	85.4	85.40
85.4	85.4	85.4	85.4	85.4	
5805	0187_00014	2	13	28.9	85.40
85.4	85.4	85.4	85.4	85.4	
5806	0187_00014	2	32	85.4	85.40
85.4	85.4	85.4	85.4	85.4	
5807	0187_00014	2	42	85.4	85.40
85.4	85.4	85.4	85.4	85.4	

Obs GFR_M1	SUBJ ID GFR_M2	TRT GFR_M3	REVI SIT GFR_M4	GFRM_OV GFR_M5	GFR_M
---------------	-------------------	---------------	--------------------	-------------------	-------

4515	0166_00002	3	1	8.4	8.40
43.1	43.1	43.1	43.1	43.1	
4516	0166_00002	3	2	14.6	14.60
43.1	43.1	43.1	43.1	43.1	
4517	0166_00002	3	3	31.1	31.10
43.1	43.1	43.1	43.1	43.1	
4518	0166_00002	3	4	45.3	43.40
43.1	43.1	43.1	43.1	43.1	
4519	0166_00002	3	4	41.5	43.40
43.1	43.1	43.1	43.1	43.1	
4520	0166_00002	3	5	52.9	52.90
43.1	43.1	43.1	43.1	43.1	
4521	0166_00002	3	6	48.4	48.40
43.1	43.1	43.1	43.1	43.1	
4522	0166_00002	3	7	50.8	50.80
43.1	43.1	43.1	43.1	43.1	
4523	0166_00002	3	8	43.3	43.30
43.1	43.1	43.1	43.1	43.1	
4524	0166_00002	3	9	45.3	45.30
43.1	43.1	43.1	43.1	43.1	
4525	0166_00002	3	10	51.9	51.90
43.1	43.1	43.1	43.1	43.1	
4526	0166_00002	3	11	47.2	47.20
43.1	43.1	43.1	43.1	43.1	
4527	0166_00002	3	12	45.0	45.00
43.1	43.1	43.1	43.1	43.1	
4528	0166_00002	3	13	45.4	43.10
43.1	43.1	43.1	43.1	43.1	
4529	0166_00002	3	13	43.1	43.10
43.1	43.1	43.1	43.1	43.1	
4530	0166_00002	3	32	43.1	43.10
43.1	43.1	43.1	43.1	43.1	
4531	0166_00002	3	42	43.1	43.10
43.1	43.1	43.1	43.1	43.1	
6306	0200_00009	3	1	5.6	5.60
72.8	72.8	72.8	72.8	72.8	
6307	0200_00009	3	2	5.0	5.00
72.8	72.8	72.8	72.8	72.8	
6308	0200_00009	3	3	27.3	27.30
72.8	72.8	72.8	72.8	72.8	
6309	0200_00009	3	4	17.6	17.60
72.8	72.8	72.8	72.8	72.8	
6310	0200_00009	3	5	46.9	46.90
72.8	72.8	72.8	72.8	72.8	
6311	0200_00009	3	6	68.1	68.10
72.8	72.8	72.8	72.8	72.8	
6312	0200_00009	3	7	73.9	73.90
72.8	72.8	72.8	72.8	72.8	
6313	0200_00009	3	8	71.3	71.30
72.80	72.80	72.80	72.80	72.80	
6314	0200_00009	3	10	67.1	67.10
72.80	72.80	72.80	72.80	72.80	

6315	0200_00009	3	11	66.4	66.40
72.80	72.80	72.80	72.80	72.80	
6316	0200_00009	3	13	71.9	72.80
72.80	72.80	72.80	72.80	72.80	
6317	0200_00009	3	13	73.7	72.80
72.80	72.80	72.80	72.80	72.80	
6318	0200_00009	3	32	73.7	73.70
72.80	72.80	72.80	72.80	72.80	
6319	0200_00009	3	42	73.7	73.70
72.80	72.80	72.80	72.80	72.80	

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission or if you would like to request a teleconference to discuss. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
11/13/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 5, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560 Requests

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Dear Mr. Van Valen:

Please refer to your Everolimus NDA, 21-560.

We have the following requests for clarification pertaining to your 12-month safety analysis of Study A2309 of New Onset Diabetes (NODM). Please provide a response to items 1 and 2 by COB 11/5/09. Please respond to items 3 and 4 at your earliest convenience.

1. In section 12.6.10 *New onset diabetes after transplantation* of the A2309 clinical study report-12 month (page 219), the percentage of NODM was reported as 5.1%, 7.9%, and 7.0% in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm groups respectively. While in Table 14.3.1-1.11a on page 1692, the total number of NODM was shown as: 25/274 (9.1%), 34/278 (12.2%) and 18/273 (6.6%) in the three treatment groups, respectively. Please clarify the discrepancy between these rates, and clarify the reason why the first set of percentages was reported in section 12.6.10.

2. According to page 132 in the clinical study report-12 month,

*“New onset diabetes, defined as diabetes post-transplantation which is identified by one of the following:*

*Diabetes was reported as an adverse event;*

*Glucose (random)  $\geq$  11 mmol/L post-transplantation;*

*Diabetes was recorded as reason for a medication given post-transplantation, in patients who were not diabetic at the time of transplantation, identified by all of the following:*

*Reason for transplantation was not diabetes;*

*Diabetes was not included in medical history;*

*Glucose (random)  $<$  11 mmol/L at the time of transplantation;”*

Please indicate if the results reported in section 12.6.10 are based on this definition. If not, please provide the criteria used to identify patients with NODM after transplantation as reported in section 12.6.10.

3. Please provide a new dataset and updated the analysis for NODM. The new dataset should include every patient in the safety population with at least five different indication variables:

- a. one variable indicating whether diabetes was reported as an adverse event for a patient;

- b. one variable indicating whether a patient ever had post-transplantation glucose (random) measurement  $\geq 11$  mmol/L;
  - c. one variable indicating whether diabetes was recorded as reason for a medication given post-transplantation to a patient;
  - d. one variable indication whether a patient had diabetes at baseline.
4. Please provide a new dataset and updated the analysis for NODM with an additional criterion of fasting plasma glucose, if this information is available. This new dataset should be similar to the dataset in item 3 with the following additional indication variable:
- a. one variable indicating whether a patient ever had fasting plasma glucose  $\geq 126$  mg/dL (7.0 mmol/L), provided that the baseline fasting plasma glucose was lower than 126 mg/dL.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
11/05/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** October 30, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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NDA 21-560

Dear Mr. Van Valen:

Please refer to your June 30, 2009 resubmission for NDA 21-560.

We have the following requests for clarification.

1. *On page 197 of the CSR in Table 12-8 patient 0543-00007 is listed as a graft loss but this patient is also included in the screening failures section of the CSR and never received the study drug. Also patient 0543-00016 is not included in table 12-18 although she lost her graft on Day 4 (Myfortic arm) according to the graft loss narratives. We plan on including patient 0543-00016 in the safety discussion of graft losses instead of patient 0543-00007 who is in the ITT population but not in the safety population.*
2. *Please confirm that all patients with graft loss were counted as SAEs, as per the protocol.*

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission.  
Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
10/30/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** October 29, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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Dear Mr. Van Valen:

Please refer to your June 30, 2009 resubmission for NDA 21-560.

We have the following requests for clarification pertaining to 12-month efficacy analysis of study A2309.

1. In Novartis' response on August 20, 2009 to Question 3 of the FDA Request for information on August 5, 2009, it is stated that patient '**0511\_00017 (Everolimus 3.0mg)** had graft loss on (b) (6) which was before the date of randomization and study drug initiation, 05MAY2007. Therefore, this patient was not considered as an efficacy failure'. In the efficacy dataset 'eff\_fda.xpt', we find that values for both **EVENT** and **DAY\_EVT** are missing for patient **0511\_00017**, suggesting that this patient was considered as an efficacy success in the analysis of primary efficacy endpoint. In fact, the last contact for this patient was on day 157 (**LASTDATE='09OCT2007'**). Based on the definition of loss to follow-up in the SAP for primary efficacy endpoint (i.e. any patient who did not experience treated BPAR, graft loss or death and whose last day of contact is prior to study Day 316), this patient should be counted as a loss to follow up and therefore meeting the primary efficacy endpoint. Please clarify this discrepancy. Please provide an updated table for analysis on primary efficacy endpoint if this patient will be counted as a loss to follow-up.
2. For the primary efficacy endpoint, **loss to follow-up** was defined in SAP as '*A loss to follow-up patient is a patient who did not experience treated BPAR, graft loss or death and whose last day of contact is prior to study Day 316, which is the protocol defined lower limit of Month 12 visit window*'. When considered as a component of the main secondary efficacy endpoint (i.e. graft loss, death or loss to follow-up), **loss to follow-up** should include all patients whose last day of contact was prior to Day 316 and who did not experience a graft loss or death. Please update the corresponding tables for analysis on composite endpoint of graft loss, death or loss to follow-up.

NDA 21-560

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission.  
Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
10/29/2009



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** October 28, 2009

<b>To:</b> Ron Van Valen	<b>From:</b> Hyun Son
<b>Company:</b> Novartis	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> (862) 778-7646	<b>Phone number:</b> 301-796-1939
<b>Subject:</b> NDA 21-560 Everolimus: REMS comments	

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**Total no. of pages including cover:** 4

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NDA 21-560

Please refer to your June 30, 2009 submission which contains your voluntarily submitted proposed Risk Evaluation and Management Strategy (REMS) for everolimus (NDA 21-560). We are in the midst of reviewing the submission and have the following preliminary comments. Please be aware that we anticipate additional comments as your submission undergoes further review, and should we determine that a REMS is necessary, we will notify you in a letter of that determination and the required elements of the REMS.

**REMS Goals**

Thus far in our review of your submission, we identified three adverse events that your REMS for everolimus should address if we determine that your application can be approved and that a REMS is necessary. These three adverse events are: proteinuria, hyperlipidemia, and wound healing complications.

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

(b) (4)

Please submit the requested information by November 9, 2009.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission.

Thank you.

Regards,

Hyun Son, Pharm.D.  
Safety Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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HYUN J SON  
10/28/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** October 16, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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authorized. If you have received this document in error, please notify us  
immediately by telephone at 301-796-1600 Thank you.**

NDA 21-560

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Everolimus Tablets, specifically the “Guidance for Industry, How to Comply with the Pediatric Research Equity Act” (attached). This document is meant to be a guide in preparation of your pediatric plan for which you have expressed your interest to submit a deferral request during our tcon on October 16, 2009.

A Pediatric Plan must be submitted to your NDA. A Pediatric Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics and/or pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation. The plan should be used as a basis for the PREA requirements. You will need to address all ages inclusive of 0 to 16 years. If you do not plan to conduct studies in a particular age subgroup (e.g., 0- to 2 years), you should state why and request a partial waiver.

In your pediatric plan please address the following:

1. Age group(s) included in deferral request.
2. When deferral is only requested for certain age groups, provide reason(s) for not including entire pediatric population in deferral request (e.g., studies have already been completed in other age groups and need not be deferred, partial waiver is being requested)
3. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):
  - i. Adult studies completed and ready for approval
  - ii. Additional safety or effectiveness data needed (describe)
  - iii. Other (specify)
4. Evidence that planned or ongoing pediatric studies are proceeding
5. Projected date for the submission of the pediatric assessment (deferral date)

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission.

Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

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# Guidance for Industry

## How to Comply with the Pediatric Research Equity Act

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Grace Carmouze, 301-594-7337 or Leonard Wilson, 301-827-0373.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
September 2005  
Procedural**

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# Guidance for Industry

## How to Comply with the Pediatric Research Equity Act

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
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## **GUIDANCE FOR INDUSTRY<sup>1</sup>**

### **How to Comply with the Pediatric Research Equity Act**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

#### **I. INTRODUCTION**

This draft guidance provides recommendations on how to interpret the pediatric study requirements of the Pediatric Research Equity Act (Public Law 108-155) (PREA). PREA amends the Federal Food, Drug, and Cosmetic Act (the Act) by adding section 505B (21 U.S.C. 355B). PREA requires the conduct of pediatric studies for certain drug and biological products.<sup>2</sup> Specifically, PREA requires new drug applications (NDAs) and biologics licensing applications (BLAs) (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (see section 505B(a) of the Act). It also authorizes FDA to require holders of applications for previously approved marketed drugs and biological products who are not seeking approval for one of the changes enumerated above (hereinafter "marketed drugs and biological products") to submit a pediatric assessment under certain circumstances (see section 505B(b) of the Act).

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<sup>1</sup> This guidance has been prepared by the PREA Working Group at the Food and Drug Administration (FDA).

<sup>2</sup> For purposes of this guidance, references to "drugs" and "drug and biological products" includes drugs approved under section 505 of the Act (21 U.S.C. 355) and biological products licensed under 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) that are drugs.

**Paperwork Reduction Act Public Burden Statement:** According to the Paperwork Reduction Act of 1995, a collection of information should display a valid OMB control number. The draft guidance contains information collections approved in OMB Nos. 0910-0001 (expires May 31, 2008) and 1910-0433 (expires March 31, 2007). In addition, the time required to complete this information collection is estimated to average from 8 to 50 hours per response, including the time to prepare and submit an application containing required studies or request a waiver from such studies.

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Although PREA applies to both new applications (or supplements to applications) and already marketed drugs and biological products, this guidance will only provide recommendations on NDAs and BLAs (or supplements to an already approved application) for drugs and biological products under section 505B(a) of the Act. Issues under section 505B(b) of the Act related to already marketed drug and biological products for which the sponsor is not seeking one of the enumerated changes may be addressed in future guidance.

This guidance addresses the pediatric assessment,<sup>3</sup> the pediatric plan (see section V.A), waivers and deferrals, compliance issues, and pediatric exclusivity provisions.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## **II. BACKGROUND**

On December 3, 2003, the Pediatric Research Equity Act (PREA) was signed into law. PREA is the most recent of more than a decade of legislative and regulatory attempts to address the lack of pediatric use information in drug product labeling. In PREA, Congress codified many of the elements of the Pediatric Rule, a final rule issued by FDA on December 2, 1998 (63 FR 66632), and suspended by court order on October 17, 2002.<sup>4</sup>

Under the Pediatric Rule, approval actions taken or applications submitted on or after April 1, 1999, for changes in active ingredient, indication, dosage form, dosing regimen, or route of administration were required to include pediatric assessments for indications for which sponsors were receiving or seeking approval in adults, unless the requirement was waived or deferred. The Pediatric Rule was designed to work in conjunction with the *pediatric exclusivity* provisions of section 505A of the Act (21 U.S.C. 355a), an incentive signed into law to encourage sponsors or holders of approved applications to voluntarily perform the pediatric studies described in a Written Request<sup>5</sup> issued by FDA, in order to qualify for an additional 6 months of marketing exclusivity.

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<sup>3</sup> For purposes of this guidance, the term "pediatric assessment" describes the required submissions under PREA that contain data, primarily from required pediatric clinical studies, that are adequate to assess safety and effectiveness and support dosing and administration for claimed indications in all relevant pediatric populations (section 505B(a)(1) and (2) of the Act). Generally, the terms "pediatric assessment" and "pediatric studies" are used interchangeably.

<sup>4</sup> The Pediatric Rule was codified at 21 CFR 314.55 and 601.27, with additional amendments to 21 CFR 201, 312, 314, and 601.

<sup>5</sup> FDA issues Written Requests for pediatric studies under 21 U.S.C. 355a.

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On January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109) was enacted. The BPCA reauthorized and amended the pediatric exclusivity incentive program of section 505A and created new mechanisms for funding pediatric studies that sponsors or holders of approved applications declined to conduct voluntarily. On April 24, 2002, FDA issued an advance notice of proposed rulemaking (ANPRM) soliciting comments on the most appropriate ways to update the Pediatric Rule in a manner consistent with other mechanisms for obtaining studies created by the BPCA.

On October 17, 2002, the U.S. District Court for the District of Columbia held that FDA had exceeded its statutory authority when issuing the Pediatric Rule and the court suspended its implementation and enjoined its enforcement (Association of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D. D.C. 2002)). When the Court enjoined FDA from enforcing the Pediatric Rule in October 2002, the ANPRM was also rendered obsolete.

As noted above, PREA codified elements of the suspended Pediatric Rule and attempted to fill gaps left by the Pediatric Rule's suspension.

**III. OVERVIEW — REQUIREMENTS OF PREA**

**A. PREA Statutory Requirements**

PREA requires all applications (or supplements to an application) submitted under section 505 of the Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505B(a) of the Act). It also authorizes FDA to require holders of approved NDAs and BLAs for marketed drugs and biological products to conduct pediatric studies under certain circumstances (section 505B(b) of the Act).

In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and pediatric populations. Products intended for pediatric-specific indications will be subject to the requirements of PREA only if they are initially developed for a subset of the relevant pediatric population.

**B. Scope of Requirements**

**1. Applications Affected by PREA**

Because section 4(b) of PREA makes the legislation retroactive, all approved applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration submitted on or after April 1, 1999 (including those approved when the Pediatric Rule was suspended), are subject to PREA. Under PREA, holders of such approved applications that did not previously include pediatric assessments, waivers, or deferrals must submit their pediatric assessments or requests for waiver or deferral (section 4(b)(2)(B) of

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PREA). If a waiver request is denied and/or studies are deferred, FDA will require the applicable studies as postmarketing studies. (For additional information on applicable deferral dates, see section IV.B and Attachment C.)

2. Orphan Drugs

PREA states, "Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526."<sup>6</sup> FDA has not issued regulations applying PREA to orphan-designated indications. Thus, submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time. However, if only one indication for a product has orphan designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s).

3. Generic Drugs Under 505(j) of the Act (21 U.S.C. 355(j))

Because PREA applies only to applications (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and because an abbreviated new drug application (ANDA) submitted under section 505(j) of the Act for a duplicate version of a previously approved drug product does not involve such changes, PREA does not impose pediatric assessment requirements on ANDAs for generic drugs. However, ANDAs submitted under an approved suitability petition under section 505(j)(2)(C) of the Act for changes in dosage form, route of administration, or new active ingredient in combination products are subject to the pediatric assessment requirements that PREA imposes. If clinical studies are required under PREA for a product submitted under an approved suitability petition and a waiver is not granted, that application is no longer eligible for approval under an ANDA.

Because PREA is retroactive, all approved and pending ANDAs submitted on or after April 1, 1999 (when the Pediatric Rule became effective) and prior to December 3, 2003 (when PREA was enacted) under suitability petitions for changes in dosage form, route of administration, or active ingredient in combination products are subject to PREA. Although some ANDAs submitted under suitability petitions after April 1, 1999, and prior to December 3, 2003, would not have been approved as ANDAs had PREA been in effect at the time of approval, PREA's retroactivity does not require FDA to revoke those previous approvals. Instead, as with NDAs and BLAs, holders of approved and pending ANDAs submitted under suitability petitions between April 1, 1999 and December 3, 2003, who have not already obtained waivers, must submit postapproval pediatric studies or a request for a waiver or deferral of the pediatric assessment requirement (section 505B(a)(2) of the Act). If a waiver request is denied for a product already submitted or approved in an ANDA based upon a suitability petition during this time frame, FDA will require the applicable studies as postmarketing studies.

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<sup>6</sup> Section 526 is codified at 21 U.S.C. 360bb.

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**IV. THE PEDIATRIC ASSESSMENT**

**A. What Is the Pediatric Assessment? (Section 505B(a)(2) of the Act)**

Under PREA, the pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to:

- Assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations
- Support dosing and administration for each pediatric subpopulation for which the drug or the biological product has been assessed to be safe and effective

**B. When to Submit the Pediatric Assessment in Compliance with PREA**

Under PREA, a pediatric assessment must be submitted at the time an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is submitted to the Agency, unless the requirement for the assessment has been deferred or waived. If a deferral has been granted, the pediatric assessment will be due on or before the date specified by the Agency (section 505B(a)(3) of the Act).

As noted above, PREA is retroactive and requires pediatric assessments for all applications submitted between April 1, 1999, and the present. To address potential gaps in pediatric information for applications approved between April 1, 1999, and the present resulting from, among other things, the suspension of the Pediatric Rule in October 2002, PREA provides for waivers or deferrals in cases where pediatric study requirements were never addressed and for extensions of certain deferrals issued previously under the Pediatric Rule (see Attachment C for a chart of deferral dates under PREA).

If an application previously was granted a waiver of pediatric studies under the Pediatric Rule, the waiver will continue to apply under PREA (section 4(b)(2)(A) of PREA).

**C. What Types of Data Are Submitted as Part of the Pediatric Assessment?**

The data submitted under PREA will depend on the nature of the application, what is known about the product in pediatric populations, and the underlying disease or condition being treated. PREA does not require applicants to conduct separate safety and effectiveness studies in pediatric patients in every case. PREA states:

If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in

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adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.

(Section 505B(a)(2)(B)(i) of the Act.)

If extrapolation from adult effectiveness data is inappropriate, adequate and well-controlled efficacy studies in the pediatric population may nevertheless be required. Additional information, such as dosing and safety data, could also be important to support pediatric labeling decisions.

PREA further provides, "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group" (section 505B(a)(2)(B)(ii) of the Act). Whether or not pediatric studies in more than one age group are necessary depends on expected therapeutic benefit and use in each age group, and on whether safety and effectiveness data from one age group can be extrapolated to other age groups. As with the use of adult data, the extrapolation may be supplemented with data to define dosing and safety for the relevant age groups.

Applicants should contact the appropriate review division to discuss the types of pediatric studies needed to complete their pediatric assessments.

**V. THE PEDIATRIC PLAN AND SUBMISSIONS**

**A. When to Develop a Pediatric Plan**

A Pediatric Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation. Furthermore, it should address whether and, if so, under what grounds, the applicant plans to request a waiver or deferral under PREA. Applicants are encouraged to submit their pediatric plans to the Agency as early as possible in the drug development process and to discuss these plans with the Agency at critical points in the development process for a particular drug or biologic.

Early consultation and discussions are particularly important for products intended for life-threatening or severely debilitating illnesses. For these products, FDA encourages applicants to discuss the pediatric plan at pre-investigational new drug (pre-IND) meetings and end-of-phase 1 meetings. For products for life-threatening diseases, the review division will provide its best judgment at the end-of-phase 1 meetings on whether pediatric studies will be required under PREA and, if so, whether the submission will be deferred until after approval. In general, studies of drugs or biological products for diseases that are life-threatening or severely debilitating in pediatric patients and that lack adequate therapy could begin earlier than studies of other products because the urgency of the need for the products may justify early trials despite the relative lack of safety and effectiveness information.

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For products that are not intended for treatment of life-threatening or severely debilitating illnesses, applicants are encouraged to submit and discuss the pediatric plan no later than the end-of-phase 2 meeting. Information to support any planned request for a waiver or deferral of pediatric studies also should be submitted as part of the background package for this meeting. The review division will provide its best judgment about (1) the pediatric assessment that will be required for the product, (2) whether its submission can be deferred, and (3) if deferred, the date studies will be due. In addition, if relevant, FDA encourages applicants to include a discussion of their intent to qualify for and the studies needed to earn pediatric exclusivity (see section VIII for a discussion of PREA and pediatric exclusivity).

When a decision to waive or defer pediatric studies is made at key meetings, the minutes from those meetings reflecting the decision generally will be provided to applicants for their records. Alternatively, a separate letter may be sent to the applicant conveying FDA's decision to either waive or defer the pediatric assessment. If a deferral of studies is granted at the time of the meeting, a due date for submission generally will also be included in the meeting minutes or separate letter.

**B. What Ages to Cover in a Pediatric Plan**

PREA requires, unless waived or deferred, the submission of a pediatric assessment for certain applications for the claimed indications in all relevant pediatric populations. As discussed in section VI, PREA authorized FDA to waive assessments when: 1) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and 2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act). Thus, PREA requires the pediatric assessment to evaluate safety and effectiveness for the claimed indication(s) for each age group in which the drug or biological product is expected to provide a meaningful therapeutic benefit over existing therapies for pediatric patients or is likely to be used in a substantial number<sup>7</sup> of pediatric patients.

Under PREA, a drug or biological product is considered to represent a *meaningful therapeutic benefit* over existing therapies if FDA estimates that (1) "if approved, the drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population," or (2) "the drug or biological product is in a class of products or for an indication for which there is a need for additional options" (section 505B(c) of the Act). Improvement over marketed products might be demonstrated by showing (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) enhancement of compliance; or

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<sup>7</sup> PREA does not define a "substantial number." In the past, FDA generally has considered 50,000 patients to be a substantial number of patients (see, for example, October 27, 1997, DHHS Public Meeting on FDA's Proposed Regulations to Increase Pediatric Use Information for Drugs and Biologics). The Agency, however, will take into consideration the nature and severity of the condition in determining whether a drug or biological product will be used in a substantial number of pediatric patients.

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(4) safety and effectiveness in a new subpopulation for which marketed products are not currently labeled.

The BPCA defines "pediatric studies" or "studies" to include studies in all "pediatric age groups (including neonates in appropriate cases)" in which a drug is anticipated to be used (section 505A(a) of the Act. For purposes of satisfying the requirements of PREA, the appropriate age ranges to be studied may vary, depending on the pharmacology of the drug or biological product, the manifestations of the disease in various age groups, and the ability to measure the response to therapy. In general, however, the pediatric population includes patients age "birth to 16 years, including age groups often called neonates, infants, children, and adolescents" (21 CFR 201.57(f)(9)).

The complex medical state of neonates and infants makes it critical to evaluate drugs specifically for their use. The Agency is also aware that trials in neonates and infants pose special ethical issues. FDA generally will require studies in neonates and infants under PREA if the drug represents an important advancement and use in these age groups for the approved indication is anticipated. However, it is possible that partial waivers for these specific age groups might be appropriate under certain circumstances when "necessary studies are impossible or highly impracticable," or when "there is evidence strongly suggesting that the drug or biologic product would be ineffective or unsafe in that age group" (section 505B(a)(4)(B)(i) and (ii) of the Act).

**C. Must the Sponsor Develop a Pediatric Formulation?**

PREA requires pediatric assessments to be gathered "using appropriate formulations for each age group for which the assessment is required" (section 505B(a)(2)(A) of the Act). Under PREA, applicants must submit requests for approval of the pediatric formulation used in their pediatric studies, and failure to submit such a request may render the product misbranded (section 505B(d) of the Act). FDA interprets the language "request for approval of a pediatric formulation" to mean that applicants must submit an application or supplemental application for any not previously approved formulation(s) used to conduct their pediatric studies. Where appropriate, applicants may need to begin the development of a pediatric formulation before initiation of pediatric clinical trials.

PREA does, however, specifically authorize FDA to waive the requirement for pediatric studies in one or more age groups requiring a pediatric formulation if the applicant certifies and FDA finds that "the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed" (section 505B(a)(4)(B)(iv) of the Act). This exception is limited to the pediatric groups requiring that formulation (section 505B(a)(4)(C)). FDA believes that this partial waiver provision will generally apply to situations where the applicant can demonstrate that unusually difficult technological problems prevented the development of a pediatric formulation. In certain cases, the Agency may seek appropriate external expert opinion (e.g., from an advisory committee) to assess whether a waiver should be granted (see section VI.A and B for more detailed information on waivers).

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**D. When to Initiate Pediatric Studies**

As discussed in section V.A, applicants may initiate pediatric studies of drugs and biologics for life-threatening diseases for which adequate treatment is not available earlier in development than might occur for less serious diseases. The medical need for these products may justify early pediatric trials despite a relative lack of safety and effectiveness data. In some cases, pediatric studies of a drug or biological product for a life-threatening disease may begin as early as phase 1 or phase 2, when the initial safety data in adults become available.

The Agency recognizes that in certain cases scientific and ethical considerations will dictate that pediatric studies should not begin until after approval of the drug or biological product for use by adults — for example, where a product has not shown any benefit over other adequately labeled products in the class, the therapeutic benefit is likely to be low, or the risks of exposing pediatric patients to the new product may not be justified until after the product's safety profile is well established in adults after initial marketing.

The Agency recommends that for products with a narrow therapeutic index, the nature of the disease in the pediatric population to be studied and the context in which the drug will be used should factor into the decision on when to initiate the studies in the affected pediatric patient population. For example, studies for an oncology drug product with a narrow therapeutic index might be conducted in children with a life-threatening cancer at an earlier stage in the drug development process than studies for a new aminoglycoside antimicrobial used to treat acute pyelonephritis infections in children. In the latter case, there are several therapeutic options available, so the investigational drug would likely be studied in children after the approval in adults for this condition.

**E. What Information Must Be Submitted to FDA**

Pediatric studies of drugs conducted under an investigational new drug application (IND) are subject to the rules governing INDs, including the content and format requirements of 21 CFR 312.23 and the IND safety and annual reporting requirements described in 21 CFR 312.32 and 312.33, respectively.

- When study reports are submitted as part of an application or supplement to an application, the content and format must meet the relevant general requirements for submission (see 21 CFR 314.50 for NDA requirements and 21 CFR 601.2 for BLA requirements).

**VI. WAIVERS AND DEFERRALS**

**A. What Is a Waiver?**

PREA authorizes FDA to waive the requirement to submit the pediatric assessment, based on established criteria, for some or all pediatric age groups. FDA can grant a full or partial waiver of the requirements on its own initiative or at the request of an applicant. If an applicant requests

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a waiver, the applicant should provide written justification for the waiver and evidence to support the request.

**B. How to Apply for a Waiver**

*1. Criteria for Full Waiver (Section 505B(a)(4)(A) of the Act)*

On FDA's initiative or at the request of an applicant, FDA will grant a full waiver of the requirement to submit pediatric assessments if the applicant certifies and FDA finds one or more of the following:

(a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (section 505B(a)(4)(A)(i) of the Act).

Another example is a drug or biological product for an indication that has extremely limited applicability to pediatric patients because the pathophysiology of these diseases occur for the most part in the adult population. FDA would be likely to grant a waiver for studies on products developed for the treatment of these conditions without requiring applicants to provide additional evidence of impossibility or impracticality. For a list of adult-related conditions that may be candidates for a disease-specific waiver, see Attachment A, Sample Waiver Request Form.

(b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups (section 505B(a)(4)(A)(ii) of the Act).

If a waiver is granted based upon evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act).

(c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act).

*2. Criteria for Partial Waiver (Section 505B(a)(4)(B) of the Act)*

On its own initiative or at the request of an applicant, FDA will grant a partial waiver of the requirement to submit pediatric assessments for a drug or biological product with respect to a specific pediatric age group, if the applicant certifies and FDA finds evidence of one or more of the following:

(a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed) (section 505B(a)(4)(B)(i) of the Act).

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(b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group (section 505B(a)(4)(B)(ii) of the Act). If a partial waiver is granted based on evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act).

(c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (2) is not likely to be used by a substantial number of pediatric patients in that age group (section 505B(a)(4)(B)(iii) of the Act).

(d) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed (section 505B(a)(4)(B)(iv) of the Act). If a waiver is granted on the basis that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation (section 505B(a)(4)(C) of the Act).

*3. Information in a Waiver Request*

As noted in section V, discussions with FDA on developing pediatric plans and initiating pediatric studies should occur early in the drug development process. If an applicant believes a full or partial waiver of the pediatric studies requirement is warranted, FDA strongly encourages the applicant to request the waiver at the earliest appropriate time. This guidance includes a sample Waiver Request to assist applicants in providing sufficient information for FDA to determine whether to grant a waiver request (Attachment A). However, the information necessary to support any particular waiver will be determined on a case-by-case basis.

To request a waiver, we recommend an applicant provide:

- Product name, applicant name, and indication
- Age group(s) included in waiver request
- Statutory reason(s) for requesting a waiver, including reference to the applicable statutory authority (i.e., one of 2(a)-(d) in Attachment A)
- Evidence that the request meets the statutory reason(s) for waiver of pediatric assessment requirements
- Applicant Certification

*4. Waiver Decision*

The Agency will grant a waiver request if FDA determines that any of the criteria for a waiver enumerated in the statute have been met. As noted above, if a full or partial waiver is granted "because there is evidence that a drug or biological product would be ineffective or unsafe in

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pediatric populations, this information shall be included in the labeling for the drug or biological product" (section 505B(a)(4)(D) of the Act).

As discussed in section V, for waivers agreed to at the end-of-phase 2 meetings, the meeting minutes will document the waiver of pediatric assessment requirements. Full or partial waiver documentation (meeting minutes or a letter from FDA) should be submitted in the Clinical Data Section of the NDA or BLA and noted in Form FDA-356h under the "Pediatric Use" part of item 8, and also under item 20, "Other." Under "Other," the applicant should identify the location (volume and page number) of the waiver documentation in the NDA or BLA submission.

Decisions to waive the requirement for submission of pediatric assessments that are made early in the pre-approval development period (e.g., end-of-phase 1 or end-of-phase 2 meetings) reflect the Agency's best judgment at that time. If, prior to approval, the Agency becomes aware of new or additional scientific information that affects the criteria on which the waiver decision was based, the Agency may reconsider its earlier decision. A waiver decision becomes final once issued in the approval letter for an NDA, BLA, or supplement.

**C. What Is a Deferral?**

A deferral acknowledges that a pediatric assessment is required, but permits the applicant to submit the pediatric assessment after the submission of an NDA, BLA, or supplemental NDA or BLA. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all of the pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product for adult use (section 505B(a)(3) of the Act).

**D. How to Apply for a Deferral**

*1. Criteria for Deferral (Section 505B(a)(3) of the Act)*

FDA may defer the timing of submission of some or all required pediatric studies if it finds one or more of the following:

- The drug or biological product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(3)(A)(i) of the Act).
- Pediatric studies should be delayed until additional safety or effectiveness data have been collected (section 505B(a)(3)(A)(ii) of the Act).

OR

- There is another appropriate reason for deferral (section 505B(a)(3)(A)(iii) of the Act) (e.g., development of a pediatric formulation is not complete).

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In addition, to obtain a deferral the applicant must submit certification of the reason(s) for deferring the assessments, a description of the planned or ongoing studies, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time (section 505B(a)(3)(B)(i)-(iii) of the Act).

*2. Information in a Deferral Request*

FDA has provided a sample Deferral Request checklist to assist applicants in providing sufficient information for FDA to determine whether to grant a deferral request (Attachment B). To request a deferral, we recommend an applicant provide:

- Product name, applicant name, and indication
- Age group(s) included in deferral request
- Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request (e.g., studies have already been completed in other age groups and need not be deferred)
- Reason(s) for requesting a deferral
- Evidence justifying that the proposed product meets the criteria for deferral of the pediatric assessment requirement
- Description of planned or ongoing studies
- Evidence that planned or ongoing studies are proceeding
- Projected date for the submission of the pediatric assessment (deferral date)
- Applicant certification

*3. Deferral Decision*

The decision to defer and the deferral date will be determined on a case-by-case basis. Considerations used in determining whether and how long to defer submission of the pediatric assessment may include:

- The need for the drug or biologic in pediatric patients
- Availability of sufficient safety data to initiate pediatric trials
- The nature and extent of pediatric data needed to support pediatric labeling
- The existence of substantiated difficulties in enrolling patients
- Evidence of technical problems in developing pediatric formulations

As discussed in section V.A, the meeting minutes or a separate letter will document the deferral of pediatric assessments agreed to at the end-of-phase 2 meetings. For a deferral granted during the pre-approval development period, it is possible that FDA may reevaluate the length of the deferral closer to the time of approval, taking into account any new information obtained while the product was in development and information reviewed in the NDA or BLA. The pediatric assessments deferred under PREA are required postmarketing studies subject to the annual status

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reporting and information disclosure provisions of 21 CFR 314.81(b)(2)(vii)(a) and (b) and 21 CFR 601.70.

**VII. COMPLIANCE WITH PREA**

If a pediatric assessment or a request for approval of a pediatric formulation is not submitted by an applicant in accordance with the statutory requirements, the drug or biological product may be considered misbranded solely because of that failure and subject to relevant enforcement action (section 505B(d)(1) of the Act). The failure to submit a pediatric assessment or request for waiver or deferral will not be the basis for withdrawing approval of a drug under section 505(e) of the Act or the revocation of a license for a biological product under section 351 of the PHSA (section 505B(d)(2) of the Act). However, the Agency could bring injunction or seizure proceedings if a product is found to be misbranded under these provisions.<sup>8</sup>

**VIII. PREA AND PEDIATRIC EXCLUSIVITY**

It is the Agency's policy to offer applicants the opportunity to qualify for *pediatric exclusivity* under section 505A of the Act for studies required and conducted under PREA. Under that policy, however, FDA will not issue a Written Request for or grant pediatric exclusivity for studies that have been submitted to the Agency before the Written Request is issued. Therefore, an applicant seeking to qualify for pediatric exclusivity should obtain a Written Request for studies from FDA before submitting the pediatric studies to satisfy PREA. (Note that for marketed drugs and biological products, the Agency is required to issue a Written Request prior to requiring studies under PREA (section 505B(b)(3) of the Act)). To qualify for pediatric exclusivity, the pediatric studies conducted to satisfy the requirements of PREA must also satisfy all of the requirements for pediatric exclusivity under section 505A of the Act (see sections 505A(d) and 505A(h) of the Act).

In addition, there is a noteworthy distinction between the scope of the studies requested under the pediatric exclusivity provisions and what is required under PREA. For pediatric exclusivity under the Act, FDA's authority to issue a Written Request extends to the use of an active moiety for all indications that occur in the pediatric population, regardless of whether the indications have been previously approved in adults or approval for those indications is being sought in adults (see section 505A(a), which refers only to "information relating to the use of a new drug in the pediatric population"). Under PREA, on the other hand, a pediatric assessment is required only on those indications included in the pending application (section 505B(a), which addresses "the safety and effectiveness of the drug or biological product for the claimed indications"). To learn more about eligibility for pediatric exclusivity, applicants should consult the guidance for industry entitled *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*<sup>9</sup> or should contact the relevant review division.

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<sup>8</sup> See section 302 of the Act (21 U.S.C. 332), Injunction Proceedings; section 304 of the Act (21 U.S.C. 334), Seizure.

<sup>9</sup> Available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

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**IX. ADDITIONAL INFORMATION**

**A. Additional Information Concerning PREA**

General information about complying with PREA can be obtained from the Division of Pediatric Drug Development (DPDD), 301-594-7337 or 301-827-7777, e-mail pdit@cderr.fda.gov. Additional pediatric information is available at <http://www.fda.gov/cder/pediatric>.

Specific information about the types of pediatric studies that must be conducted and requirements for submission of assessments for your drug product can be obtained from the appropriate review division.

**B. Additional Information Concerning Pediatric Exclusivity**

General information and the latest statistical information regarding pediatric exclusivity are located at <http://www.fda.gov/cder/pediatric>. You can also refer to the guidance for industry on *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*.

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**ATTACHMENT A — SAMPLE WAIVER REQUEST**

Product name:

IND/NDA/BLA number (as applicable):

Applicant:

Indications(s):

(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. Identify pediatric age group(s) included in your waiver request.
2. With regard to each age group for which a waiver is sought, state the reason(s) for waiving pediatric assessment requirements with reference to applicable statutory authority (i.e., one of the options (a)-(d) listed below — choose all that apply):
  - (a) Studies are impossible or highly impractical (because, for example, the number of pediatric patients is so small or geographically dispersed). If applicable, please check from the following list of adult-related conditions that may qualify the drug product for disease-specific waivers:

<input type="checkbox"/> Age-related macular degeneration	<input type="checkbox"/> Basal cell and squamous cell cancer
<input type="checkbox"/> Alzheimer's disease	<input type="checkbox"/> Breast cancer
<input type="checkbox"/> Amyotrophic lateral sclerosis	<input type="checkbox"/> Colorectal cancer
<input type="checkbox"/> Arteriosclerosis	<input type="checkbox"/> Endometrial cancer
<input type="checkbox"/> Infertility	<input type="checkbox"/> Hairy cell cancer
<input type="checkbox"/> Menopause symptoms	<input type="checkbox"/> Lung cancer (small cell and non-small cell)
<input type="checkbox"/> Osteoarthritis	<input type="checkbox"/> Oropharynx cancers (squamous cell)
<input type="checkbox"/> Parkinson's disease	<input type="checkbox"/> Ovarian cancer (non-germ cell)
<input type="checkbox"/> Other (please state and justify)	<input type="checkbox"/> Pancreatic cancer
	<input type="checkbox"/> Prostate cancer
	<input type="checkbox"/> Renal cell cancer
	<input type="checkbox"/> Uterine cancer
  - (b) The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.
  - (c) The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
  - (d) Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. Please document previous attempts to make a pediatric formulation and describe reasons for failure.
3. Provide evidence that the statutory reason(s) for waiver of pediatric studies have been met (not necessary if a 2(a) category is checked).
4. Applicant certification.

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**ATTACHMENT B — SAMPLE DEFERRAL REQUEST**

Product name:

IND/NDA/BLA number (as applicable):

Applicant:

Indications(s):

(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. What pediatric age group(s) are included in your deferral request?
2. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):
  - (a) Adult studies completed and ready for approval
  - (b) Additional postmarketing safety data needed (describe)
  - (c) Nature and extent of pediatric data needed (explain)
  - (d) Evidence provided of technological problems with development of a pediatric formulation
  - (e) Difficulty in enrolling pediatric patients (provide documentation)
  - (f) Other (specify)
3. What pediatric age group(s) is/are not included in your deferral request?
4. Reason(s) for not including the pediatric age group(s) listed in number 3 in the deferral request (address each excluded age group separately and for each such age group — choose all that apply):
  - (a) Adequate pediatric labeling exists
  - (b) Studies completed in the specified age group
  - (c) Requesting a waiver
  - (d) Currently conducting pediatric studies that will be submitted with application
  - (e) Other (specify)
5. Has a pediatric plan been submitted to the Agency?
  - If so, provide date submitted.
  - If not, provide projected date pediatric plan is to be submitted.
6. Suggested deferred date for submission of studies.

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**ATTACHMENT C — COMPLIANCE DATES FOR  
APPLICATIONS SUBJECT TO PREA**

Categories of Application	Expected Date of Compliance
Application or supplement submitted between 4/1/99 and 12/3/03, no waiver or deferral was granted and no studies were submitted	Immediate unless FDA specifies later date
Application or supplement submitted between 4/1/99 and 10/17/02, studies were deferred to a date after 4/1/99, but no studies were submitted	Deferral date + 411 days
Application or supplement submitted between 10/17/02 and 12/3/03 and approved after 12/3/03, studies were deferred	Immediate unless later date is specified in deferral letter
Applications submitted after 12/3/03, studies were deferred	Date specified in deferral letter

The dates in the chart are relevant as follows:

- 4/1/99            The date the Pediatric Rule became effective
- 10/17/02        The date that implementation and enforcement of the Pediatric Rule was suspended by court order
- 12/3/03         The date that PREA was enacted

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
10/16/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**TRANSMITTAL SHEET**

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**DATE:** October 13, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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**Total no. of pages including cover: 4**

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Dear Mr. Van Valen:

Please refer to your Everolimus NDA, 21-560, specifically our September 14, 2009 correspondence sent to you via email.

Thank you for your submission of Oct 6th. We would like to clarify our request #9 from the September 14, 2009 correspondence.

Please submit a revised subgroup analysis of adverse events (AEs)  $\geq 2\%$  by treatment group for the following subpopulations: age, race, and gender. For example, the analysis of gender should compare rates of AEs for men and women within the 1.5 mg everolimus arm, the 3.0 mg everolimus arm, and the Myfortic arm. See mock table as an appendix to this communication.

Please also provide a discussion of your findings and conclusions. If the background rate of particular events (e.g., myocardial infarction) is not expected to be similar between males and females, young and old, etc. please also include that as part of the discussion of why rates are different between males/females, young/old, etc.

Additionally, please provide a detailed discussion regarding any differences between treatment groups in adverse event rates, particularly the comparison between the everolimus 1.5 mg and the Myfortic arms, in the subgroup of female patients, male patients, patients <65 years of age and patients  $\geq 65$  years of age.

We note in your submitted gender analysis that differences of more than 10% in the incidence of AEs between males and females by Primary System Organ Classes (SOCs) were discussed in detail. Please provide a rationale as to why the cut-off of a 10% difference was selected as being “clinically meaningful.”

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

## Analysis of adverse events by gender

Summaries of all AEs/Infections are presented by gender in [Table 14.3.1-1.1b\_30] while summaries of the most common AEs/Infections are presented by gender in [Table 14.3.1-1.2d\_30].

Incidence rates of AEs were higher in females than in males across all treatment groups in the blood and lymphatic system disorders class, mainly driven by anemia, as well as in the infections and infestations class, mainly driven by an incidence of urinary tract infections in females twice that in males. Incidence of neoplasms was low in both genders with incidence in females approximately one third of that in males.

Differences of more than 10% in the incidence of AEs between males and females were observed in the following Primary System Organ Classes (SOCs):

- cardiac disorders (lower incidence in males receiving everolimus 1.5mg vs. females but higher incidence in males receiving everolimus 3.0mg, and no gender difference in those receiving Myfortic);

- gastrointestinal disorders and general disorders (lower incidence in males receiving everolimus 1.5mg and Myfortic vs. females, and higher incidence in those receiving everolimus 3.0mg; differences mainly associated with abdominal pain, constipation and nausea);

- injury, poisoning and procedural complications (lower incidence in males receiving everolimus 1.5mg vs. females, and higher incidence in males receiving Myfortic);

- renal and urinary disorders (lower incidence in males receiving everolimus 1.5mg vs. females, and higher incidence in males receiving everolimus 3.0mg and Myfortic);

- skin and cutaneous tissue disorders (higher incidence in males receiving everolimus 1.5mg

vs. females);

- vascular disorders (lower incidence in males receiving everolimus vs. females, and higher

incidence in males receiving Myfortic; differences mainly associated with hypertension).

In most of these SOC's males receiving the lower everolimus dose had a lower incidence of

AEs than females, and males receiving Myfortic had a higher incidence of AEs than females.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
10/13/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

---

**DATE:** September 17, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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**Total no. of pages including cover: 7**

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Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Certican (everolimus) Tablets.

We are continuing our review of the NDA 21-560 resubmission for everolimus, Study A2309, and have identified a number of safety issues that we propose to address at the upcoming Advisory Committee (AC) meeting scheduled for December 7, 2009. Based on our preliminary review of Study A2309 we have not identified any major differences between our results and those provided in the submission on the primary efficacy endpoint; however we are still completing this review. We anticipate some discussion of the renal function findings (i.e., GFR endpoint) and we anticipate that the following issues and adverse events will be discussed in more detail during our presentation. Therefore, we recommend that the following issues be addressed in your AC background package. In addition, we would like to discuss these issues and the clinical implications with you at our AC planning meeting on October 28, 2009.

### **1. Proteinuria**

In most of the analyses of proteinuria (urinary protein/urinary creatinine or UP/UC ratio) provided in the submission there is a statistically significant difference between the everolimus treatment arms and the Myfortic control arm in favor of the control arm at all time points especially starting at month six post-transplant.

For example, in the CSR see Table 14.3-2.6d on page 1091, Table 14.3-2.6.5b on page 1259, and Table 16.1.9-2.3. Additional analyses of proteinuria that do not reach statistical significance but show numeric differences are reported in Table 14.3-2.6.2 on page 1250 and Table 14.3-2.6.2a on page 1253 of CSR.

Please provide a discussion of these findings, including the clinical significance of the higher incidence of proteinuria in the everolimus arms (especially in the 1.5 mg arm) compared to the control arm and comment on the clinical implications and long-term consequences of a higher incidence and greater degree of proteinuria on short-term and long-term kidney graft function, graft survival, overall patient health and survival.

### **2. Hyperlipidemia**

In most of the analyses, there is a statistically significantly higher incidence of hyperlipidemia, including total cholesterol and triglycerides, between the everolimus treatment arms and the Myfortic control arm in favor of the control arm. Please discuss the short and long-term consequences of higher incidence of hyperlipidemia on cardiovascular morbidity, atherosclerotic events in general, and mortality. Furthermore, discuss the role and use of lipid-lowering agents in the treatment and control arms, including the doses used, the lipid levels achieved, and the safety/adverse event reports related to the use of these products. Include a discussion of the finding that CK (creatinine kinase) levels were significantly higher

in both of the everolimus arms compared to the control arm (which may be an initial sign of rhabdomyolysis), as well as other adverse events (e.g., myalgia, rhabdomyolysis) or benefit (e.g., degree of lipid control achieved).

Discuss how the findings may be further confounded (against everolimus) by the drug-drug interaction between everolimus and statins.

### 3. Premature Treatment Discontinuations Due to Adverse Events

As shown in your table below, the proportion of premature treatment discontinuation was significantly higher in the both everolimus treatments compared to the Myfortic control arm. Please discuss this finding, including the nature and type of the specific adverse events leading to discontinuation, the timing of onset and severity, and the clinical implication of these events for patients. Additionally, please provide information regarding immunosuppressant therapy received after premature treatment discontinuation of study drug for all treatment arms.

	<b>Everolimus 1.5 mg, n (%)</b>	<b>Everolimus 3.0 mg, n (%)</b>	<b>Myfortic 1.44 g, n (%)</b>
Total no. of patients	277 (100)	279 (100)	277 (100)
<b>Discontinued study medication</b>	<b>83 (30.0)</b>	<b>95 (34.1)</b>	<b>60 (21.7)</b>
<b>Adverse events</b>	<b>50 (18.1)</b>	<b>57 (20.4)</b>	<b>26 (9.4)</b>

### 4. Glomerular Filtration Rate (GFR)

In previous discussions with you regarding everolimus, we stated our concern about the impact everolimus/cyclosporine treatment on renal function, specifically GFR. In the initial studies which used standard dose cyclosporine and non-TDM everolimus (i.e, B201, B251) the difference in GFR at month 12 favored the Cellcept control arm by month 3 and the difference persisted through the 36 months follow-up. The median estimated creatinine clearance was in the 50 mL/min range for the everolimus arms and in the 60-70 mL/min range in the MMF arm of Studies B201 and B251. In Study A2309, the difference between everolimus and the control arm has been reduced, such that and at 12 months there is a 2 mL difference between the mean values in favor of the everolimus 1.5 mg arm. However, there is also a different level of exposure to cyclosporine in the two arms, with less exposure in the everolimus arm compared to the control arm. Cyclosporine is known to decrease GFR due to constriction of the afferent arteriole of the glomerulus.

Given that patients in the everolimus arm received lower doses/lower exposure to cyclosporine than patients in the control arm, discuss how

difference exposures to cyclosporine in the treatment arms may have impacted/affected the results (in favor of everolimus) and resulted in a smaller than expected difference between the arms.

**5. Cyclosporine Doses/Exposures and Trough Concentrations**

Please provide a discussion of the targeted and achieved trough cyclosporine concentrations in the three treatment arms, and implications on GFR. In addition, we note in your proposed package insert that it is recommended that cyclosporine and everolimus concentrations be measured and adjusted concurrently. Please discuss whether this practice was implemented in Study A2309 and the consequences, if any, of not adjusting trough concentration of both drugs simultaneously.

**6. Mortality**

Please comment on the numerically higher 12-month mortality rate in the everolimus treatment arms compared to the Myfortic control arm, including a discussion of the specific causes and nature of deaths between the everolimus arms and the control arm.

**7. Graft Loss**

In Table 12-14 on page 189 of CSR, only some of the graft losses are reported as Serious Adverse Events (SAEs). We note that in the protocol it states that all events of graft loss were to be considered SAEs. Given that the SAEs are lower than the numbers provided in the efficacy analysis for graft loss, please explain the discrepancy and why all of the graft losses were not considered to be SAEs.

**8. HUS/TTP/TMA and Interstitial Lung Disease**

Please comment on the incidence and the implications of less common but potentially more lethal adverse events in Study A2309 which may be represent an mTOR class effect, such as HUS/TTP/TMA and interstitial lung disease, including alveolar proteinosis; since two of the reported deaths in Study A2309 (0549-0001 and 0304-00016) may be associated with these rare adverse events.

**9. Lymphocele and Other Wound-Related Events**

In the analysis of wound-related adverse events, which you provided based upon our request (dated August 24, 2009, Table 1-2 on page 5), you present an overall analysis of fluid collections. Please provide an additional analysis and discussion of findings and clinical implications, which excludes hematomas and urinomas and including only lymphoceles, seromas and perinephric collections since hematomas and urinomas may be due to different causative factors. Also please provide another analysis similar to Table 1-3 in the August submission including excluding umbilical hernias and only including dehiscence and incisional hernias only because dehiscence and incisional hernia are more directly related to the wound healing process.

In addition, we note that in the August 24, 2009 analysis, the total numbers of patients with seroma and lymphocele are different from the numbers in the original submission (Table 12-6 Page 215 of CSR). Please explain the discrepancy.

#### **10. Anemia**

Provide a MedDRA listing of all anemias by subcategory, including aplastic and hemolytic anemias, reported in Study A2309. Provide comparisons between the everolimus treatment arms and the Myfortic control arm and include a discussion with implications.

#### **11. Edema**

We are continuing to review the adverse event of “edema”, including conducting an analysis inclusive of all applicable search terms under the MEDDRA System Organ Class (SOC) terms, Higher and Lower Level Terms and Preferred Terms (PT), to cover all reports and sites of clinically significant edema and related conditions. Please perform a search of the edema related adverse events reported using the MEDDRA terms listed below and perform an analysis comparing the incidences, severity and duration of these events across the study arms.

##### MEDDRA TERMS:

- Localised oedema
- Oedema
- Oedema due to renal disease
- Oedema peripheral
- Pitting oedema
- Fluid overload
- Fluid retention
- Lymphoedema
- Generalised oedema
- Gravitational oedema
- Localised oedema

In addition please perform an exploratory multivariate analysis including the three different treatment regimens and factors that possibly affect the occurrence of edema like BMI, age, serum albumin level and range of proteinuria (mild, subnephrotic, etc.) as covariates.

Please provide a discussion of the clinical significance of the edema data and the results of the related analyses in Study A2309. In the summary of this analysis, please include the MEDDRA codes used to search for the above listed terms.

#### **12. Risk Evaluation and Mitigation Strategy (REMS)**

You have proposed REMS(with Medication Guide and Communication Plan to Health Care Professionals as its elements) as an approach to managing the risks

associated with the use of everolimus specifically the risk of wound-healing complications in patients receiving everolimus and monitoring of everolimus blood levels as a means of reducing the risk for rejection and for impaired renal function.

Please discuss if this approach will mitigate adverse events such as those listed above, and include examples of events and how they were prevented, mitigated or managed during Study A2309.

### **13. Risk/Benefit Assessment**

Please provide a more detailed risk/benefit assessment of everolimus in kidney transplant recipients than what is currently included in the submission, including discussions specific to efficacy and safety advantages, if any. Include a discussion of the drug-drug interactions between cyclosporine and everolimus and the potential impact on the ability of prescribers to simultaneously manage two TDM drugs when monitoring is inter-related. Also discuss the impact of other drug-drug interactions on the use of everolimus including other drugs that kidney transplant patients frequently receive such as statins, and other CYP3A4 inhibitors or inducers. Finally, given the efficacy and safety profile of the proposed everolimus regimen please discuss its role in the marketplace given the currently approved drugs/regimens.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
09/17/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 14, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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**Total no. of pages including cover:**

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Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Certican (everolimus) Tablets, specifically the outstanding issues listed below.

Please address and respond to these issues as soon as possible.

### **Statistical**

We have the following requests for clarification pertaining to 12-month adverse event and infection (i.e. dataset 'adverse.xpt' and 'infect.xpt') for study A2309.

1. According to footnote 3 of Table 14.3.1-1.1 in the clinical study report-12 month, "*Adverse events/infections with onset date eight or more days after the discontinuation of randomized study medication are not included in this analysis*". Please clarify the reason and rationale for choice of an eight-day cut-off for inclusion of AEs/infections.
2. Please clarify if this eight-day cut-off was also used for the analysis of SAEs.
3. Please update the corresponding tables of adverse events (for example, Table 12.5, Table 12.6, etc) based on all adverse events/infections, including those with onset date eight or more days after the discontinuation of randomized study medication.
4. In dataset 'adverse.xpt' or 'infect.xpt', nine patients (**SUBJID**='0124 00074', '0168 00002', '0168 00016', '0301 00002', '0511 00015', '0517 00005', '0517 00006', '0530 00002', '0553 00020') were reported with AE name or infection name = 'None' and MedDRA preferred term = 'No adverse event'. Please clarify why these nine patients were included in both datasets with no adverse event.
5. After removing those nine patients from both datasets, there were **271, 276, 271** subjects in the Certican 1.5 mg group, Certican 3.0mg and Myfortic 1.44g group respectively with at least one record in either 'adverse.xpt' or 'infect.xpt' and having **SAF12M** equal to 1. In Table 12-6 of the study A2309 CSR report, the number of patients with 'Any AE/Infection' was **271, 276 and 270** in each of the treatment groups. Please clarify this discrepancy.
6. Please include adverse events/infections with onset date up to 30 days [instead of 8 days] after the discontinuation of randomized study medication in your analyses of adverse events and redo the analyses with this new cut-off date.

### **Clinical**

7. Thank you for your submission dated September 2, 2009 which contains your rationale for assuming applicability of foreign data to US population. Unfortunately your submission does not fully address our request. Please provide additional information which discusses the similarities and differences between the non-North American and North American populations in terms of pre- and post- transplant

factors that would be expected to affect outcome [e.g. underlying kidney disease, race of the recipient, donor age and standard of care].

To support your discussion please compare the demographics of the recipients/donors and outcome parameters between the North American and non-American populations for the overall study in addition to the breakdown by treatment arm.

8. In your submission about the analysis of wound related events in study A2309 dated 02-September-09 in Table 1-2 on page 5, the group sums within the 1.5 mg column [lymphocele, hematoma etc.] do not add up to the number at the top of the column [56]. Please clarify this discrepancy.
9. In your Clinical Study Report we could not find subgroup analyses of adverse events (AEs) by age, race, or gender. If this has been already provided in the submission please point us to the location, otherwise please submit an analysis of each of the subgroups: age (< 65 and  $\geq$  65 years), race (as reflected in your study population), and gender for all AEs. In addition to providing the SAS output for all adverse events, please create summary tables of the most common AEs ( $\geq$  2%). In addition, discuss your findings and the conclusions that can be drawn from the results.
10. We note that in your analysis of serum lipids (total cholesterol, subfractions and triglycerides etc.), the results are reported in units of mmol/L. For purposes of interpretability of the results, especially for the Advisory Committee members, please resubmit all the related datasets and results of the analysis and the tables using the US units of mg/dL instead of mmol/L. Also, in all of the analyses related to serum lipids (including total cholesterol, triglycerides, HDL, LDL and the total cholesterol/HDL ratios) please submit the absolute values (instead of the changes from baseline) in mg/dL at all time points throughout the study period in the safety population as a 12 Month on-treatment analysis with comparisons across the treatment arms.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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JACQUELYN E SMITH  
09/14/2009



NDA 21560

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

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

ATTENTION: Ronald G. Van Valen  
Executive Director

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) dated December 19, 2002, received December 20, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Everolimus Tablets, 0.25 mg, 0.5 mg, 0.75 mg, and 1 mg.

We also refer to your June 30, 2009 correspondence, received July 1, 2009, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, Complete Submission for the Evaluation of Proprietary Names, [HTTP://www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) and “Pdufa Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Jacqueline E. Smith at (301) 796-1002

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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CAROL A HOLQUIST  
09/03/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 1, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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**Total no. of pages including cover: 4**

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Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Certican (everolimus) Tablets.

We have some issues with your disposition dataset for statistical analyses, so we have the following requests for clarification pertaining to 12-month premature treatment and study discontinuation (i.e. dataset 'discon.xpt') in Study A2309.

1. In Novartis' response on August 20, 2009 to FDA Request 2, it was mentioned that patient with **SUBJID**=0519\_00003 withdrew consent after randomization. This patient was included in the ITT population and reported as lost to follow-up in dataset 'eff\_fda.xpt'; however, this patient was not included in dataset 'discon.xpt'. Please explain this discrepancy.
2. For patient with **SUBJID**=0537\_00011, in the 'discon.xpt' dataset, we find that **DCRSN**=7 (patient withdrew consent), and **CMP\_STUD** is missing. Please explain why this patient was not indentified as not completing study (i.e. **CMP\_STUD**=0 rather than missing), when a reason of discontinuation was provided?
3. According to Table 10-1 of the clinical study report-12 month, 99 patients prematurely discontinued study in the 12-month analysis. In Novartis' response to FDA Request 6, other than the 94 patients identified as discontinued study in the 'discon' dataset with variable **CMP\_STUD**=0, five additional patients (0503\_00002, 0537\_00011, 0553\_00020, 0111\_00013, 0543\_00007) had missing **CMP\_STUD** and last contact day < 316 study days. Should these five patients be reported as not completing study due to loss to follow-up? Also please clarify as to if these five patients prematurely discontinued study medication. For example, patient with **SUBJID**=0543\_00007 had missing **DISC\_SM** and was originally indentified as completed study medication.
4. The patient with **SUBJID**=0540\_00010 was indentified as having completed study based on **CMP\_STUD**=1 in the 'discon' dataset; however, the last contact day reported for this patient was 71. Please clarify why this patient was considered having completed study when the last contact day was day 71.
5. If the discontinuation dataset (i.e. discon.xpt) is to be updated given the concerns addressed in items 1-4 above, please submit the revised dataset as quickly as possible.

NDA 21-560

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission.  
Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

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/s/  
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JACQUELYN E SMITH  
09/01/2009



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**TRANSMITTAL SHEET**

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**DATE:** August 25, 2009

<b>To:</b> Ronald G. Van Valen Executive Director Drug Regulatory Affairs	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via E-mail	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862- 778-7646	<b>Phone number:</b> 301-796-1600
Email: ronald.vanvalen@novartis.com	

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**Subject:** NDA 21-560 Certican™ (everolimus) Tablet-DSPTP Information Request Regarding Study A2309, Study B201, and B251

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**Total no. of pages including cover:** 3

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**Comments: Concurrence**

H. Ergun Velidedeoglu, M.D., Joette Meyer, Pharm.D.

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**Document to be mailed:**  YES  NO

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Dear Mr. Van Valen,

In order to assist in the review of NDA 21-560, please address the following requests from our review team regarding the incidence of thrombosis seen in Study A2309, Study B201, and B251.

1. Submit in tabular format the distribution of the following thrombotic adverse events related to the graft across the study arms for Study A2309, Study B201, and B251. For patients in Study A2309, include patient identifiers and the day of diagnoses in the table.

All cases of:

- Renal artery thrombosis
  - Renal vein thrombosis
  - Graft thrombosis
  - Renal necrosis
  - Renal infarct or infarction
2. Submit in tabular format the distribution of the following other thromboembolic events across the study arms for Study A2309, Study B201, and B251. For patients in Study A2309, include patient identifiers and day of diagnoses in the table.
    - Deep vein thrombosis (DVT)
    - Myocardial infarction (MI)
    - Pulmonary emboli (PE)
    - Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome/Thrombotic Microangiopathy (TTP/HUS/TMA)
  3. Submit narratives for the cases identified in #1 and #2 above that occurred in Study A2309, if not already included in the NDA resubmission. If a narrative was previously submitted, please provide information on where the narrative is located within the submission.

Please officially submit this material no later than August 31, 2009.

If you have any questions regarding this transmittal, please contact me at 301-796-1600.

Sincerely,

*{See appended electronic signature page}*

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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GREGORY F DIBERNARDO

08/25/2009

Clinical Information Request Regarding  
Study A2309, Study B201, and B251

## REQUEST FOR CONSULTATION

TO (Office/Division): OSE/Chris Jones

FROM (Name, Office/Division, and Phone Number of Requestor):

Jacquelyn Smith, PM/Dr. Ozlem Belen, DDS  
Division of Special Pathogen and Transplant Products  
(DSPTP)

DATE  
August 24, 2009

IND NO.

NDA NO.  
21-560

TYPE OF DOCUMENT

DATE OF DOCUMENT  
August 24, 2009

NAME OF DRUG  
Certican (everolimus)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
Immunosuppressant

DESIRED COMPLETION DATE  
October 14, 2009

NAME OF FIRM: Novartis

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |   |
|--|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input checked="" type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input checked="" type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS   |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |   |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** DSPTP received the resubmission for NDA 21-560, Certican (everolimus) (seeking indication for the prophylaxis of organ rejection in renal transplantation) in eCTD format via Gateway (EDR link: \\Cdsesub1\evsprod\NDA021560\0010). The letter and receipt date is June 30, 2009. The PDUFA date is December 30, 2009. There will be an Advisory Committee held on December 7, 2009. Also, please note there will be an NDA Mid-Cycle Meeting held on October 14, 2009. Certican (everolimus) is approved in Europe for this indication and has been approved in the U.S. for the indication of renal cell carcinoma, under the Trade Name, Afinitor, NDA number 22-334.

The Review Division would like OSE to examine the post marketing events pertaining to the following adverse events for Certican (everolimus) approved in Europe and for Afinitor, NDA 22-334 since its U.S. approval:

Proteinuria, Interstitial Lung Disease (please see if alveolar proteinosis is available under this or as a separate term),

Serious Infections (leading to death, hospitalization or prolongation of a hospitalization), Fluid Collection/Edema, Thromboembolic events, Thrombocytopenia [under this section we are particularly interested in Hemolytic Uremic Syndrome (HUS), Thrombotic Thrombocytopenic Purpura (TTP, and Thrombotic Microangiopathy (TMA)].

SIGNATURE OF REQUESTOR

Jacquelyn Smith, PM

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21560	ORIG 1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS
NDA 21560	ORIG 1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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GREGORY F DIBERNARDO

08/24/2009

OSE Postmarketing Adverse Event Consult Request on behalf of Jacquelyn Smith



**GENERAL ADVICE**

NDA 21-560

Novartis Pharmaceutical Corporation  
Attention: Mr. Ronald Van Valen  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Certican (everolimus) Tablets, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg.

We have reviewed your proposed labeling in structured product labeling (SPL) submitted on June 30, 2009 and the following formatting deficiencies have been identified:

**HIGHLIGHTS**

- Highlights, excluding the boxed warning, should be limited in length to one-half page if printed on 8.5" x 11 paper, single spaced, 8 point type with ½ inch margin on all sides, in a two-column format. If it is not possible to accommodate all the required information within one-half page, you may submit a waiver request from the one-half page requirement explaining why the requirement could not be met.
- There should be no white space between the heading and the second sentence.
- **Drug names, dosage form and route of administration** needs to be bolded.
- Please do not use the <sup>TM</sup> symbol after the trade name in the Highlights section. You may use this symbol only once upon first use in the full prescribing information (FPI). Please delete throughout the label.
- **BOXED WARNING** should summarize information in bulleted format, with each bullet communicating a discrete warning or contraindication and be listed in decreasing order of importance.
- Delete **RECENT MAJOR CHANGES**; this section applies to supplements that contain "substantive labeling changes" to the **Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warning and Precautions** sections that have been approved by FDA.
- Under **INDICATIONS AND USAGE** section, drug indication needs to be bulleted, but not bolded.
- Under **DOSAGE AND ADMINISTRATION** section, a concise bulleted summary should be used.

- Under **CONTRAINDICATIONS** section, a concise bulleted summary should be used.
- **WARNINGS AND PRECAUTIONS** section should contain a concise summary of the most clinically significant safety concerns along with recommendations for patient monitoring to ensure safe use and measures that can be taken to prevent or mitigate harm.
- **DRUG INTERACTIONS** section should contain descriptive subheadings (e.g., CYP3A4 inhibitors) followed by practical instructions for preventing or decreasing the likelihood of the interaction.

## **FULL PRESCRIBING INFORMATION: CONTENTS**

- The **BOXED WARNING** should include the word “**WARNING**” along with other words that identify the subject of the warning. The text of the warning is not consistent with the information in the abbreviated Boxed Warning in Highlights. Please also provide a cross-reference to the other sections of the package insert where additional information can be found. See draft Guidance for Industry “*Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format*” (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf>)

## **FULL PRESCRIBING INFORMATION:**

- **WARNINGS AND PRECAUTIONS** should be cross-referenced to Boxed Warning for specific subsections (e.g., "5.1 Infectious Complications and Malignancies"). The specific Warnings and Precautions should be ordered to reflect the relative public health significance of the adverse reaction. Factors to consider include the relative seriousness, the ability to prevent or mitigate, the likelihood of occurrence, and the size of the population that is potentially affected.
- **ADVERSE REACTIONS:** the following statement, or an appropriate modification, should precede the presentation of adverse reactions from clinical trials: *Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.*
- **ADVERSE REACTIONS:** The presentation of adverse reactions information identified from clinical trials must be preceded by information necessary to interpret the adverse reactions (§ 201.57(c)(7)(i)). This information would ordinarily include a description of the overall clinical trial database from which adverse reaction data have been drawn, including a discussion of overall exposure (number of patients, dose, schedule, duration), demographics of the exposed population, designs of the trials in which exposure occurred (e.g., placebo-controlled, active-controlled), and any critical exclusions from the safety database.

Sample Database Description

*The data described below reflect exposure to drug X in [n] patients, including [n] exposed for 6 months and [n] exposed for greater than one year. Drug X was studied primarily in placebo and active-controlled trials (n = \_\_, and n = \_\_\_\_, respectively), and in long-term follow up studies. The population was [age range], [gender distribution], [race distribution] and had [diseases/conditions]. Most patients received doses [describe range, route of administration, frequency, duration, as appropriate].*

Please also see the *Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* regarding the presentation of adverse event data and the number and types of tables to be included. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf>)

- **DRUG INTERACTIONS** section should be ordered based on clinical relevance. Specific information with regards to changes in the pharmacokinetic (PK) parameters is not appropriate in this section. A discussion of the changes in PK parameters resulting from specific interactions should be included in Section 12.3 "Pharmacokinetics."

Please address the identified deficiencies/issues and re-submit labeling by August 30, 2009. This updated version of labeling will be used for further labeling discussions.

These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency.

If you have any questions, call me at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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JACQUELYN E SMITH  
08/18/2009



NDA 21-560

**ACKNOWLEDGE CLASS 2 RESPONSE**

Novartis Pharmaceuticals Corporation  
Attention: Mr. Ronald G. Van Valen  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

We acknowledge receipt of your June 30, 2009 resubmission to your new drug application for Certican (everolimus) Tablets, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg.

We consider this a complete, class 2 response to our August 27, 2004 action letter. Therefore, the user fee goal date is December 30, 2009.

Although we have acknowledged your resubmission as a complete response, we have the following comments and requests for information.

**Clinical/Statistics**

1. Please provide an analysis and a table showing all the wound-related complications (including infection, dehiscence, fluid collection, hernia etc.) in Study A2309 denoting the ones that required surgical or other type of intervention for their treatment and the type of anesthesia used during the intervention. In the same analysis and table include age, gender, BMI and the diabetic status of the patient. Also perform a cross-study comparison of these findings across studies A2309, B201 and B251.
2. Please provide the CRFs for all the patients who had wound-related complications.
3. Please provide a rationale for assuming the applicability of foreign data in the submission to the U.S. population.
4. Please provide the Case Report Forms (CRFs) for the attached 10% random sample (N=84) of patients enrolled into Study A2309. See Appendix. Please note that CRFs from some of these patients may have previously provided as deaths, discontinuations, and serious adverse events in the NDA resubmission. In addition, we are requesting additional CRFs related to patients with wound-related complications in #2 above. If any of the patients contained in the random sample were previously submitted to the NDA or correspond to patients with wound-related complications, please acknowledge that the CRF was provided for another

reason and cite the reason and the submission. You do not need to submit these CRFs twice.

5. Please re-submit the efficacy.xpt, entry.xpt and enroll.xpt datasets for study A2309 as discussed during the 8/11/09 teleconference with the Division. Please ensure that these datasets contain complete and accurate information, including outcome at 12-months post-transplant in the efficacy.xpt dataset, pertaining to all randomized patients.

**Clinical Pharmacology**

6. Please provide the pharmacogenetics study and the associated patient level data for the exploratory pharmacogenetic assessments with everolimus (NDA21560) as described in section 9.5.4.3 in the clinical study report (study number RAD001A2309).

**Center for Devices and Radiological Health (CDRH)**

7. Since therapeutic drug monitoring, and maintenance of everolimus blood levels within the narrow range of 3-8 ng/mL, based on chromatographic methods, may be important for safe use of this drug, please clarify :
  - (a) The specific assay used during the clinical trials.
  - (b) Whether you are planning to coordinate with the manufacturer of this, or another, chromatographic assay to facilitate availability of an FDA cleared chromatographic everolimus assay if needed.

If you have any questions, call me at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Jacquelyn Smith, M.A.  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

APPENDIX – 10% Random Sample from Study  
A2309

PID	STYSID1A	SUBJID	SUBJ_INI
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/s/  
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JACQUELYN E SMITH  
08/13/2009

## Teleconference Minutes

**Teleconference Date:** August 11, 2009  
**Application Number:** NDA 21-560  
**Name of Drug:** Certican® (everolimus) Tablets  
**Sponsor:** Novartis Pharmaceuticals Corporation  
**Type of Meeting:** Teleconference  
**Meeting Chair:** LaRee Tracy, Ph.D.  
**Minutes Preparer:** Jacquelyn Smith, M.A.

### **Attendees:**

#### **Novartis Pharmaceuticals:**

Kevin Mange, MD	US Head Medical Affairs
Marc Lorber, MD	Certican Global Program Head
Luen Lee, PhD	Head Biostatistics
Hai Jang, PhD	Certican Lead project Statistician
Zailong Wang, PhD	Certican Project Statistician
Anthony Mastropolo	US Head Programming
Martin Hall	Certican Principal Statistical Programmer
Beatrice Metivier	Certican Program Programmer
Paula Chu	Certican Program Director
John Cutt, PhD	US Head of Drug Regulatory Affairs
Ronald G. Van Valen	Global Regulatory Director

#### **FDA/Division of Special Pathogen and Transplant Products (DSPTP):**

Eileen Navarro, MD	Acting Deputy, OND/OAP/DSPTP
Joette Meyer, Pharm.D	Clinical TL, OND/OAP/DSPTP
Ergun Velidedeoglu, MD	Clinical Reviewer, OND/OAP/DSPTP
Shukal Bala, PhD	Micro TL, OND/OAP/DSPTP
Karen Higgins, ScD	Stat TL, OTS/OB/DBIV
LaRee Tracy, PhD	Stat Reviewer, OTS/OB/DBIV
John Yap, PhD	Stat Reviewer, OTS/OB/DBVI
Xiao Ding, PhD	Stat Reviewer, OTS/OB/DBVI
Philip Colangelo, Pharm.D, PhD	Clinical Pharmacology Team Leader, OTS/OCP/DCP4
Kevin Krudys, PhD	Pharmacometrics Reviewer, OTS/OCP
Pravin Jadhav, PhD	Pharmacometrics TL, OTS/OCP
Mina Hohlen	Regulatory Information Specialist, OTS/OCP/PS
Jacquelyn Smith, MA	Project Manager, OND/OAP/DSPTP

## **Background**

Based on a preliminary review of the electronic datasets and clinical study report (CSR) provided for study A2309 included in NDA 21-560, DSPTP had some questions for Novartis that they wanted to discuss as soon as possible. Thus, a teleconference was subsequently scheduled. A preliminary summary of some of the inconsistencies identified, up to the point of the meeting, were sent to Novartis on August 5, 2009; however, DSPTP was still in the process of reviewing the contents of the resubmission. On August 10, 2009, Novartis replied via email to summary of issues.

## **Discussion**

The teleconference began with Novartis sharing their appreciation for the teleconference, followed by introductions. The Division began the discussion by addressing the questions/discrepancies pertaining to data submitted for study A2309, specifically identifying several inconsistencies between the 'listings' and the 'analysis' electronic datasets and between datasets and the clinical study report. The Division explained that the datasets did not follow the format used in prior submissions. Specific to 'analysis' datasets, including efficacy, discontinuation, and entry or enroll, the Division informed Novartis that generally a complete dataset, i.e. all patients in the intent-to-treat population, is preferred.

The Division requested that Novartis re-submit the efficacy.xpt, entry.xpt and enroll.xpt datasets for study A2309 and ensure that these datasets contain complete and accurate information, including outcome at 12-months post-transplant in the efficacy.xpt dataset, for all randomized patients. The Division emphasized the importance of being able to replicate the findings presented in the CSR, particularly the primary efficacy results, using submitted datasets. As such, it is important that accurate and complete study datasets are included in the submission.

There were problems locating the datasets related to Appendix 16.2.5 Report of exposure-efficacy/exposure-safety analyses (Addendum 1 to Clinical Study Report RADOOIA2309). Therefore, the Division requested that Novartis submit all datasets related to the efficacy/exposure-safety analyses along with the SAS code files used for the analyses in the Addendum 1 to Clinical Study Report RADOOIA2309. The Division also requested that Novartis submit the datasets using the same template as used in a previous submission (NDA 21-628, submitted February 27, 2004).

As an action item, the Division sent the template used in NDA 21-628, submitted February 27, 2004 to aid Novartis in preparing the datasets needed for this NDA resubmission.

The Division requested all the available donor information for study A2309, including the last serum creatinine values measured before donation. Additionally, they asked Novartis to calculate the CADI (chronic allograft dysfunction index) scores of the transplanted kidneys based on the baseline biopsies obtained per the study protocol. Novartis responded that it would be possible to send all the donor information collected, including the last serum creatinine values, but stated that it may not be possible to calculate the CADI scores of the transplanted kidneys if some of the information was not collected.

The formats dataset (fmtdat.xpt) submitted by Novartis had missing formats (TROR11 and BCLT11), therefore, the Division requested a new and complete formats dataset from Novartis which can be re-converted back into a formats catalog.

The Division was unable to locate a coding dictionary for the conversion of investigator verbatim terms into preferred terms and requested that Novartis submit, if it had not already been submitted. Novartis agreed to submit the coding dictionary by August 14, 2009.

**Addendum:**

- On August 14, 2009, in response to FDA request, Novartis provided a coding dictionary document containing mappings of the unique investigator verbatim terms to MedDRA preferred terms for all the adverse events included in the 12-month analysis of Study A2309.
- On August 24, 2009, Novartis submitted the replacement tables for A2309 Clinical Study Report.
- On August 28, 2009, in response to FDA Request, Novartis submitted the exposure-response datasets.

\_\_\_\_\_  
Jacquelyn Smith, M.A.  
Regulatory Project Manager

\_\_\_\_\_  
Date

\_\_\_\_\_  
LaRee Tracy, Ph.D.  
Statistics Reviewer

\_\_\_\_\_  
Date

Division of Special Pathogen and Transplant Products  
OAP/OND/CDER/FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

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LAREE A TRACY  
09/08/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** August 5, 2009

**To:** Mr. Ron Van Valen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, MA, Regulatory  
Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560

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**Total no. of pages including cover: 7**

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## NDA 21-560

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Certican (everolimus) Tablets.

Based on a preliminary review of the electronic datasets and clinical study report (CSR) provided for study A2309 included in NDA 21-560, we have some questions we would like to discuss as soon as possible. We are providing a preliminary summary of some of the inconsistencies identified up to this point; however, we are still in the process of reviewing the contents of the submission.

### Statistical

In general, as noted below, we have identified several inconsistencies between the 'listings' and the 'analysis' datasets as well as between datasets and the CSR. Additionally, these datasets do not generally follow the format used in prior submissions. Lastly, specific to analyses datasets, including efficacy, discontinuation, and entry or enroll, we would generally expect a complete dataset, e.g. to include all patients in the ITT population.

1. Please clarify the difference between 'listings' and 'analysis' datasets. Additionally, please clarify which datasets were used to generate results provided in the CSR and other summary reports including in the submission.
2. In an effort to understand the difference between the listings and analysis datasets we compared similar (based on name and/or content) datasets between the two files and found some discrepancies. Please provide clarification for the following.

For instance, the **enroll.xpt** dataset has n=835 unique rows; however there are 3 entries missing a SUBJID. Additionally, the number of patients per treatment group in the enroll.xpt dataset is as follows:

.	3	# no PTID
1	276	
2	279	
3	277	

This indicates that there were n=832 assigned to treatment; however, according to the clinical study report there were n=833 patients in the ITT analysis.

Another example is from the **entry.xpt** dataset. This dataset has n=833 unique SUBJID and the distribution of patients/treatment group based on the entry.xpt dataset is:

1	277
2	279
3	277

Where 1=everolimus 1.5 mg, 2=everolimus 3.0 mg and 3=Myfortic 1.44 g

Please explain the discrepancy between the two datasets and please indicate which dataset was used for the primary analyses.

3. On page 147 of the study A2309 CSR report, the stated number of patients meeting the primary endpoint (composite) at 12-months was 70, 60 and 67 in the everolimus 1.5 mg, everolimus 3.0 mg and Myfortic 1.44 g treatment arms respectively.

Assessment of data provided in the '**efficacy.xpt**' dataset finds that the number of patients experiencing the 12-month primary endpoint (based on the 'event' variable) was 70, 61 and 68 in the everolimus 1.5 mg, everolimus 3.0 mg and Myfortic 1.44 g treatment arms respectively.

Please clarify this discrepancy. Also, we are assuming that the 'event' variable corresponds to the primary endpoint (12-month composite); however, this is not clear in the data definition document.

4. Please explain the variables in the '**RNDTGP.xpt**' dataset. For instance, the variable 'RND1N' is described as the randomization number in the 2309define document. There are n=1650 unique RND1Ns.
5. The screening log datasets, '**scr.xpt**' located in listing file and '**scrlog.xpt**' located in the analysis file contain only n=153 rows. Should this dataset include more patients given that there were n=833 patients included in the study? Please clarify the purpose of this dataset.
6. Please clarify the contents of the discon/completion dataset '**discon.xpt**'. Specifically, this dataset has n=310 unique rows for n=310 unique patients. The breakdown of patients by treatment group in this dataset resulted in n=106, 116 and 88 for the everolimus 1.5, 3.0 and Myfortic groups respectively. However, it is unclear if these data correspond to patients who discontinued treatment or study or neither. We could not match these numbers with information reported in the CSR regarding patient disposition (table 10-1, page 138 for example).
7. For Table 5-1, Renal function (MDRD calculated GFR) at 12 months (page 29 of the Clinical Overview):
  - i. The following table was obtained from the Renal dataset using the ITT population, REVISIT=42 and non-missing values for GFR\_M1:

The MEANS Procedure

Analysis Variable : GFR\_M1 Imputed M12 GFR(MDRD) Method 1

Treatment		
group	N Obs	Mean
1	275	54.5527273
2	278	51.2888489
3	277	52.1781588

Although the means are exactly the same as in Table 5-1 (rounded to two decimal places), the numbers of subjects are different (For Table 5-1, they are 277, 279 and 277 for treatments 1, 2, 3, respectively). Can you please clarify this inconsistency?

- ii. Because some subjects have multiple GFR measurements at some given values of REVISIT, how did you choose a value to use for the calculations?
8. For Table 5-6 Urinary protein to creatinine ratio (page 35 of the Clinical Overview):
- i. Was the spot urine protein/creatinine ratio calculated by dividing the variable USRSLT (Lab result in US unit, in mg/g) by 8.84 (mmol/g) (since 1 mg/mmol=8.84 mg/g, as given at the bottom of Table 5-7 on page 36 of the Clinical Overview)?
  - ii. Did you use the REVISIT variable with REVISIT=1, 5, 6, 8, 10 and 13, which correspond, respectively to Baseline, Day 14, Month 1, Month 3, Month 6, and Month 12 (see page 8 of the “Data Derivation and Handling Methods for Derived Datasets”), to calculate the mean, sd, median and range of the urinary protein to creatinine ratio for each treatment arm? How were the starting day and ending day of the window for each REVISIT chosen or determined?
  - iii. Were the calculations based on the Safety population?
  - iv. Because some subjects have multiple measurements (urinary protein to creatinine ratios) at some given values of REVISIT, how did you choose a value to use for the calculations?
9. For Table 5-23 Lipid parameters across studies (page 54 of the Clinical Overview) and Table 5-7 Lipid parameters across studies – Safety populations – 12 month analysis (page 37 of the Comparative-Safety-Update-Report):
- i. Total cholesterol is given in mmol/L. However, in the lab data set LABB1, the USRSLT variable is given in mg/dL. Can you please provide the conversion formula?
  - ii. Was the variable REVISIT=6, 10, 13 used for Month 1, 6, and 12, respectively for Table 5-23 and REVISIT=6, 8, 10, 12, 13, 32 for Month 1, 3, 6, 9, 12, 12 TEP, respectively for Table 5-7?

- iii. How did you choose one value from multiple measurements, when they occurred?

### **Clinical Pharmacology**

10. We are not able to locate the datasets related to Appendix 16.2.5 Report of exposure-efficacy/exposure-safety analyses (Addendum 1 to Clinical Study Report RAD001A2309). Each of the datasets should include the time-averaged trough concentrations of cyclosporine and everolimus as well as efficacy or safety data variables. Please submit all datasets related to those exposure-efficacy/exposure-safety analyses together with the SAS code files used for the analyses in the Addendum 1 to Clinical Study Report RAD001A2309. If you have provided the datasets already in the NDA resubmission, please indicate the location of the datasets and clarify which data variables were used in each analysis. We also recommend that you clarify how to calculate/generate each data variable (e.g., time-averaged trough concentrations of CsA and everolimus) in the define.pdf file.

### **Clinical**

11. The fmtdat dataset could not be converted directly into a format catalog and it required some manipulations due to duplication of formats. Furthermore, the following formats were missing: TROR11 and BCLT11. Therefore, please re-send the datasets without formats (and likely including a variable on the dataset that is the formatted field – ex: sex-coded variable=1 or 2 and sex-decoded variable=male or female).
12. We are not able to locate a coding dictionary for the conversion of investigator verbatim terms into preferred terms. If you have provided the dictionary in the NDA resubmission, please indicate the location.
13. Please submit a separate dedicated dataset for the analysis proteinuria only. Include columns which show demographic patient data, cause of kidney failure, urine protein, urine albumin, UP/UC ratios, serum creatinine, calculated GFR in standardized units and for different time points so that 0, 1, 3, 6, 9 and 12 month data will be under different columns and each column should contain only one parameter for a specific time point and there should be only one row for each patient. Patients should be grouped together according to their treatment assignments. This dataset should also include as much donor information as possible such as donor demographics, cold ischemia time, biopsy findings if available.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

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/s/  
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JACQUELYN E SMITH  
08/05/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): Dr. John Yap, OTS/OB/DBVI  
SafetyDivisionConsultRequest@fda.hhs.gov

FROM (Name, Office/Division, and Phone Number of Requestor):  
Jacquelyn Smith, PM/Dr. Ergun Velidedeoglu, Clinical  
Reviewer  
Division of Special Pathogen and Transplant Products  
(DSPTP)

DATE  
July 16, 2009

IND NO.

NDA NO.  
21-560

TYPE OF DOCUMENT  
NDA Resubmission

DATE OF DOCUMENT  
June 30, 2009

NAME OF DRUG  
Certican (everolimus)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
Immunosuppressant

DESIRED COMPLETION DATE

NAME OF FIRM: Novartis

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input checked="" type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input checked="" type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE            |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: DSPTP received the resubmission for NDA 21-560, Certican (everolimus) for the indication of prophylaxis of organ rejection in renal transplantation. The letter and receipt date is June 30, 2009. The PDUFA date is December 30, 2009. There will be an Advisory Committee meeting on Dec. 7, 2009.

The EDR link to the resubmission is \\CDSESUB1\EVSPROD\NDA021560\0010.

The pivotal study in this resubmission is RADOOIA2309, A 24-month, multicenter, randomized, open-label noninferiority study of efficacy and safety comparing concentration-controlled Certican in two doses (1.5 and 3.0 mg/day starting doses) with reduced dose Neoral (cyclosporine) versus Myfortic (mycophenolic acid) with standard dose Neoral in de novo renal transplant recipients.

The most important difference with this study and prior studies conducted in the initial NDA is the utilization of TDM (therapeutic drug monitoring) of everolimus. The initial NDA submission in 2002 was for indications in both kidney. The applicant received two approvable letters: first in 2003 (for kidney) and then later in 2004 (for heart). An Advisory Committee in 2005 did not recommend approval of Certican for the heart indication mainly due to unacceptable renal toxicity especially when it is combined with cyclosporine (no TDM).

Certican is an MTOR inhibitor, similar to sirolimus (Rapamune). The major safety concerns for the MTOR inhibitors are delayed wound healing after surgery, wound dehiscences, hernias, proteinuria, fluid collections in different compartments in the body (lymphocelle, pleural and pericardial effusions, peripheral edema), hyperlipidemia, stomatitis (oral ulcers), pneumonia, viral infections (CMV, BK virus), all infections in general, and malignancies.

Of note, the applicant is requesting approval of everolimus at a dose of 1.5 mg per day. The higher dose (3.0 mg) does not appear to have acceptable safety results for consideration for approval.

We request your help in the analysis of the safety data in this resubmission focusing on Study 2309 giving special emphasis to the well-known following issues:

- 1 - Evaluate whether or not there is an increase over the duration of the study (1 year) in the degree of proteinuria or hyperlipidemia on an individual patient basis in the everolimus arms compared to the cyclosporine arm adjusting for baseline differences.
- 2 - Evaluate the decrease in GFR over time, in the same manner as in number 1 above.
- 3 - Evaluate whether there are any subgroups of patients, based on baseline factors, who are more likely to develop worse proteinuria or lower GFR at the end of one year in the everolimus arms?
- 4 - Perform outlier analyses evaluating degree of proteinuria, GFR, and hyperlipidemia in the everolimus arms compared to the cyclosporine arm.
- 5 - Evaluate whether degree of renal function impairment (as assessed by GFR) is associated with degree of proteinuria.

SIGNATURE OF REQUESTOR Jacquelyn Smith, PM	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Jacquelyn Smith  
7/16/2009 09:12:37 AM

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Risk Management (DRISK)**  
**Claudia Karwoski, DD/Darrell Jenkins, RPM**

FROM (Name, Office/Division, and Phone Number of Requestor):

**Jacquelyn Smith, PM/Dr. Ozlem Belen, DDS**  
**Division of Special Pathogen and Transplant Products (DSPTP)**

DATE  
**July 1, 2009**

IND NO.

NDA NO.  
**21-560**

TYPE OF DOCUMENT

DATE OF DOCUMENT  
**June 30, 2009**

NAME OF DRUG  
**Certican (everolimus)**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
**Immunosuppressant**

DESIRED COMPLETION DATE  
**November 2, 2009**

NAME OF FIRM: **Novartis**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** DSPTP received the resubmission for NDA 21-560, Certican (everolimus) (seeking indication for the prophylaxis of organ rejection in renal transplantation) in eCTD format via Gateway. The letter and receipt date is June 30, 2009. The PDUFA date is December 30, 2009.

A proposal for REMS was included in the resubmission. The elements of the proposed REMS include the Medication Guide and a communication plan. For your convenience, the EDR link to access Novartis' REMS proposal is \\CDSESUB1\EVSPROD\NDA021560\001. There will be Advisory Committee held on December 7, 2009.

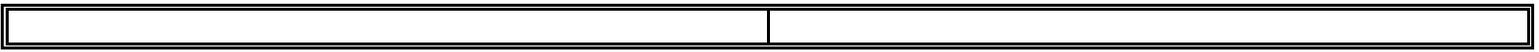
SIGNATURE OF REQUESTOR  
**Jacquelyn Smith, PM**

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER



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/s/

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Jacquelyn Smith  
7/1/2009 03:58:59 PM

## Teleconference Minutes

**Teleconference Date:** June 15, 2009  
**Application Number:** NDA 21-560  
**Name of Drug:** Certican® (everolimus) Tablets  
**Sponsor:** Novartis Pharmaceuticals Corporation  
**Type of Meeting:** Teleconference  
**Meeting Chair:** Joette Meyer, Pharm.D.  
**Minutes Preparer:** Jacquelyn Smith, M.A.

### **Attendees:**

#### **Novartis Pharmaceuticals:**

Marc Lorber, M.D., Global Program Head  
Kevin Mange, M.D., Medical Franchise Head  
Catherine Cornu-Artis, M.D., Global Brand Medical Director  
Luen (Steve) Lee, Ph.D., Statistics  
Hia Jiang, Ph.D., Project Lead Statistician  
Paula Chu, Global Program Director  
Ronald Van Valen, Global Program Regulatory Director

#### **Division of Special Pathogen and Transplant Products (DSPTP):**

Joette Meyer, Pharm.D., Clinical Team Leader  
Ergun Velidedeoglu, M.D., Clinical Reviewer  
Jacquelyn Smith, M.A., Regulatory Health Project Manager

### **Discussion**

The teleconference began with discussion of whether or not an additional 120-day Safety Update would be required for the Certican kidney transplant NDA resubmission. Novartis asked the Division's guidance on this issue during the May 6, 2009 meeting.

DSPTP requested clarification on the submission date of the Certican NDA for the kidney transplant indication resubmission and the 24 month report of the pivotal Study A2309: Novartis replied that the planned date of NDA submission is June 30, 2009 as stated previously.

DSPTP asked when the last patient visit for the 24 month data would be completed and when this 24 month data of study A2309 would be ready for submission. Novartis replied that the last

patient visit for the 24 month data would be completed in September 2009 and the data would be ready for submission in January 2010.

DSPTP acknowledged that a standard NDA review period of 10 months would typically include a 120-day safety update. However in this case, with a re-submission of the NDA with a new clinical study in response to an approvable letter, the NDA review period is 6 months. As a consequence DSPTP may not have enough time to review the 120 day safety update which will be submitted only 2 months prior to the due date of the NDA. In lieu of a 120-day safety update, DSPTP requested that Novartis submit new safety information only for patients who die during the 12-24 month follow-up period and that any additional information on patient deaths be submitted during the NDA review as the information becomes available.

DSPTP asked about the cut-off date for the information contained in the NDA resubmission. Novartis replied that the database lock was in January 2009 for the 12 month study report, however, the NDA resubmission will contain additional data up to April 24, 2009 on any additional patient deaths with accompanying narratives.

DSPTP responded that this was useful information and also reiterated the request that Novartis submit to the NDA any additional patient deaths with narratives on an ongoing basis until the last patient visit is completed for the 24 month portion of the study in September 2009. Novartis agreed to this request and offered to evaluate the feasibility of submitting either by individual cases or other frequency (eg. bi-weekly) to support the Division's review.

The Division requested that Novartis provide the list of study A2309 investigators so the Division can start evaluating a potential list of experts and to exclude those with conflicts of interest for a possible advisory committee (AC) meeting. Novartis asked if the Division had decided on having an AC meeting. The Division responded that no decision has been made at this time, but it takes advance planning to sort out all the logistics. It is anticipated that the Division will make a decision by the August planning meeting if an AC meeting is required and the timing. Novartis stated that a list of study investigators will be submitted with the clinical study report on June 30.

**Addendum:** A list of study A2309 US investigators, including affiliation, role and the number of subjects enrolled per site were submitted to the Division via email on June 23, 2009.

The teleconference ended amicably.

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/s/

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Jacquelyn Smith  
6/30/2009 02:14:15 PM  
CSO

Joette Meyer  
6/30/2009 02:30:23 PM  
MEDICAL OFFICER



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 28, 2009

**To:** Ron VanValen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560/REMS

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**Total no. of pages including cover: 6**

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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NDA 21-560

Dear Mr. Van Valen,

Please refer to NDA 21-560, Certican (everolimus), specifically as it relates to submitting a risk evaluation and mitigation strategy (REMS).

In your submission dated 10/23/2008, you indicated that you will submit a (REMS) for the Division's review. If you are planning to include a REMS proposal in the Certican NDA resubmission, please note the following.

**A complete review of the full risk management plan after the NDA is resubmitted will be necessary to determine whether it is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA. If you plan to submit a Risk Evaluation and Mitigation Strategy (REMS) with the NDA resubmission, please submit all planned materials identified within the plan that will be necessary to implement your proposal. Education provided as part of a REMS should emphasize the safety messages important for the safe use of the product. Product marketing materials generally are not appropriate to educate about product risks.**

We are including a template to help you in preparing and submitting all the necessary information needed to review your REMS proposal.

The above information is being provided by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

Enclosure: REMS Template

## **APPENDIX A: REMS TEMPLATE**

*If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.*

### **Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

#### **I. GOAL(S):**

List the goals and objectives of the REMS.

#### **II. REMS ELEMENTS:**

##### **A. Medication Guide or PPI**

*If a Medication Guide is included in the proposed REMS, include the following:*

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

##### **B. Communication Plan**

*If a Communication Plan is included in the proposed REMS, include the following:*

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

##### **C. Elements To Assure Safe Use**

*If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:*

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

- A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

#### **D. Implementation System**

*If an Implementation System is included in the proposed REMS, include the following:*

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

#### **E. Timetable for Submission of Assessments**

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

## **APPENDIX B: SUPPORTING DOCUMENT**

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
  - a. Additional Potential Elements
    - i. Medication Guide
    - ii. Patient Package Insert
    - iii. Communication Plan
  - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
  - c. Implementation System
  - d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

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/s/

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Jacquelyn Smith  
5/28/2009 02:30:40 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

Novartis Pharmaceutical Corporation  
Attention: Mr. Ronald Van Valen  
Global Program Regulatory Director  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Certican (everolimus) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on May 6, 2009. The purpose of the meeting was to discuss the 12 month results of Phase 3 kidney transplant study, CRAD001 A2309 and obtain feedback on final proposals for resubmission of the NDA.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Ms. Jacquelyn Smith at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and  
Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes  
Study CRAD001 A2309 Presentation

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** May 6, 2009

**TIME:** 1:00 PM

**LOCATION:** 10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Building #22, RM 1419

**APPLICATION:** NDA 21-560

**DRUG NAME:** Certican (everolimus)

**INDICATION:** Kidney Transplantation

**TYPE OF MEETING:** C

**MEETING CHAIR:** Renata Albrecht, M.D.

**MEETING RECORDER:** Jacquelyn Smith, M.A.

### FDA Attendees

Renata Albrecht, M.D., Director, DSPTP  
Eileen Navarro, M.D., Acting Deputy Director, DSPTP  
Ergun Velidedeoglu, M.D., Clinical Reviewer, DSPTP  
Patrick Archdeacon, M.D., Clinical Reviewer, DSPTP  
Marc Cavaille-Coll, M.D., Clinical Reviewer, DSPTP  
John Lazor, Ph.D., Director, OCP, DCP4  
Dakshina Chilukuri, Ph.D., Clinical Pharmacology Reviewer, OCP, DCP4  
Karen Higgins, Sc.D., Statistics Team Leader, DSPTP  
LaRee Tracy, M.A., Statistical Reviewer, DSPTP  
Sherry Spriggs, M.P.H., Regulatory Health Project Manager, DSPTP  
Jacquelyn Smith, M.A., Regulatory Health Project Manager, DSPTP

### Novartis Attendees

Marc Lorber, M.D., Global Program Head  
Kevin Mange, M.D., Medical Franchise Head  
Catherine Cornu-Artis, M.D., Global Brand Medical Director  
Hia Jiang, Ph.D., Project Lead Statistician  
Zailong Wang, Ph.D., Project Statistician  
Paula Chu, Global Program Director  
John Cutt, Ph.D., US Head of Drug Regulatory Affairs  
Chin Koerner, Ph.D., Regulatory

Luen (Steve) Lee, Ph.D., Statistics  
Ronald Van Valen, Global Program Regulatory Director

**BACKGROUND:**

Novartis submitted a request for meeting to discuss the 12 month results of the Phase 3 kidney transplant study, A2309 and to obtain feedback on final proposals for resubmission of the NDA. Preliminary responses to the questions included in the briefing package was emailed to Novartis on May 4, 2009.

**MEETING OBJECTIVES:**

The purpose of the face-to-face meeting is to discuss the 12 month results of Phase 3 kidney transplant study A2309 and to obtain feedback on final proposals for resubmission of the Certican NDA for kidney transplantation.

**DISCUSSION:**

Attendees introduced themselves. Novartis thanked FDA for their preliminary responses to the questions submitted in the briefing package. Novartis began their presentation with the proposed agenda, followed by their objectives for the meeting. Novartis also gave a brief discussion on the regulatory chronology. The presentation continued with a list of key issues to assess the primary and secondary endpoints and preliminary safety results of Study A2309 in terms of whether it could serve as a complete response to NDA 21-560. A copy of the presentation is included in the minutes for a more detailed reference. Discussion of the preliminary responses to Novartis' questions is also included, followed by the meeting discussion presented in *italics*.

**Question 1:**

Does the Division agree that the various analyses of the primary efficacy endpoint (treated BPAR, graft loss, death or loss to follow-up) demonstrate that Certican in a regimen with reduced dose Neoral is non-inferior to the myfortic and standard dose Neoral group?

**FDA Response:**

**Preliminary results provided in the meeting briefing document suggest that the non-inferiority objective was achieved; however, a detailed review and assessment of the completed A2309 study is necessary in order to conclude that one or both Certican regimens is non-inferior to the active control.**

**Additionally, either in the resubmission or as a separate submission to the IND, please provide a detailed quantitative justification for the chosen 10% non-inferiority margin used in study A2309.**

*Novartis asked for clarification regarding an acceptable NI margin.*

*The Division recommended that Novartis use an approach similar to that taken to justify the NI margin for the AEB071 study. Given that Myfortic was used in this trial and the published*

*literature summarized studies that used Cellcept, consider including how the efficacy of CellCept is equivalent to that of Myfortic.*

**Question 2:**

Does the Division agree that the various analyses of the renal function endpoint appropriately show non-inferiority and that these results are acceptable for NDA resubmission?

**FDA Response:**

**The Division does not consider non-inferiority approaches appropriate for evaluation of renal function in kidney transplantation. Additionally, the Division did not agree to the chosen renal function non-inferiority margin. Ultimately evaluation of the renal function including different key components such as proteinuria will be a review issue, data on efficacy endpoints will be assessed to determine if a favorable benefit to risk ratio was achieved. Although GFR is an important component of renal function, proteinuria is also another component and is an important marker of kidney injury and a predictor of graft survival. While on the surface the results based on GFR may seem acceptable for a resubmission, the review will closely assess whether the reduction in CNI nephrotoxicity is offset by a different and equally concerning type of nephrotoxicity such as proteinuria. In table 11-9 of the summary report for study 2309 there seems to be a trend towards progressive increase of proteinuria in both the 3mg and the 1.5mg Certican arms compared to the Myfortic arm starting at month 6. Since we only have data up to 12 months it is not possible to say if this differential increase in proteinuria will continue over time but it is known that this is a class effect of M-TOR inhibitors and may require treatment with ACE inhibitors in some cases.**

*Novartis asked for clarification.*

*The Division commented that assessing the data at a single time point is misleading, and recommended that Novartis evaluate the full range of the data as well as the means and medians. In addition, review of subgroups and outliers will help the Division to evaluate the data better. It was suggested the data be analyzed using mixed effects modeling and a time-to-event approach to account for the longitudinal nature of the data. Also, it was suggested Novartis consider assessing the data with respect to baseline values using ANCOVA. Differential change over time especially compared to baseline values, is more informative than values at a particular point in time for the evaluation of both GFR and proteinuria.*

**Question 3:**

Does the Division agree that study results show a reasonable compliance with everolimus and cyclosporine drug levels to support safe dose recommendations?

**FDA Response:**

**We noticed that the proportion of patients whose CsA concentrations were within the target ranges was declining as a function of time in the everolimus arms. In other words, during Months 3 and above, for the majority of patients, the CsA concentrations were actually above the target ranges for both everolimus treatment arms. In comparison the Myfortic group of patients had a higher proportion of patients whose CsA concentrations were within the target range throughout the study.**

**We recommend that you perform exposure-response analyses as a function of both CsA and everolimus concentrations in the resubmission, as you had previously performed in NDAs 21-560 and 21-628 (three-dimensional plots to describe the relationship of CsA and everolimus concentrations vs. effectiveness and safety endpoints).**

*Novartis asked for clarification.*

*The Division clarified that such plots will be useful to assess the relationship between exposure of CsA and everolimus in relation to the effectiveness and safety.*

**Question 4:**

Does the Division agree that preliminary safety results suggest an acceptable profile for recommending use of Certican in kidney transplantation?

**FDA Response:**

**In this 1:1:1 randomized study the total number of deaths are 9, 7 and 6 in the 3mg , 1.5mg and the Myfortic arms respectively. In the Myfortic arm one of the deaths is due to a traffic accident and one more is listed as caused by “injury, poisoning and procedural complications”. Before having the narratives of these cases it is not possible to say to what extent these deaths are related to the treatment regimens. In the Certican heart transplant study 2310 which utilized similar treatment arms and regimens as in this study, the 3mg arm was terminated early due to three times as many deaths compared to the control arm. We see a similar trend in this study as well in the 3mg Certican arm, and if the same trend exists in the 1.5 mg arm remains to be seen.**

**Drug discontinuations due to adverse events in the Certican arms are approximately twice as many as in the control arm (18%, 20% vs 9%). The summary data suggests that there may be an advantage in favor of the Certican arms regarding the incidence of leucopenia, CMV and BK virus infections and neoplasms but a disadvantage regarding proteinuria, hypercholesterolemia, peripheral edema, wound problems, lymphocele and mouth ulcers. Wound complications requiring surgery were seen in 19 and 24 patients in the 1.5 mg and 3 mg arms vs. 10 patients in the Myfortic arm. Although the preliminary results do not suggest an acceptable safety profile for any of the Certican arms ultimately this will be a review issue. The Division requests additional information about the cases with interstitial lung disease and FSGS if available.**

*Novartis asked for clarification.*

*In order to facilitate an adequate review of the safety information, the Division asked Novartis to provide as much detail as possible about the adverse events and deaths to be able to evaluate the rate between the study arms. Because accessing cause of death in transplant patients is difficult, detailed narratives on patients who died should be provided for review. Information on serious adverse events should be detailed, for example, include information on the severity, timing, duration, management, and outcome of the event.*

**Question 5:**

Do the Division statisticians have any further comments on the revised Statistical Analysis Plan? Does the Division recommend analysis beyond those in the SAP version 2.0 to further characterize the safety profile of Certican?

**FDA Response:**

**The division would like to see the detailed narratives of the deaths, lost to follow-up cases, drug discontinuations and detailed analyses of the cases with proteinuria, hyperlipidemia and peripheral edema including the percentage of patients with high end values. A detailed description of the methodology utilized in the assessment of UP/UC ratio and the definitions of CMV and BK virus infections will also be helpful. The Division also requests a grading system be utilized for cases with peripheral edema if this was included in the CRFs.**

*Novartis asked for further discussion.*

*Novartis asked if the Division could provide additional guidance on specific analysis for proteinuria, hyperlipidemia and peripheral edema. The Division replied that the peripheral edema grading system currently in use in clinical practice (grade 0-4) is generally inadequate for assessing the severity of the edema accurately, however, if a grading system was utilized as part of the protocol and data captured in the CRFs, such information should be provided in the datasets. As part of the analysis, provide information on any drugs used to treat these adverse events. For example, provide information on the use of products such as ACE inhibitors to manage proteinuria, or statins to manage hyperlipidemia, including the timing relative to the adverse event when these were started (or dosing changed) and any amelioration/resolution of the adverse event after drug initiation.*

*Additionally, Novartis noted that they are still attempting to collect follow-up information on patients lost to follow-up patients. It was acknowledged that loss to follow-up in study was largely due to regulatory restrictions (e.g. inability to contact patients who withdraw from study) at some of the participating clinical sites (e.g Europe).*

**Question 6:**

Do the Division medical reviewers want a similar evaluation of wound healing and related complications to that presented in the recent publication by Tiong HY, et. al. (Transplantation 2009)

**FDA Response:**

**The analysis method used in the Tiong paper is not very helpful in assessing the cases with wound dehiscences including superficial and fascial dehiscences and eviscerations. If Novartis prefers to do a similar analysis in addition to the standard analysis of wound related complications this will be considered as supportive.**

*Novartis asked if there were any additional recommendations from the Division.*

*The Division stated that a standard analysis of the wound related complications (including complete information on various findings such as dehiscence, evisceration, and need for surgery) as provided in the background material is preferred. The methodology used in Tiong paper does not take into account wound eviscerations and does not provide sufficient information on wound healing complication. The overall incidence of wound related complications requiring surgical treatment is an important indicator of the severity of the wound healing problem. Therefore, wound dehiscences, eviscerations and infections requiring surgery should be included in the evaluation. Fascial dehiscences need to be distinguished and reported separately from cases of more superficial skin level dehiscences.*

**Question 7:**

Will the Division accept a Clinical Overview (eCTD Module 2.5) providing summary information without an accompanying separate Summary of Clinical Efficacy and Summary of Clinical Safety?

**FDA Response:**

**This approach is acceptable.**

*The Division further clarified that both the efficacy and the safety summaries need to be extensive and comprehensive.*

*Novartis asked whether a 120 day safety update needed to be submitted. The Division responded that it will follow up with Novartis after further internal discussion.*

*The Division asked how many patients completed the 24 month follow-up, and Novartis stated that all the patients enrolled in the study will have completed their final evaluations by September 2009.*

*The Division suggested that the justification for the NI margin can be submitted early to the IND.*

**Additional Comment:**

Please plan to submit analysis data sets with this NDA submission. These analysis data sets should contain both source and derived variables and allow for easy recreation of analyses related to primary and safety objectives.

*This was acknowledged by Novartis.*

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/s/

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Renata Albrecht  
6/5/2009 07:39:22 PM



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 4, 2009

**To:** Ron VanValen, Director, Drug Regulatory Affairs

**From:** Jacquelyn Smith, Project Manager

**Company:** Novartis

Division of Special Pathogen and Transplant Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Subject:** NDA 21-560/ Preliminary responses for 050609 meeting

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**Total no. of pages including cover: 6**

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notify us immediately by telephone at 301-796-1600 Thank you.**

The following are the Division's responses to the briefing package submitted April 3, 2009. We anticipate there will be further discussion of our responses to your questions and our additional comments at the meeting on Wednesday, May 6, 2009. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these comments. Please note that if there are any major changes to your proposed plan/to the purpose of the meeting/to the questions, based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting.

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### Responses to Novartis' Questions

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**NDA:** 21-560  
**Drug:** Certican (everolimus)  
**Applicant:** Novartis  
**Meeting Date:** May 6, 2009  
**Meeting Time:** 1:00-2:00 PM

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**Background:** Novartis submitted a request for meeting to discuss the 12 month results of the Phase 3 kidney transplant study, A2309 and to obtain feedback on final proposals for resubmission of the Certican NDA for kidney transplantation.

**Question 1:**

Does the Division agree that the various analyses of the primary efficacy endpoint (treated BPAR, graft loss, death or loss to follow-up) demonstrate that Certican in a regimen with reduced dose Neoral is non-inferior to the myfortic and standard dose Neoral group?

**FDA Response:**

**Preliminary results provided in the meeting briefing document suggest that the non-inferiority objective was achieved; however, a detailed review and assessment of the completed A2309 study is necessary in order to conclude that one or both Certican regimens is non-inferior to the active control.**

**Additionally, either in the resubmission or as a separate submission to the IND, please provide a detailed quantitative justification for the chosen 10% non-inferiority margin used in study A2309.**

**Question 2:**

Does the Division agree that the various analyses of the renal function endpoint appropriately show non-inferiority and that these results are acceptable for NDA resubmission?

**FDA Response:**

**The Division does not consider non-inferiority approaches appropriate for evaluation of renal function in kidney transplantation. Additionally, the Division did not agree to the chosen renal function non-inferiority margin. Ultimately evaluation of the renal function including different key components such as proteinuria will be a review issue, data on efficacy endpoints will be assessed to determine if a favorable benefit to risk ratio was achieved. Although GFR is an important component of renal function, proteinuria is also another component and is an important marker of kidney injury and a predictor of graft survival. While on the surface the results based on GFR may seem acceptable for a resubmission, the review will closely assess whether the reduction in CNI nephrotoxicity is offset by a different and equally concerning type of nephrotoxicity such as proteinuria. In table 11-9 of the summary report for study 2309 there seems to be a trend towards progressive increase of proteinuria in both the 3mg and the 1.5mg Certican arms compared to the Myfortic arm starting at month 6. Since we only have data up to 12 months it is not possible to say if this differential increase in proteinuria will continue over time but it is known that this is a class effect of M-TOR inhibitors and may require treatment with ACE inhibitors in some cases.**

**Question 3:**

Does the Division agree that study results show a reasonable compliance with everolimus and cyclosporine drug levels to support safe dose recommendations?

**FDA Response:**

**We noticed that the proportion of patients whose CsA concentrations were within the target ranges was declining as a function of time in the everolimus arms. In other words, during Months 3 and above, for the majority of patients, the CsA concentrations were actually above the target ranges for both everolimus treatment arms. In comparison the Myfortic group of patients had a higher proportion of patients whose CsA concentrations were within the target range throughout the study.**

**We recommend that you perform exposure-response analyses as a function of both CsA and everolimus concentrations in the resubmission, as you had previously performed in NDAs 21-560 and 21-628 (three-dimensional plots to describe the relationship of CsA and everolimus concentrations vs. effectiveness and safety endpoints).**

**Question 4:**

Does the Division agree that preliminary safety results suggest an acceptable profile for recommending use of Certican in kidney transplantation?

**FDA Response:**

**In this 1:1:1 randomized study the total number of deaths are 9, 7 and 6 in the 3mg , 1.5mg and the Myfortic arms respectively. In the Myfortic arm one of the deaths is due to a traffic accident and one more is listed as caused by “injury, poisoning and procedural complications”. Before having the narratives of these cases it is not possible to say to what extent these deaths are related to the treatment regimens. In the Certican heart transplant study 2310 which utilized similar treatment arms and regimens as in this study, the 3mg arm was terminated early due to three times as many deaths compared to the control arm. We see a similar trend in this study as well in the 3mg Certican arm, and if the same trend exists in the 1.5 mg arm remains to be seen.**

**Drug discontinuations due to adverse events in the Certican arms are approximately twice as many as in the control arm (18%, 20% vs 9%). The summary data suggests that there may be an advantage in favor of the Certican arms regarding the incidence of leucopenia, CMV and BK virus infections and neoplasms but a disadvantage regarding proteinuria, hypercholesterolemia, peripheral edema, wound problems, lymphocele and mouth ulcers. Wound complications requiring surgery were seen in 19 and 24 patients in the 1.5 mg and 3 mg arms vs. 10 patients in the Myfortic arm. Although the preliminary results do not suggest an acceptable safety profile for any of the Certican arms ultimately this will be a review issue. The Division requests additional information about the cases with interstitial lung disease and FSGS if available.**

**Question 5:**

Do the Division statisticians have any further comments on the revised Statistical Analysis Plan? Does the Division recommend analysis beyond those in the SAP version 2.0 to further characterize the safety profile of Certican?

**FDA Response:**

**The division would like to see the detailed narratives of the deaths, lost to follow-up cases, drug discontinuations and detailed analyses of the cases with proteinuria, hyperlipidemia and peripheral edema including the percentage of patients with high end values. A detailed description of the methodology utilized in the assessment of UP/UC ratio and the definitions of CMV and BK virus infections will also be helpful. The Division also requests a grading system be utilized for cases with peripheral edema if this was included in the CRFs.**

**Question 6:**

Do the Division medical reviewers want a similar evaluation of wound healing and related complications to that presented in the recent publication by Tiong HY, et. al. (Transplantation 2009)

**FDA Response:**

**The analysis method used in the Tiong paper is not very helpful in assessing the cases with wound dehiscences including superficial and fascial dehiscences and eviscerations. If Novartis prefers to do a similar analysis in addition to the standard analysis of wound related complications this will be considered as supportive.**

**Question 7:**

Will the Division accept a Clinical Overview (eCTD Module 2.5) providing summary information without an accompanying separate Summary of Clinical Efficacy and Summary of Clinical Safety?

**FDA Response:**

**This approach is acceptable.**

**Additional Comment:**

Please plan to submit analysis data sets with this NDA submission. These analysis data sets should contain both source and derived variables and allow for easy recreation of analyses related to primary and safety objectives.

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Jacquelyn Smith  
5/4/2009 11:05:35 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-560

Novartis Pharmaceuticals Corporation  
ATTENTION: Mr. Ronald G. Van Valen  
Executive Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) file for Certican (everolimus) Tablets.

We also refer to your March 20, 2009 correspondence requesting a meeting to discuss the 12 month results of the Phase 3 kidney transplant study, A2309 and to obtain feedback on final proposals for resubmission of the Certican NDA for kidney transplantation.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: May 6, 2009  
Time: 1:00 PM-2:00 PM EST  
Location: 10903 New Hampshire Avenue  
Building # 22  
Silver Spring, MD 20993

**CDER Participants:**

**Division of Special Pathogen and Transplant Products**

Renata Albrecht, M.D.	Director
Eileen Navarro, M.D.	Acting Deputy Director
Joette Meyer, Pharm.D.	Acting Clinical Team Leader
Ergun Velidedeoglu, M.D.	Clinical Reviewer
Patrick Archdeacon, M.D.	Clinical Reviewer
Philip M. Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader
Dashina Chilukuri, Ph.D.	Clinical Pharmacology Reviewer
Laree Tracy, M.A.	Statistics Reviewer
Karen M. Higgins, Sc.D.	Statistics Team Leader
Jacquelyn Smith, M.A.	Regulatory Health Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at [jacquelyn.smith@fda.hhs.gov](mailto:jacquelyn.smith@fda.hhs.gov) so that I can give the security staff time to prepare temporary badges in advance.

We acknowledge receiving your briefing package on April 6, 2009. It has been distributed to our review team.

Prior to the meeting date, we will send an email addressing the questions in your meeting package. If the responses we provide in the email satisfactorily address your questions and you believe the meeting is no longer needed, please contact me at (301) 796-1002 to cancel the meeting.

If you have any questions, please call me at (301) 796-1002.

Sincerely,

*{See appended electronic signature page}*

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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Jacquelyn Smith  
4/9/2009 08:58:03 AM

**Mesmer, Deborah**

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**From:** Mesmer, Deborah  
**Sent:** Friday, January 16, 2009 10:41 AM  
**To:** 'jane.xiang@novartis.com'  
**Subject:** RE: NDA 22334 CMC Amendment in relation to PAI

Dear Dr. Xiang,

Thank you for the update and courtesy copies regarding your CMC amendment to the pending NDA 22334 Afinitor. Please also amend your NDA 21560 with the new drug substance information.

Please acknowledge receipt of this request, and call me at the number below if you have any questions.

Sincerely,

Debbie Mesmer

Deborah Mesmer  
Regulatory Health Project Manager  
FDA/CDER  
Office of New Drug Quality Assessment  
Division of Pre-Marketing Assessment III and Manufacturing Science  
301-796-4023  
deborah.mesmer@fda.hhs.gov

1/27/2009

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Deborah M Mesmer  
1/27/2009 03:35:27 PM

## Teleconference Minutes

**Teleconference Date:** December 17, 2008  
**Application Number:** NDA 21-560  
**Name of Drug:** Certican® (everolimus) Tablets  
**Sponsor:** Novartis Pharmaceuticals Corporation  
**Type of Meeting:** Teleconference  
**Meeting Chair:** Philip Colangelo, PharmD, Ph.D.  
**Minutes Preparer:** Jacquelyn Smith, M.A.

### Attendees:

#### Novartis Pharmaceuticals:

Ronald G. Van Valen      Drug Regulatory Affairs  
John M. Kovarik          Expert, Drug Metabolism and Pharmacokinetics

#### FDA/Division of Special Pathogen and Transplant Products:

Philip Colangelo, PharmD, Ph.D.      Clinical Pharmacology Team Leader, DCP4  
Dakshina Chilukuri, Ph.D.              Clinical Pharmacology Reviewer, DCP4  
Jacquelyn Smith, M.A.                    Regulatory Health Project Manager

### Background

During the November 24, 2008 teleconference, Novartis asked for a follow-up meeting to discuss the following issue in the August 27, 2004 approvable letter regarding the half life of everolimus: *“Although not a condition of approval, we strongly recommend that you continue to adequately determine the terminal t1/2 of everolimus in the target population following the administration of the proposed everolimus-cyclosporine regimen...”* FDA agreed to schedule the meeting.

### Meeting Objectives

The meeting objectives were to address Novartis’ request for clarification of the everolimus half-life issue concerning the resubmission of the proposed Certican NDA for kidney transplantation.

### Discussion

The teleconference began with Novartis sharing their appreciation for the teleconference. The discussion began with FDA addressing the issue Novartis requested clarification on.

The meeting discussion is presented in *italics*.

*The FDA Clinical Pharmacology recommendation in the August 27, 2004 Approvable Letter was discussed. Specifically, Novartis was asked to adequately determine the half-life of everolimus at steady state in kidney transplant patients who are receiving cyclosporine together with Certican as the to-be-marketed tablet formulation or a formulation that is bioequivalent to the to-be-marketed formulation.*

*It was discussed to use the everolimus half-life estimates from Study W101 from the two cohorts of kidney transplant patients who received single doses of 0.75 mg or 2.5 mg everolimus during steady-state treatment with cyclosporine (based on individual half-life values from the total of 12 patients in the two dose cohorts). These dose levels were chosen because they are the most clinically relevant and they are in a dose range in which the pharmacokinetics of everolimus are linear. The capsule formulation used in study W101 was not linked to the to-be-marketed formulation with a bioequivalence study. However, since the elimination half-life of a drug is formulation independent for drugs administered from oral immediate-release formulations, these data are considered acceptable as relevant for determination of everolimus  $t_{1/2}$ .*

*FDA recommended that the everolimus half-life be expressed in product labeling as a range using mean  $\pm$  s.d., plus the range of half-life estimates, along with an accompanying description of the supporting clinical trial W101.*

***Action Item:***

*FDA requested that Novartis submit a listing of the individual half-life data in addition to the summary statistics mentioned above from original NDA study W101 together with the new clinical study to the Certican kidney transplant NDA 21560 submission planned in 2Q 2009.*

*Novartis also offered to provide a summary of the teleconference.*

*The teleconference ended amicably.*

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/s/

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Jacquelyn Smith  
2/5/2009 03:53:58 PM  
CSO

Phil Colangelo  
2/5/2009 04:07:31 PM  
BIOPHARMACEUTICS



NDA 21-560

Novartis Pharmaceutical Corporation  
Attention: Mr. Ronald Van Valen  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Certican (everolimus) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on November 24, 2008. The purpose of the meeting was respond to your November 21, 2008 email request for clarification on several issues concerning your proposals for the Certican Kidney transplant NDA resubmission. A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Ms. Jacquelyn Smith at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and  
Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

## Teleconference Minutes

**Teleconference Date:** November 24, 2008  
**Application Number:** NDA 21-560  
**Name of Drug:** Certican® (everolimus) Tablets  
**Sponsor:** Novartis Pharmaceuticals Corporation  
**Type of Meeting:** Teleconference  
**Meeting Chair:** Renata Albrecht, M.D.  
**Minutes Preparer:** Jacquelyn Smith, M.A.

### **Attendees:**

#### **Novartis Pharmaceuticals:**

Kenneth Somberg, M.D.	US Head of Drug Regulatory Affairs
Kevin Mange, M.D.	Global Brand Medical Director
Marc Bouiller, PhD	Global Program Director
Marc Lorber, M.D.	Global Program Head
Steve Lee, Ph.D.	Global Head, Biostatistics
Catherine Cornu-Artis, MD	Certican Global Brand Medical Director
Zailong Wang, PhD	Certican Kidney Project Statistician
John Cutt, PhD	US Head of Drug Regulatory Affairs
Ronald G. Van Valen	Certican Global Regulatory Director

#### **FDA/Division of Special Pathogen and Transplant Products:**

Renata Albrecht, M.D.	Director
John Lazor, Ph.D.	Director, Clinical Pharmacology
Ergun Velidedeoglu, M.D.	Clinical Reviewer
Philip Colangelo, Ph.D.	Clinical Pharmacology Team Leader
Dakshina Chilukuri, Ph.D.	Clinical Pharmacology Reviewer
Karen Higgins, Sc.D.	Statistics Team Leader
LaRee Tracy, M.A.	Statistical Reviewer
Sherry Spriggs, M.P.H	Regulatory Health Project Manager
Jacquelyn Smith, M.A.	Regulatory Health Project Manager

### **Background**

On August 21, 2008 Novartis submitted a request for a meeting to discuss their proposals and timeline for resubmission of the Certican NDA for kidney transplantation. FDA met internally to

discuss the questions and provide responses. On November 20, 2008 Novartis' received FDA's preliminary responses to the questions included in their October 23, 2008 briefing package. After review, Novartis determined that a face-to face meeting was unnecessary, but a brief teleconference to get clarification on several questions would suffice. At Novartis' request, a teleconference was held.

### **Meeting Objectives**

The meeting objectives are to address Novartis' request for clarification of several questions concerning the resubmission of proposed Certican NDA for kidney transplantation.

### **Discussion**

The teleconference began with Novartis sharing with the review team their appreciation for the teleconference, followed by introductions of all attendees. The discussion began with FDA addressing the questions Novartis requested clarification on. The meeting discussion is presented in *italics*.

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#### **2.3.1.5 Benefit/risk assessment for kidney transplant NDA resubmission**

##### **Novartis comments Nov. 21, 2008:**

Does the Division's response imply there are no additional comments on the Statistical Analysis Plan for study A2309 submitted in April 2008 (IND 52,003; serial no. 724)? Or, should Novartis expect more detailed comments from the Division?

*FDA responded that there are no additional comments at this time over what has been already sent regarding study A2309.*

#### **2.4.1.1 SAS datasets and transfer of SAS programs**

##### **Novartis comments Nov. 21, 2008:**

We confirm that we plan to include both raw and derived datasets in the CRT submission for study A2309.

For studies B201/B251 we plan to submit the CRTs for each study. The CRT submission will include raw and derived datasets used in the analyses of the 12-month data in the original NDA (N21-560) submission and its amendments, along with data derivation and handling methods documents, data definition tables and annotated CRFs.

In the cross-study comparisons analyses, data from studies B201/B251 are re-analyzed using the visit windows and data cut-off points used in study A2309, which are different from those used in the original NDA submission. To aid the Division review, we plan to submit the derived datasets with combined data from studies B201, B251 and A2309 for these analyses, along with

data derivation and handling methods documents, and data definition tables. Are these proposals acceptable to the Division?

*Novartis asked for clarification on what is required for the resubmission, specifically how extensive does the datasets need to be. FDA responded that the datasets should be resubmitted to include any additional data and asked for clarification regarding Novartis' intent of the proposed cross-study comparisons. Novartis stated that it was in response to an FDA request for a comparison of the old information to the new information, rather than to draw statistical inferences. FDA suggested side-by-side comparison of data would be appropriate. Study A2309 is expected to stand on its own in order to support safety and efficacy rather than in a combined analysis with other studies.*

**Two Additional topics:**

1. Novartis would like to submit by mid Dec 2008 additional statistical proposals to support the Divisions' review of exposure-response relationships (pk/pd analyses). Is this acceptable?

*Novartis reiterated plans to submit additional statistical proposals by December, 2008 and plans for database lock by mid-January, 2009.*

2. Novartis requests clarification with reference to the FDA communication/NDA action letter (dated August 24, 2004: page 3) and the statement:

*'Although not a condition of approval, we strongly recommend that you continue to adequately determine the terminal t1/2 of everolimus in the target population following the administration of the proposed everolimus-cyclosporine regimen....'*

Our biopharmaceutics expert would like to have additional clarification for this request. Can we schedule a follow-up teleconference for this discussion in the near future?

*Novartis was told that a follow-up teleconference for this discussion would be scheduled in the near future.*

*FDA had a question on question 2.1.1.1 - the cross reference for Afinitor. What is the intent of cross-referencing that NDA?*

*Novartis's answered that cross-reference will be made to the Afinitor™ (everolimus) NDA, 22-234, for relevant information under review within FDA's Division of Drug Oncology Products (DDOP) because the drug product information is similar. The project manager mentioned that this was discussed in a teleconference on August 6, 2008 between CMC and DDOP. As an action item, the project manager agreed to look in to the matter and follow up.*

**Action Item:**

*The project manager reviewed the minutes from the August 6, 2008 teleconference and found the following documentation under the **Background** section:*

*“Novartis’ NDA-22-334, Afinitor, that is currently under review by the Division of Drug Oncology Products (DDOP) also has the same DS, RAD001 (everolimus), as its API.”*

*“In the discussion prior to t-con the Afinitor CMC reviewer recommended that since the referenced NDA is unapproved, the complete drug substance section should be submitted in NDA 22-334. The participating ONDQA management came up with the final decision that it is acceptable to reference NDA 21-560.”*

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Renata Albrecht  
12/18/2008 07:51:30 PM



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 20, 2008

**To:** Ron VanValen, Director, Drug  
Regulatory Affairs

**From:** Jacquelyn Smith, M.A., Project  
Manager

**Company:** Novartis

Division of Special Pathogen and Transplant  
Products

**Fax Number:** (973) 781-8364

**Fax Number:** 301-796-9881

**Phone Number:** (862) 778-7646

**Phone Number:** 301-796-1002

**Email:** ronald.vanvalen@novartis.com

**Email:** jacquelyn.smith@fda.hhs.gov

**Subject:** NDA 21-560/Certican

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**Total no. of pages including cover: 8**

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Dear Mr. Van Valen:

The following are the Division's preliminary responses to the questions posted in your briefing package dated October 23, 2008. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). Please note that if there are any major changes to your development plan/the purpose of the meeting/to the questions, based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting.

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**RAD001A / Certican™ (everolimus) Tablet  
Kidney Transplantation (NDA No. 21-560)**

**2.1.1.1 Regulatory topic: NDA submission format and Cross-Reference to Existing Documentation**

Novartis wishes to cross-refer to previously submitted information in the original Certican NDAs (No. 21-560, 21-628) and related amendments. We will provide a detailed table that identifies previously submitted studies and related information (dates of correspondence; file name/location) to aid the Division's review. Cross-reference will also be made to the Afinitor™ (everolimus) NDA No. 22234 for relevant information under review within the FDA Division of Oncology Products.

Is this approach acceptable for the Divisions NDA review?

***FDA Response:***

*In so far as comparisons will be made in your submission between previously reported studies 201 and 251 and their related amendments, we would prefer that these materials be resubmitted with your future complete resubmission so that all referenced material is available in one location. This would increase the efficiency of our review if it does not represent an unreasonable burden to you.*

**2.1.1.2 Additional pediatric study B351 (cohort 2) report**

a) Is it acceptable to include the pediatric study in the NDA 21-560 submission, or does the Division prefer that Novartis submit the clinical report to Certican Tablet for Oral Suspension NDA 21-561; b) does the Division agree with the proposal to accept the pediatric study B351 report (cohort 2) in advance of the supporting CMC documentation?

***FDA Response:***

*The Division recommends that the pediatric study B351 report (Cohort 2) be submitted as part of a submission to Certican Tablet for Oral Suspension NDA 21-561 including the supporting CMC documentation.*

### **2.1.1.3 Followup meeting to evaluate the regulatory value of Study A2309**

We propose a 2nd preNDA submission meeting in late 1Q 2009 to present the 12m results from study A2309. We will provide preliminary summary of efficacy and safety results for the Division's review and consideration prior to the meeting. Novartis would appreciate a preliminary read-out from the FDA on the regulatory value of the data and our final proposals for the NDA review and a complete response.

Does the Division accept this proposal?

#### ***FDA Response:***

*The Division agrees. Please provide as much detail and discussion as possible in your presentation of preliminary efficacy and safety results to allow for a preliminary assessment.*

## **2.2 Quality**

### **2.2.2 Question(s):**

Novartis will provide updated chemistry manufacturing and controls documentation relevant to drug product portion of the Certican Tablet NDA 21-560 resubmission only. We propose to submit updated CMC documentation for the Certican Tablet for Oral Suspension NDA 21-561 after the FDA determines that the Certican Tablet NDA resubmission is a complete response and acceptable for an approval decision.

Are these proposals acceptable to the Division?

#### ***FDA Response:***

*Yes, the proposals are acceptable.*

## **2.3 Clinical**

### **2.3.1 Question(s):**

#### **2.3.1.1 Use of everolimus therapeutic drug monitoring (TDM)**

What is the Division's medical reviewers expectation for use of TDM for everolimus with reduced dose cyclosporine in kidney transplantation? Does the Division require TDM to improve the safety profile associated with everolimus?

#### ***FDA Response:***

*The use of TDM for everolimus with reduced dose cyclosporine in organ transplantation should maintain adequate protection against rejection while providing an adequate safety profile. Specifically, a concentration controlled regimen of everolimus using TDM - should minimize renal function impairment, and not result in an increased risk of wound healing complications or infections.*

*Our expectation is that you demonstrate adequate investigator compliance with the TDM regimens for everolimus and cyclosporine and that whole blood trough everolimus and*

*cyclosporine are reasonably within protocol specified target ranges. In addition, we expect that exposure-response analyses, using trough whole blood everolimus and CNI (cyclosporine) concentrations be performed to explore any potential relationships between trough drug concentrations and both efficacy and safety endpoints. Thus, we further intend to evaluate whether the proposed TDM regimens adequately preserve renal function. The assessment of adverse events associated with everolimus, such as wound healing complications and infections and any potential relationships between these AE's and everolimus trough concentrations will be a review issue and taken into consideration in the overall risk/benefit evaluation of the Certican NDA.*

### **2.3.1.2 Ongoing kidney transplant study A2309**

In view of the anticipated safety profile of everolimus would demonstration of non-inferiority for the prespecified primary efficacy endpoint (i.e. composite efficacy endpoint of BPAR, graft loss or death, including loss to follow-up at 12 months) for study A2309 provide adequate evidence of benefit?

#### ***FDA Response:***

*This is a review issue and the Division's decision will be based on a thorough analysis of risk/benefit balance of the proposed regimen for the specified population. Demonstration of noninferiority with respect to the pre-specified primary endpoint may not be sufficient to overcome a serious safety problem. Conversely, if you demonstrate a benefit with respect to graft loss or death it could offset the risk of rare serious adverse events.*

### **2.3.1.3 Class- related safety considerations in kidney transplantation**

We request feedback from the Division to better appreciate safety concerns of particular interest for the Division for the use of everolimus in kidney transplantation. Based on recent discussions with the Division related to the use of everolimus in cardiac transplantation, Novartis is capturing additional data to support expanded analyses on wound healing and related complications.

Can the Division offer additional guidance on current safety related considerations to support the evaluation of a complete response?

#### ***FDA Response:***

*Safety concerns of particular interest include but are not limited to:*

- *Renal function*
- *Infectious complications*
- *Wound healing*
- *Lymphocele, ascites, and pleural effusions*
- *Peripheral edema*
- *Delayed graft function*
- *Proteinuria*

- *Gastrointestinal ulcers*
- *Stomatitis and oral ulcers*
- *Thrombocytopenia*
- *Neutropenia*
- *Anemia*
- *Serum lipid profile changes*
- *New onset diabetes after transplantation*

*Your assessment of safety should include detailed analyses of incidence, time to event, time to resolution (if resolved) and severity at a minimum. The Division would be open to further discussion about how to effectively assess and report safety findings.*

**2.3.1.4 NDA Safety Update to provide side-by-side comparisons between studies A2309 and B201/B251, foreign marketing history, labeling.**

We will provide side-by-side comparisons of key safety data between study A2309 and studies B201 and B251 in the same format as the original NDA. Comparisons of key efficacy analyses will also be included for all efficacy data observed as well as on-treatment analysis. The Safety Update will be located in eCTD Module 5 (5.3.5.3: Reports of Analyses from More than One Study).

The NDA submission will also include revised labeling, an update of foreign marketing history and copies of selected approved Certican labeling from major countries. This information will be located in eCTD Module 1 Regional Administrative Information.

In addition, and with consideration to our recent NDA submission (NDA 21-628; December 17, 2007) to support the use of Certican in heart transplantation, Novartis requests that the core contents of the NDA resubmission for kidney transplantation be limited to the inclusion of *de novo* kidney transplant study data only. Data from other clinical trials and uses (studies in maintenance transplant patients, study in patients with autosomal dominant polycystic kidney disease), will not be included in the NDA resubmission and available upon request.

Are these proposals acceptable to the Division? Does the Division request additional analyses or information to support their review of the kidney transplant NDA?

***FDA Response:***

*These proposals appear acceptable. Please summarize in tabular format all of the other clinical trials of everolimus in renal transplant recipients. We are particularly interested in clinical trials where everolimus is introduced in the immunosuppressive regimen more than one month after kidney transplantation.*

**2.3.1.5 Benefit/risk assessment for kidney transplant NDA resubmission**

We will evaluate the overall efficacy and safety profile of Certican in study A2309 in comparison to the original NDA kidney transplant studies B201/B251. In addition, we

will compare the benefit/risk profile of the TDM regimen of everolimus with reduced doses of cyclosporine to the overall efficacy and safety profile of the MPA active control group used with full dose cyclosporine in the Certican kidney transplant Phase 3 studies respectively.

Is this proposal acceptable for a thorough benefit risk assessment?

***FDA Response:***

*In general the Division agrees with Novartis's proposal for the evaluation of the results of study 2309 including the proposed comparisons. We would consider cross-study comparisons as supportive only to the primary analyses of each confirmatory trial.*

**2.3.1.6 Risk Management Plan / Risk Evaluation and Mitigation Strategy**

We will submit for the Division's review a risk management plan and/or risk mitigation strategy to instruct US physicians on the use of Certican in kidney transplantation. This document will identify specific safety risks based on the outcome of study A2309 and the inventory of all relevant sources of safety information in kidney transplant studies, but also other sources as appropriate. We will also identify specific risk avoidance measures.

Can the FDA provide recommendations to help guide the Novartis efforts for the preparation of a risk management/risk mitigation plan? Does the Division want to review a formal proposal in the Certican NDA resubmission?

***FDA Response:***

*The Division agrees to review a risk management/risk mitigation plan if submitted as a part of the NDA resubmission. Discussions should be held prior to NDA submission regarding the specific elements of this plan and how they will be implemented.*

**2.4.1.1 SAS datasets and transfer of SAS programs**

We will provide SAS datasets to support the Divisions review of study A2309:

Data submission will be through the Case Report Tabulations (CRTs), with data in SAS version 5 transport files, along with the data derivation and handling methods documents, data definition tables and annotated Case Report Forms (CRFs).

(b) (4)

Are these proposals acceptable?

***FDA Response:***

*The first proposal is acceptable; however, we would request that you also include the raw datasets with the derived datasets for study A2309.*

NDA 21-560

*Regarding the second proposal, as discussed in our response to question 2.1.1.1, we would prefer that you submit all referenced materials, including SAS datasets and data derivation and handling methods for studies B201/B251 in your planned resubmission. If this poses a problem, please explain.*

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
FDA/CDER/OND/OAP

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/s/

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Jacquelyn Smith  
11/20/2008 01:43:20 PM  
CSO



NDA 21-560

Novartis Pharmaceuticals Corporation  
ATTENTION: Mr. Ronald G. Van Valen  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) file for Certican (everolimus) Tablets.

We also refer to your August 22, 2008 correspondence requesting a meeting to discuss your proposals and timeline for resubmission of the Certican NDA for kidney transplantation.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: November 24, 2008  
Time: 11:30 a.m. EST  
Location: 10903 New Hampshire Avenue  
Building # 22  
Silver Spring, MD 20993

**CDER Participants:**

**Division of Special Pathogen and Transplant Products**

Renata Albrecht, M.D.	Director
Steven Gitterman, M.D., Ph.D.	Deputy Director
Marc Cavaille-Coll, M.D.	Clinical Team Leader
Ergun Velidedeoglu, M.D.	Clinical Reviewer
Philip M. Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology/Biopharmaceutics/Team Leader
Dashina Chilukuri, Ph.D.	Clinical Pharmacology/Biopharmaceutics Reviewer
Laree Tracy, M.A.	Biostatistics Reviewer
Karen M. Higgins, Sc.D.	Biostatistics Team Leader
Jacquelyn Smith, M.A.	Regulatory Health Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at [jacquelyn.smith@fda.hhs.gov](mailto:jacquelyn.smith@fda.hhs.gov) so that I can give the security staff time to prepare temporary badges in advance.

Provide the background information for this meeting at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by October 24, 2008 we may cancel or reschedule the meeting.

Prior to the meeting date, we will send a facsimile transmission (FAX) addressing the questions in your meeting package. If the responses we provide in the FAX satisfactorily address your questions and you believe the meeting is no longer needed, please contact me at (301) 796-1002 to cancel the meeting.

If you have any questions, please call me at (301) 796-1002.

Sincerely,

*{See appended electronic signature page}*

Jacquelyn Smith, M.A.  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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Jacquelyn Smith  
9/10/2008 02:48:42 PM  
Updated Response to Meeting Request Granted letter

## MEMORANDUM OF TELECON

**DATE:** August 6, 2008 (3:15 PM)

**APPLICATION NUMBER:** NDA 21-560 [Certican® (everolimus) Tablets]

**BETWEEN:**

**Novartis Pharmaceuticals:**

Jane Xiang, Ph.D., Associate Director, Global regulatory CMC

Sheryl LeRoy., US Unit Head, Global Regulatory CMC

Lynne McGrath, MPH, PhDUS Head, DRA Oncology Global Development

Sibylle Jennings, Ph.D., Associate Director, DRA Oncology Global Development

Ron Van Valen, DRA Global Manager, Certican (everolimus) Project

**PHONE:** (862) 778-7646

**AND**

**FDA:**

Norman Schmuff, Ph.D., Branch Chief, OPS/ONDQA/DPA II

Mark Seggel, Ph.D., Chemistry Reviewer, OPS/ONDQA/DPA II

Sarah Pope, Ph.D., Acting Branch Chief, OPS/ONDQA/DPAMS

Richard Lostritto, Ph.D., Division Director, OPS/ONDQA/DPAMS

Ravindra Kasliwal, Ph.D., Chemistry Reviewer, OPS/ONDQA/DPAMS

Jacquelyn Smith, M.A., Regulatory Health Project Manager, DSPTP

**Subject: NDA 22-334, Afinitor**

**Background:**

Among the four API RAD001 (everolimus) NDAs, 21-560, 21-561, 21-628, and 21-631, that are active under the Division of Special Pathogen and Transplant Products (DSPTP), the drug substance (DS) information was submitted and maintained under unapproved NDA 21-560. The other NDAs cross reference NDA 21-560 for the CMC information of their API RAD001 (everolimus).

In addition, Abbott's everolimus drug eluting stent (PROMUSTM), which was approved by FDA, CDRH, on July 2, 2008, also cross-referenced to the NDAs 21-560 and 21-628 for drug substance information in their application. Although during the discussion prior to industry discussion it was pointed out by the CMC reviewer that for CDRH products, there is no CFR 314.70 for post approval changes.

Novartis' NDA-22-334, Afinitor, that is currently under review by the Division of Drug Oncology Products (DDOP) also has the same DS, RAD001 (everolimus), as its API.

In the discussion prior to t-con the Afinitor CMC reviewer recommended that since the referenced NDA is unapproved, the complete drug substance section should be submitted in NDA 22-334. The participating ONDQA management came up with the final decision that it is acceptable to reference NDA 21-560.

The teleconference began with attendee introductions, followed by meeting discussion.

### **Discussion**

*Although the DS information was submitted and maintained under NDA 21-560, Novartis stated that FDA asked them to provide the DS information for NDA 22-334 because NDA 21-560 is not approved.*

*Novartis communicated that FDA advised them to consider a DMF submission as an option for providing the DS information. Novartis wanted to know if it was possible to withdraw the DS information from the Certican NDAs and submit the same information under a separate DMF. Novartis was anxious for advice from FDA because they needed to make a decision on how to submit the DS information (i.e., as DS information under NDA 22-334 or as a separate DMF), and subsequently submit it to NDA 22-334 in a short time frame.*

*It was confirmed that the original NDA (21-560) was submitted in paper; October, 2002 submission submitted in eNDA, not eCTD format. All information from November, 2007 to present is in eCTD format.*

*FDA suggested several options for obtaining DS information; they are as follows:*

- *DMF (paper or eCTD)*
- *Convert all submissions to eCTD*
- *keep primary review under one division*
- *eCTD Cross-Application Linking*

*Novartis was asked to provide their proposal to facilitate the completion of the FDA oncology chemistry review of everolimus DS information, including the chronology of all related CMC drug substance submissions. Novartis submitted a Table of the CMC drug substance information chronology on August 12, 2008.*

*On August 7, 2008, FDA forwarded Novartis the eCTD Cross-Application Linking information which allows linking to the original via the eCTD backbones. It was strongly recommended that Novartis test it before using it with a real application.*

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### **August 13, 2008; 1:15 PM Follow-up TELECON**

### **Discussion**

*The teleconference began with attendee introductions; below are the discussion points.*

- *It was confirmed that the CMC drug substance information previously reviewed and approved by FDA does not require a second review.*
- *A correlation table, mapping the previously submitted and reviewed eNDA modules to the respective CTD modules is sufficient.*
- *Novartis will submit the CMC information which has yet not been reviewed by the FDA to NDA 22-334 in eCTD format (November 27, 2007 amendment). Novartis will also provide a correlation table, which will map the previously submitted and reviewed eNDA modules to the respective CTD modules. This correlation table will be provided in pdf format.*
- *The submission will be sent to FDA by Aug 29, 2008.*
- *Novartis was willing to submit the remaining eCTD modules by converting the eNDA modules, which were previously submitted and reviewed by the FDA, to eCTD format to NDA 22-334.*

*Novartis appreciated FDA reviewing their proposals and the opportunity to facilitate the final review of the remaining drug substance information.*

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/s/

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Jacquelyn Smith  
9/2/2008 10:29:40 AM  
CSO

Richard Lostritto  
9/10/2008 03:50:19 PM  
CHEMIST



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** December 3, 2004

<b>To:</b> Ron Van Valen	<b>From:</b> Andrei Nabakowski
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
<b>Fax number:</b> 973-781-8364	<b>Fax number:</b> 301-827-2475
<b>Phone number:</b> 862-778-7646	<b>Phone number:</b> 301-827-2127
<b>Subject:</b> Comments on Certican Concept Sheets	

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**Total no. of pages including cover:** 4

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**Comments:** (none)

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**Document to be mailed:** " YES  NO

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The following comments are made based on your concept sheets for RAD001A2309 and RAD001A2310. When available, please provide the complete study protocols. Upon review of these protocols, the Division may have additional comments.

### **Comments Pertaining to Both Concept Sheets A2309 and A2310**

(1.) Submission of your Data Safety Monitoring Board (DSMB) charter and statistical analysis plan to the Division prior to commencement of the study is recommended as these studies are proposed as open-label studies. If the DSMB will be reviewing analyses that are linked to the efficacy endpoints for these studies, you should have a type one error spending function in place for these interim analyses. This will help assure that your studies will not be stopped for positive efficacy results unless a certain high level of significance is obtained. Please note that the penalties for the interim analyses can be very small (such as a Habittle-Peto approach), leaving the majority of the type I error remaining for the final analyses.

(2.) We note that both concept sheets plan for studies with three treatment groups (i.e., Certican dosed to provide an exposure measured by C<sub>0</sub> of 3-8 ng/ml with reduced dose Neoral, Certican dosed to provide an exposure measured by C<sub>0</sub> of 8-12 ng/ml with reduced dose Neoral, and 2.0 g MMF with standard dose Neoral). It appears that the statistical analyses will compare each Certican regimen individually to the MMF regimen. The protocol should include a plan for controlling the overall type I error due to multiple comparisons in this regard. We also note that your sample size calculations may need to be revised in accordance with the multiple comparison method you choose.

(3.) As you are aware, the premature treatment discontinuation rates were not equal across treatment groups in Studies B201, B251, and B253. Therefore, assessment of the premature treatment discontinuation rates will be of importance to the Division at the time of review of these studies. We request that information relevant to this issue be carefully collected and summarized.

(4.) As part of both protocols, please provide justification for the choice of the non-inferiority margin for the analyses of creatinine clearance. It is important that the pre-specified fixed NI margin is scientifically justified and discussed with the Division prior to study initiation.

(5.) The starting doses for each everolimus regimen are not specified in the concept sheets. Please include in the study protocol what starting dose you intend to study and the respective target concentrations.

(6.) Please specify the procedures that will be used to keep pathologist(s) blinded to treatment assignment and clinical status when assessing the allograft biopsies.

### **Comments Specific to Concept Sheet A2309**

(1.) Concept Sheet A2309 proposes to evaluate efficacy as a secondary outcome. It is the opinion of the Division that demonstration of the efficacy of this regimen is needed prior to approval and therefore, should be considered a primary objective of the study. In addition, the concept sheet proposes using a composite of biopsy proven acute rejection, death, graft loss, or loss to follow-up as the measure of efficacy. However, the composite including graft loss, death, or loss to follow-up is of significant importance to the Division and we request that the two composites be defined as co-primary efficacy endpoints.

(2.) Please collect biopsy information on chronic allograft nephropathy as a secondary endpoint. Note that unless this information is collected on protocol biopsies at prospectively specified times on all subjects it may be difficult to draw reliable conclusions from comparisons across treatment groups.

**Comments Specific to Concept Sheet A2310**

(1.) Concept Sheet A2310 proposes to utilize the step-function approach to determine a non-inferiority margin in the primary analysis. This Division considers this approach unacceptable and recommends that a fixed margin approach. Sufficient information exists from previous clinical trials to determine a scientifically appropriate non-inferiority margin. It is important that the pre-specified fixed NI margin is scientifically justified and discussed with the Division prior to study initiation. As stated in ICH E9, section 3.3.2 regarding selection of an appropriate NI margin, "An equivalence margin should be specified in the protocol; this margin is the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator. The choice of equivalence margins should be justified clinically."

(2.) Due to the high number of missed protocol biopsies in patients who prematurely discontinued treatment in study B253, the Division recommends that protocol specified biopsies are collected in all patients regardless of treatment status.

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

Sincerely yours,

*{See appended electronic signature page}*

Andrei Nabakowski, Pharm.D.  
Regulatory Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Andrei Nabakowski  
12/3/04 09:21:34 PM  
NDA 21-560 & NDA 21-628



## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** November 10, 2004

**Location:** U.S. Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Special Pathogen and Immunologic Drug Products (DSPIDP)  
9201 Corporate Blvd.  
Rockville, MD 20850

**NDA:** 21-560 and 21-628

**Drug:** Certican® (everolimus)

**Sponsor:** Novartis Pharmaceuticals Corporation

**Type of Meeting:** End of Review Meeting

**Meeting Chair:** Renata Albrecht, M.D., Director DSPIDP

**Meeting Recorder:** Andrei Nabakowski, Regulatory Project Manager, DSPIDP

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Mark Goldberger, M.D.	Director, ODE IV
Ed Cox, M.D.	Deputy Director, ODE IV
David Roeder	ADRA, ODE IV
Renata Albrecht, M.D.	Director, DSPIDP
Steve Gitterman, M.D.	Deputy Director, DSPIDP
Marc Cavaille-Coll, M.D.	Medical Team Leader, DSPIDP
Arturo Hernandez, M.D.	Clinical Reviewer, DSPIDP
Karen Higgins, Ph.D.	Statistical Team Leader, DSPIDP
LaRee Tracy, M.A.	Statistical Reviewer, DSPIDP
Ruthanna Davi, M.S.	Statistical Reviewer, DSPIDP
Shukal Bala, Ph.D.	Microbiology Team Leader, DSPIDP
Avery Goodwin, Ph.D.	Microbiology Reviewer, DSPIDP
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology/Biopharmaceutics Team Leader, DSPIDP
Jang-Ik Lee, Ph.D.	Clinical Pharmacology/Biopharmaceutics Reviewer, DSPIDP
Steven Hundley, Ph.D.	Pharmacology/Toxicology Reviewer, DSPIDP
Steven Kunder, Ph.D.	Pharmacology/Toxicology Reviewer, DSPIDP
Andrei Nabakowski	Regulatory Project Manager, DSPIDP
Ellen Molinaro	Chief Project Manager, DSPIDP
Robert O'Neill, Ph.D.	Director, OB

Charles Anello, Ph.D.

Deputy Director, OB

**NOVARTIS PHARMACEUTICALS CORPORATION ATTENDEES AND TITLES:**

Gilles Feutren, Global Head of Development, TxBU, Switzerland  
Mathias Hukkelhoven, Global Head of Regulatory Affairs, Novartis, E. Hanover  
Hans van Bronswijk, Global Head of Regulatory Affairs, TxBu Switzerland  
Luen Lee, Global Head Biostatistics, TxBU, E. Hanover  
Kenneth Somberg, Global Head, Clinical Research, TxBU, E. Hanover  
Jonathan Jaffe, International Project Leader (Certican), TxBU, E. Hanover  
Shreeram Adadhya, International Project Leader (FTY-720), TxBU, E. Hanover  
Frank von Arx, International Project Leader, TxBU, Switzerland  
Gurmit Sandhu, International Brand Manager, TxBU, Switzerland  
Yulan, Li, Project Statistician, TxBu, E. Hanover  
Chin Koerner, Liaison Office, Rockville, MD  
Lawrence Hauptman, Director, Regulatory Affairs, Novartis, E. Hanover  
Ronald Van Valen, Director, Regulatory Affairs, TxBU, E. Hanover

(b) (4)

**Background:** On September 23, 2004, Novartis Pharmaceuticals Corporation submitted a request to the Agency for a Type A, End-of-Review meeting for NDAs 21-560 and 21-628 in response to the Approvable letter from the Division dated August 27, 2004. These NDAs are for Certican® (everolimus) for prophylaxis of organ rejection in allogeneic kidney transplants and in heart transplant patients.

The purpose of the meeting was to discuss the Division's NDA review findings as well as Division and Office level conclusions regarding the overall safety and efficacy of Certican in both indications. In addition, the sponsor wanted to discuss available options that would ultimately lead to NDA approval including an Advisory Committee wherein all available data could be discussed.

**Presentation:** The two reviewing statisticians, Ms. Tracy and Ms. Davi, gave statistical slide presentations on the Efficacy and Safety of Certican in Heart transplantation and Kidney transplantation respectively. The slides presented are attached to the end of these minutes.

**Discussion:** The following is a summary of the sponsor's questions followed by the Division's response and discussion (in italics):

**1. Heart Indication-**

(b) (4)

- [REDACTED] (b) (4)

## 2. Kidney Indication-

- A. Please provide details on the medical review of our resubmission dated February 27, 2004 as a basis for the August approvable letter.
- B. Our consultants believe that clinical outcomes have not changed significantly over several years and that the demographic characteristics of studies A2306 and A2307 are sufficiently similar to the phase 3 trials that valid comparison may be made. Please clarify the Division's concern that "...the demographic characteristics of the (A2306 and A2307) populations studied showed the patient population was not comparable to either study B201 or B251."
- *Based on results in the two pivotal kidney studies, B201 and B251, the Division considers the risk of renal toxicity greater than the benefit of prevention of acute rejection .*
  - *ICH guideline E10 does not recommend using external controls as comparators in clinical trials due to the potential for baseline and demographic imbalances. Inclusion of a random control avoids this potential bias. Therefore, the Division considers the analyses of studies A2306 and A2307 flawed because they utilized an external control.*
  - *Because of the importance of conserving renal function in kidney transplantation, the Division acknowledged holding a high standard for renal safety as part of a safe and effective Certican with CsA regimen.*

## 3. Additional Issue-

What is the regulatory status of the NDA chemistry reviews, and the pharmacology/toxicology reviews? Are these reviews complete and final?

- *The chemistry and pharmacology/toxicology reviews are complete and there are no outstanding questions or concerns.*

#### **4. Advisory Committee-**

We would like to discuss having an Advisory Committee (AC) with the Division to allow for additional expert review and comment on all available NDA data. Please comment on this approach.

- *The Division will allow Novartis to determine if having an Advisory Committee is appropriate. Dr. Goldberger noted that during the AC meeting, there will be a public discussion concerning the negative findings of renal toxicity and methodological issues. Dr. Goldberger further noted that he considers the benefit/risk issues for heart important for the AC discussions. Due to a lack of clear benefit of Certican over existing therapies in kidney transplantation, the kidney indication should not be a topic during the AC meeting.. Dr. Goldberger agreed that AC questions would be broad and balanced based on overall data, and that the Division would consider the AC's advice. The Division will ask the AC for clear guidance on dose recommendations and management of renal function in heart transplantation. In addition, the Division will seek advice on design of future prospective Certican clinical trials in heart and kidney transplantation.*

#### **5. New Proposal for Studies-**

It is our intention to submit additional proposals to support a separate discussion for new clinical study(ies) with Certican in 4Q2004 after the end-of-review meeting.

- Due to time restrictions, study proposals were not discussed during this meeting. Novartis informed FDA that new studies will be started and conducted in agreement with FDA requirements.
- *The Division stated that starting acceptable studies prior to the AC meeting would be useful information to provide to the AC. In addition, these studies would suggest Novartis' commitment to studying an appropriate regimen in heart and kidney transplantation.*

#### **Action Items:**

##### **Novartis Pharmaceuticals Corporation**

1. The sponsor agreed to decide on whether to have an AC and for which indications.
2. The sponsor will submit their decisions to the Agency as soon as possible.

##### **FDA**

1. The review team will provide additional comments to the sponsor concerning new studies in heart and kidney transplantation.
2. The Division will schedule a teleconference to discuss Novartis' concept proposals for future clinical studies.

**Minutes Preparer:** Christine Lincoln, RN, MS, MBA, Regulatory Project Manager, DSPIDP

**Chair Concurrence:** Renata Albrecht, M.D., Director, DSPIDP

**Attachment:** Slides

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/s/

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Renata Albrecht  
11/14/2005 05:07:27 PM

## MEMORANDUM OF INTERNAL TELECONFERENCE MINUTES

**TELECON DATE:** August 25, 2004  
**TIME:** 12:00 - 12:30 PM  
**APPLICATIONS:** NDAs 21-560 and 21-628  
**DRUG NAME:** Certican (everolimus) Tablets

**TELECON CHAIR:** Marc Cavaille-Coll, MD, PhD

**TELECON RECORDERS:** Quynh Nguyen, PharmD  
Andrei Nabakowski, PharmD

### ATTENDEES:

#### Division of Special Pathogens and Immunologic Drug Products (DSPIDP), HFD-590

Marc Cavaille-Coll, MD, PhD	Medical Team Leader
Arturo Hernandez, MD	Medical Officer
Andrei Nabakowski, PharmD	Regulatory Project Manager

#### Division of Biometrics III, HFD-725

Karen Higgins, Sc.D.	Statistician Team Leader
Tracy LaRee, M.A.	Statistician
Ruthanna Davi, M.S.	Statistician

#### Division of Drug Risk Evaluation (DDRE), HFD-430

Mary Willy, PhD, MPH	Epidemiologist Team Leader
Andrew Mosholder, MD	Epidemiologist
Rita Ouellet-Hellstrom, PhD	Epidemiologist
Quynh Nguyen, PharmD	Regulatory Project Manager

### BACKGROUND:

Certican (everolimus) Tablet is a macrolide immunosuppressant proposed for use in the prophylaxis of organ rejection in allogeneic heart (NDA 21-628) and kidney (NDA 21-560) transplantations. Novartis Pharmaceuticals Corporation submitted the original NDAs on December 19, 2002, which received an approvable action on October 17, 2003. The sponsor re-submitted these NDAs on February 27, 2004, which relies heavily on analyses of the efficacy and safety across studies. The Division of Drug Risk Evaluation (DDRE) was consulted on June 6, 2004 by the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) to assess the validity of these cross-study comparisons, specifically the comparison of pooled results of studies B201 and B251 with A2306 and the comparison of results of study B156 with A2307.

### MEETING OBJECTIVES:

The purpose of this teleconference was to discuss DDRE's current assessment of this consult with DSPIDP.

### DECISIONS (AGREEMENTS) REACHED:

- DDRE and DSPIDP agreed that the sponsor has not provided adequate justification for their approach to rely on efficacy and safety analyses from studies A2306 and A2307 based on cross study comparisons using historical controls.

- DDRE and DSPIDP noted that the sponsor's use of historical controls in this case was not justified. Due to dissimilarities in study design and in the methods used for dosage adjustments with cyclosporine, comparisons of results are difficult to interpret. They further noted that in general the use of cross-study comparisons are useful mostly for hypotheses generating and should not be used as the basis for regulatory decisions.
- It was also noted that the patient and donor characteristics were not comparable (e.g., there were more African American patients enrolled in Study B251 compared to Studies B201 and A206); therefore, it is invalid to base safety and efficacy regulatory decisions on analyses of the pooled data from these studies.

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/s/

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Andrei Nabakowski  
9/8/04 07:32:11 PM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: June 2, 2004**

<b>To:</b> Ron Van Valen Director, Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (862) 778-7646	<b>Phone number:</b> (301) 827-2127

**Subject:** Information request (NDAs 21-560 and 21-628)

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**Total no. of pages including cover:** 6

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**Reviewers:** Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader/Arturo Hernandez, M.D., Medical Officer/Philip M. Colangelo, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader/Jang-Ik Lee, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer

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**Document to be mailed:** " YES  NO

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**NDA 21-560**  
**NDA 21-628**

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> (everolimus) Tablets and your submission of April 14, 2004, to these applications. Our clinical pharmacologists found these materials inadequate for their review and we would like to request additional information (in the bold, italicized typeface) to remedy that situation. (We have included the original questions and responses for your guidance.) The last item relates to our teleconference dated January 6, 2004. We strongly recommend that you be accurate, specific, and complete, in your response to this request and in future submissions.

**Question #1 - from FDA facsimile communication dated 24 March 2004**

For Appendix 3 in the NDA Amendment and Final Safety Update, please provide electronically both SAS data and command files that generated the SAS outputs and graphs for the regression analyses (i.e., Cox regression, logistic regression, and assessment of interaction) so that we may fully understand the statistical models used for these analyses. Please also provide the mathematical formulas for the regression models with brief explanations.

**Response #1**

For Appendix 3 in the NDA Amendment and Final Safety Update, SAS data as well as data specifications were already provided. They are provided again in Novartis response to FDA March 24 requests. Specifically, the location of the SAS data, data specifications and the analysis programs (Cox regression and logistic regression, with and without interaction term) are detailed in **Novartis response to FDA March 24 question #4**. [Q4 24Mar04] These programs give results for the key safety and efficacy events as defined in the resubmission of February 27, 2004; in addition the newly FDA defined event (30% CrCl change from median time) is included.

- 1. It appears that you did not provide us SAS command files and output files already in the resubmission of February 27, 2004. The reviewer browsed every single folder and every single file in the resubmission again but could not find the command and output files that have the file name extension of .cmd and .lst, respectively. We again request that you provide the files or their locations including exact folder and file names.*

**Question 3 - from FDA letter 24 March 2004**

For Appendix 3 of the NDA Amendment and Final Safety Update, please provide the results of the regression analyses for azathioprine control group for each safety and efficacy event (i.e. probability of event as a function of cyclosporine exposure). Please provide raw data, SAS data files, SAS command files, SAS outputs, and graphs.

### **Response #3**

Regression analyses for AZA control group were done for the same key efficacy and safety events to assess the impact of CsA trough level on these responses (also including the newly defined safety event=CrCl 30% decrease from median-baseline as requested by FDA).

#### Location of data specifications, SAS datasets and SAS command files:

The location of data specifications is under the folder: FDArequest24mar2004, where SAS datasets and SAS command files are all located under the sub-folders as the following:

- FDArequest24mar2004
  - [derived] (to hold all input SAS datasets)
  - [SAS codes for analysis] (to hold all SAS command files)
  - [SAS Outputs] (to hold all analysis outputs)

**2. The folder 'FDArequest24mar2004' does not appear in your response dated April 14, 2004. Please resubmit the folder with its complete contents.**

#### **Question #4 - from FDA facsimile communication dated 24 March 2004**

For Appendix 3 of the NDA Amendment and Final Safety Update, for the probability analyses and plots of 30% reduction in creatinine clearance (CrCL) vs. concentration, in addition to your analyses using the 1-month CrCL values as baseline, please perform similar analyses using CrCL values at a "median time" post transplant as baseline (y-axis) and the corresponding time-normalized drug concentrations starting at the "median time" to the time of the renal event (x-axis). The "median-time" is the median time at which maximum CrCL values are determined post transplant. In our preliminary analysis, the median time to attain "maximum" CrCl appears to be 1 week or 2 weeks post transplant. Please provide raw data, SAS data files, SAS command files, SAS outputs, and graphs for both everolimus treatment and azathioprine control groups for this latter analysis.

### **Response #4**

Based on FDA's request, a new "median time" baseline value of CrCl (named as Median-Baseline value below) was defined as follows to assess the impact of concentrations (RAD and CsA troughs) on 30% reduction in creatinine clearance (CrCl) from the median-baseline using regression analyses for both RAD and AZA groups:

- The "median time" is defined as the median time at which maximum CrCL values are determined post transplant.
- The CrCL values at the "median- time" is then defined as the median-baseline value
- safety event of 30% reduction in CrCl from this median-baseline is then derived
- Time-normalized mean of RAD or CsA concentrations will be calculated similarly but using concentrations starting at the "median-time" to the time of event or Day 225.

**3. Please provide the value of 'median time' with raw data and descriptive statistics (i.e., value observed in each patient, median, mean, standard deviation, and range) for the time at which maximum CrCL values were observed post transplant. Please also provide the values of CrCL at the median time with raw data and descriptive statistics.**

#### **Question #5 - from FDA facsimile communication dated 24 March 2004**

For Section 8 of the NDA Amendment and Final Safety Update, please provide what concentration values (e.g., simple mean value calculated using concentrations measured up to 6 months or time-normalized mean value calculated using concentrations measured up to a specific event) was used in each figure and table.

#### **Response #5**

For Section 8 of the NDA Amendment and Final Safety Update, the time-normalized mean value (calculated using concentrations measured up to a specific event) was used in each figure and table. The simple mean value (calculated using concentrations measured up to 6 months) was not used for analysis.

- 4. From our review, it appears that simple mean values were used in some figures and tables rather than time-normalized mean values. If time-normalized values were indeed used, then please provide an explanation, with raw data, for why the exposure-response relationships in the amendment (Figure 8-1) in which you used time-normalized mean values are not different from the exposure-response relationships in your original reports (Figure 6-4 in B253, and Figures 6-4 and 6-5 in B251) in which you used simple mean values. For Table 8.2.1-1 in the amendment, it appears that you did not compute time-normalized mean values in your study reports for Studies A2306, B201, and B251 and therefore it is unclear to the reviewer how the ranges can be based on time-normalized concentrations. Please provide again what concentration values were used in each graph and table.*

#### **Question #6 - from FDA facsimile communication dated 24 March 2004**

For Study Report A2306 (Table 6-2 in Page 3231), please provide an explanation of why and how everolimus doses were reduced over time (i.e., from 1.5 mg at Day 1 to 1.2 mg at Month 12) in upper dose arm (1.5 mg bid). You provided in the report dose increase plan (i.e., to achieve everolimus trough concentration > 3ng/mL) but no dose reduction plan. Furthermore, such dosage reduction is not reported in Study A2307.

#### **Response #6**

The reasons for dose reduction were summarized in Post-text table 8.1-5 of A2306 and A2307 12-month clinical study reports (CSRs) submitted on February 27, 2004 (see below pages 2-21). The RAD 3mg group has a much higher rate of dose reduction than did the RAD 1.5mg group. The reasons were As per protocol, Adverse event, Platelet Abnormality, WBC abnormality, Cholesterol abnormality and Triglyceride abnormality. An increase in adverse events and laboratory abnormalities leading to dose reduction is an expected outcome of increased RAD exposure. The algorithm for dose reduction can be found in the respective clinical protocols (see clinical study reports, Appendix 1, post text supplement 4 entitled 'Algorithm for RAD dose reductions': for Study A2306 on page 2983, and, for Study A2307 on page 2924).

In Post Text Table 8.1-3 of the A2306 and A2307 12-month CSRs, the mean daily dose of RAD in 3mg group is lower than 3mg at 12 months. However, the median is consistently 3.0mg from Day 1 to Month 12. As the mean is easily influenced by outliers, a distribution of the average daily dose of RAD at Day 1, month 6 and month 12 are provided for study A2306 for illustration (see below figures; pages 22-24).

**5. Please compare and contrast Study A2306 with Study A2307 with respect to everolimus and cyclosporine doses and concentrations over time. If there is any difference, please provide a reason for the difference and the effect of the difference on the efficacy and safety outcomes of the studies.**

**6. Everolimus Elimination Half-Life**

***As we noted in the teleconference dated January 6, 2004 (please refer to the minutes), the overall mean half-life value for everolimus estimated in Study W101 in renal transplant patients received cyclosporine is not acceptable: the number of subjects were too small (n = 6 each dose group); everolimus pharmacokinetics were not linear around the proposed clinical doses when using dose-normalized AUC, apparent clearance, and apparent volume of distribution; the difference of the mean values at doses of 0.75 mg and 2.5 mg was very large (by 10 hours); and the overall mean half-life value (28 ± 7 hr) is unreasonably shorter than the value determined in healthy subjects who received no concomitant cyclosporine administration (40 - 50 hr).***

***As you proposed in the teleconference, we have reviewed the half-life values determined in Study B154. In agreement with your statements in the resubmission, the values in Study B154 are not adequate because the study seems to have underestimated the true half-life due to inadequate blood sampling on outpatient basis.***

***Thus, we have concluded from our review of the data provided thus far that you have not submitted adequately determined half-life values for everolimus in transplant patients. If possible, we request you to provide the half-life values determined adequately from other additional studies following steady-state administration of the proposed everolimus-cyclosporine combination regimens to transplant patients.***

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Matthew Bacho  
6/2/04 06:10:28 PM  
CSO  
NDAs 21-560 & 21-628

## REQUEST FOR CONSULTATION

TO (Division/Office):

**Quynh Nguyen, Sr. Regulatory Management Officer  
OPSS/ODS/DDRE**

FROM: **Ruthanna Davi/Andrei Nabakowski**

HFD-725 (Division of Biometrics III) and HFD-590 (Division of Special Pathogen and Immunologic Drug Products)

DATE:  
**June 2, 2004**

IND NO.:

NDA NO.:  
**21560  
21628**

TYPE OF DOCUMENT :  
**NDA re-submission**

DATE OF DOCUMENT:  
**2/27/04 submission**

NAME OF DRUG:  
**Certican (everolimus)**

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG:  
**Immunosuppressant, TOR  
inhibitor**

DESIRED COMPLETION DATE:  
**September 3, 2004**

NAME OF FIRM: **Novartis**

### REASON FOR REQUEST

#### I. GENERAL

<p>G NEW PROTOCOL G PROGRESS REPORT G NEW CORRESPONDENCE G DRUG ADVERTISING G ADVERSE REACTION REPORT G MANUFACTURING CHANGE/ADDITION G MEETING PLANNED BY</p>	<p>G PRE—NDA MEETING G END OF PHASE II MEETING G RESUBMISSION G SAFETY/EFFICACY G PAPER NDA G CONTROL SUPPLEMENT</p>	<p>G RESPONSE TO DEFICIENCY LETTER G FINAL PRINTED LABELING G LABELING REVISION G ORIGINAL NEW CORRESPONDENCE G FORMULATIVE REVIEW <b>X OTHER (SPECIFY BELOW):</b></p>
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#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

G TYPE A OR B NDA REVIEW  
G END OF PHASE II MEETING  
G CONTROLLED STUDIES  
G PROTOCOL REVIEW  
G OTHER:

G CHEMISTRY REVIEW  
G PHARMACOLOGY  
G BIOPHARMACEUTICS  
G OTHER:

#### III. BIOPHARMACEUTICS

G DISSOLUTION  
G BIOAVAILABILITY STUDIES  
G PHASE IV STUDIES

G DEFICIENCY LETTER RESPONSE  
G PROTOCOL-BIOPHARMACEUTICS  
G IN-VIVO WAIVER REQUEST

#### IV. DRUG EXPERIENCE

G PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL  
G DRUG USE e.g. POPULATION EXPOSURE,  
ASSOCIATED DIAGNOSES  
G CASE REPORTS OF SPECIFIC REACTIONS (List below)  
G COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

G REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY  
G SUMMARY OF ADVERSE EXPERIENCE  
G POISON RISK ANALYSIS

#### V. SCIENTIFIC INVESTIGATIONS

G CLINICAL

G PRECLINICAL

#### COMMENTS/SPECIAL INSTRUCTIONS:

**This NDA re-submission relies heavily on an analysis across studies. We would like ODS to assess the validity of the cross-study comparisons (i.e. the comparison of pooled results of studies B201 and B251 with A2306 and the comparison of results of study B156 with A2306).**

**Links to the relevant electronic submissions:**

**Original NDA 21560 – 12/19/02 – original study reports for B201, B251 and B156**

**\\Cdsub1\N21560\N 000\2002-12-19**

**Resubmission NDA 21560 – 2/27/04 – study report for A2306 and cross-study comparison**

**\\Cdsub1\N21560\N 000\2004-02-27**

**The Division appreciates ODS' willingness to assist us in request. An epidemiologist's perspective would greatly enhance our ability to better point out the pros and cons of this type of analysis at an upcoming advisory committee, tentatively scheduled for October 2004. Should ODS' epidemiologist have any specific questions, please don't hesitate to contact:**

**Ruthie Davi (Statistical Reviewer) 301-827-2114**

**LaRee Tracy (Statistical Reviewer) 301-827-2212**

**Karen Higgins (Stats Team Leader) 301-827-2171**

**Arturo Hernandez (Medical Officer reviewer) 301-827-2375**

**Marc Cavaille-Coll (Medical Officer Team Leader) 301-827-2414**

**Andrei Nabakowski (Project Manager) 301-827-2424**

SIGNATURE OF REQUESTER:

**Andrei Nabakowski**

METHOD OF DELIVERY (Check one):

**E-Mail**

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Andrei Nabakowski  
6/2/04 10:15:29 AM  
Certican ODS consult request



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: April 9, 2004**

<b>To:</b> Ron Van Valen, Director, Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (973) 781-7646	<b>Phone number:</b> (301) 827-2127
<b>Subject:</b> Certican Tablets Resubmission (NDAs 21-560 and 21-628)	

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**Total no. of pages including cover:** 3

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**Reviewers:** Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader/Arturo Hernandez, M.D., Medical Officer/Karen Higgins, Sc.D., Statistics Team Leader/LaRee Tracy, M.A., Statistics Reviewer/Ruthanna Davi, M.S., Statistics Reviewer/Philip M. Colangelo, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader/Jang-Il Lee, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer

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## **NDA 21-560 and 21-628**

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets and your resubmission of February 27, 2004, to these applications. Our reviewing medical officer, clinical pharmacologist, and statisticians would like to request the following information:

1. Please resubmit the efficacy and renal function electronic data sets in a format that is conducive to conducting the cross-study comparisons that are being proposed. The data sets should include one line per patient and incorporate data from all studies from which comparisons are being made.
2. As discussed during our teleconference on April 1, 2004, we would like a detailed table of contents (or index) of your February 27, 2004 resubmission organized by indication and discipline.

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Matthew Bacho  
4/9/04 10:58:13 AM  
CSO  
NDAs 21-560 & 21-628

## MEMORANDUM OF TELECONFERENCE MINUTES

DATE: April 1, 2004

APPLICATION NUMBER: NDAs 21-560 & 21-628 [Certican<sup>®</sup> (everolimus) Tablets]

BETWEEN:

Name: Gilles Feutren, M.D., Head of Development (Switzerland)  
Kenneth Somberg, M.D., Vice President, Clinical (U.S.)  
Jonathan Jaffe, M.D., Clinical Project Leader (U.S.)  
Yulan Li, Ph.D., Biostatistics Project Leader (U.S.)  
Ronald G. Van Valen, Director, Drug Regulatory Affairs (U.S.)  
Hans van Bronswijk, M.D., Ph.D., Global Head, DRA (Switzerland)  
Mathias Hukkelhoven, Ph.D., Corporate Vice President, DRA (U.S.)  
Representing: Novartis Pharmaceuticals Corporation (Transplantation & Immunology)

AND

Name: Renata Albrecht, M.D., DSPIDP Director and Meeting Chairperson  
Marc Cavaillé-Coll, M.D., Ph.D., Medical Team Leader  
Arturo Hernandez, M.D., Medical Officer  
Karen Higgins, Sc.D., Statistics Team Leader  
Ruthanna Davi, M.S., Statistics Reviewer  
LaRee Tracy, M.A., Statistics Reviewer  
Philip Colangelo, Pharm.D., Ph.D., Clin. Pharmacology & Biopharm. Team Leader  
Jang-Ik Lee, Pharm.D., Ph.D., Clin. Pharmacology & Biopharm. Reviewer  
Matthew A. Bacho, Regulatory Health Project Manager  
Representing: Division of Special Pathogen and Immunologic Drug Products

SUBJECT: The Division requested a teleconference with Novartis (or the applicant) to discuss various issues regarding the latter's February 27, 2004 resubmission to NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets.

BACKGROUND: Novartis' IND for everolimus was originally submitted to the FDA on November 15, 1996. Four pre-NDA meetings were conducted on December 3, 1999; January 27, 2000; February 6, 2001; and March 25, 2002, to discuss the applicant's proposed marketing applications for this drug product. Novartis subsequently submitted NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets for the prophylaxis of organ rejection in allogeneic renal and cardiac transplant patients on December 19, 2002, for which the Division issued an approvable letter on October 20, 2003.

DISCUSSION POINTS:

After a brief introduction from both sides, the discussion turned to the applicant's resubmission.

1. The Division noted that their ultimate goal was to determine a safe and effective Certican<sup>®</sup> regimen. The Division added that during the review they had encountered problems in the applicant's February 27, 2004 resubmission,

specifically in organization, in the transparency of information presentation, and lack of justification for the scientific data analyses. Because these problems were impeding the team from conducting its review, the Division brought their concerns to Novartis' attention, especially in light of the short, 6-month review clock and the possibility of having to prepare for an Advisory Committee meeting this summer. The Division also wished to discuss with the applicant those additional steps that would be necessary to effectively continue the development of Certican<sup>®</sup> for the prophylaxis of organ rejection in allogeneic renal and cardiac transplant recipients.

2. The Division provided examples of problems with the organization within the February 27, 2004 resubmission from the perspective of the clinical pharmacologist. The resubmission was poorly indexed and there were no clear indications as to the kinds of information Novartis had provided until every single folder and file was opened. In addition, the data to be reviewed were intermingled with those required by the Division's other disciplines and there were obvious omissions and synoptic summaries rather than complete reports. (A memorandum requesting clarification and further information was faxed to the applicant on March 24, 2004.) In short, the Division noted that the inconvenience and extra effort brought on by Novartis' poorly organized resubmission would necessitate further remedy in order to complete their review.
3. The applicant responded that resubmissions were usually not organized along the lines of an original NDA; as an example, they noted that there were no standards for how to organize a "typical" clinical pharmacology section. Novartis stated that this resubmission had followed the order of the deficiencies from the approvable letter of October 20, 2003. The Division acknowledged the applicant's goal of organizing their resubmission around the deficiencies mentioned above and had accepted its completeness in good faith, but it was difficult to confirm since the required analyses could not be located without a prolonged search. Novartis asked the Division to elaborate on the kinds of clarification required and which data the latter had a problem locating.
4. The Division provided an example of the lack of transparency concerning the foreign regulatory history of Certican<sup>®</sup>: initially, it looked as though no one had given the drug product a negative recommendation until a thorough reading uncovered them under the heading, "Other Health Authorities and Regulatory Action." The inconsistent use of, and inexplicit, title headings in the table of contents, as evidenced by the easily found list of countries that *had given* Certican<sup>®</sup> a positive recommendation, makes it difficult to accept the resubmission at face value. The Division expressed their need to feel confident that this resubmission was thorough and complete, and so far, finding the information relevant to their review had been extremely time consuming. The applicant agreed to provide a new, more detailed table of contents and inquired about the format that would make it more user friendly. The Division stated that it should be able to point to specific data by organ type and contain accurate references to original NDA data as well, since many of Novartis' analyses would need to be recreated. The Division added that the data on individual subjects would need to be clearly delineated and the title headings needed to be consistent (as stated above).

5. From the statistical reviewers' point of view, the Division noted that the original pivotal study data from Studies B201, B251, and B253 had not been resubmitted, and in order to replicate the efficacy analyses provided in the resubmission, or to perform new analyses, the Division would need to merge these data with those from the resubmission. The Division noted the dramatic increase in workload this complex exercise would entail as well as the greater chance for creating an error while trying to verify the applicant's analyses. Novartis apologized for this oversight and asked for additional feedback from the other disciplines in order to get a better handle on the resubmission.
6. The Division noted the following additional problems:
  - The clinical pharmacology section of the amendment was not complete for review (and the Division had requested clarification and additional analyses on March 24, 2004).
  - The updated safety and efficacy statistical analyses within the Integrated Safety Summary (ISS) were mixed in with the pharmacokinetic/ pharmacodynamic analyses. Additionally, these analyses were not differentiated according to indication.
  - The analyses do not refer to the appropriate appendices and there are no links between these analyses and the datasets used to generate them.
  - Many of the analyses involve multiple observations and the absence of a dataset that assigned each subject a single line of complete information made it problematic to review them.
  - The statistical analysis plan was not submitted with the resubmission.

Novartis noted that only new data had been included with the resubmission and agreed to quickly provide them from the original NDAs so that the reviewers could reproduce the necessary analyses. The applicant then added that they had not included the statistical analysis plan with their February 27, 2004 resubmission (this document had been published prior to the Division's communication of February 18, 2004, regarding the same) and agreed to provide it for review.

7. The Division stated that prior to their first action on Certican<sup>®</sup> Tablets, Novartis had reminded them about Studies A2306 and A2307 and expressed confidence in the outcome of these trials to support the successful use of Certican<sup>®</sup> therapeutic dose monitoring (TDM) in renal and cardiac transplantation. Despite the Division's expressed concerns about the design of these studies\*, and in the spirit of continuing a productive dialogue about this drug product, the Division agreed to consider these data for review to evaluate whether they supported the safe and effective use of Certican<sup>®</sup>. However, with respect to their scientific concerns, the Division noted that their previous reservations regarding the inadequacies of these two trials (e.g., no active controls) had not changed. The Division drew the applicant's attention to the guidances, such as ICH-E10, that discussed the problematic nature of cross-study comparisons. The Division acknowledged the similar aspects between these two studies and the pivotal trials that were

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\* Please see the Division's memoranda of September 13, 2001, and February 18, 2004, as well as the Division's minutes for the pre-NDA meeting on March 25, 2002, and teleconference on November 25, 2003.

evaluated during the first review cycle (e.g., demographics and endpoints) but they were ultimately not comparable enough to make any substantial claims other than generating hypotheses that would require further testing. The Division stated that Novartis had not provided sufficient statistical justification for the pooling of study arms from Studies B251 and B201 (renal transplantation) to compare against the treatment arms in Studies A2306 and A2307 or for basing new efficacy claims on exposure-response analyses.\* All of these analyses, the Division added, are retrospective in nature (and referred Novartis to the guidance, ICH-E4) and only a prospective study, like 2411 for cardiac transplantation and something similar for renal transplant recipients, could be used to confirm the hypotheses produced by Studies A2306 and A2307 as well as support a safe and effective Certican® dose.

8. The applicant noted that these were the types of issues they believed should be discussed with an Advisory Committee. The Division responded that the results of these non-comparative Studies A2306 and A2307 did not provide adequate safety and effective data or address the deficiencies in the approvable letter to NDAs 21-560 and 21-628. The Division added that an Advisory Committee meeting would be convened to consider any scientific questions about the adequacy and interpretation of safety and efficacy data in an application; however, based on the review of the current resubmission, the Division's conclusion was that these data are inadequate to reach an approval decision. Under these circumstances, the Division stated that their next regulatory action on Certican® Tablets would be clear, thus obviating the need for such a meeting. The applicant expressed their view that it was the Advisory Committee's role, in this particular instance, to weigh in on the issues of an acceptable risk-benefit ratio for Certican® in the setting of heart transplantation and, equally as important, the impact of this drug product on the heart transplant community as a whole. Aware of the currently acceptable level of renal toxicity, the Division pointed out that Novartis had not yet addressed how to improve renal function in transplant patients treated with their proposed Certican® regimen. The Division added that the previous era, which dealt mostly with cyclosporine and azathioprine, was no longer relevant to the current transplant community's views on renal toxicity; for example, Rapamune® was recently approved as part of a cyclosporine-sparing regimen that could be tolerated by the majority of renal transplant recipients. In short, the Division stated that the renal toxicity associated with the proposed regimen and dose of Certican® was unacceptable.
9. The applicant noted that transplant drug regimens have evolved and improved over time through clinical practice, which would then be reflected in label updates. Novartis stated their view that Study B253 was still a positive study in which graft survival outweighed the safety problems discussed above, an issue that should be taken to the Advisory Committee for discussion. The Division observed that graft survival among these patients was not higher at the 12- and 24-month endpoints compared to the control arm. The Division also noted that they could not operate without taking the latest Rapamune®, cyclosporine-sparing regimen approval into consideration. The Division reminded the applicant that

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\* Post-Teleconference Note: Please see Comments #1 and #3 from the Division's communication of February 18, 2004.

the original Certican<sup>®</sup> regimen had been altered 12 months after initiation of the pivotal cardiac study, which left both sides without any notion of how a TDM regimen would be tolerated in patients soon after transplantation.

10. Novartis acknowledged and understood the Division's position and asked the latter to consider the heart transplant community when they made their decision. The Division noted their goal of reviewing all applications with consistency, and when a drug product has a safety issue, such as this one, they always looked for an advantage that balanced the equation. The Division's responsibility was to write a label that described the proper use of Certican<sup>®</sup> and a large part of that task would be to include a safe and effective dose, a piece of information that was still missing for this drug product. The Division stated that they were not searching for the optimal dose, and while acknowledging the fact that both sides disagreed with each other regarding when safety and efficacy has been achieved, the Division has to be satisfied that the best information could be given to transplant physicians. The Division noted that their current position, as described above, would have to be presented to the proposed Advisory Committee.
11. The applicant inquired whether the Division had concluded its review of the resubmission. The Division answered that a safe and effective Certican<sup>®</sup> regimen had not been established and they were unaware of any other analyses that Novartis could provide that would alter this situation. The applicant asked the Division to explain why they had accepted the resubmission for review given their earlier reservations about Studies A2306 and A2307. The Division stated that they had not seen the data from these trials prior to submission of the February 27, 2004 resubmission and they did not want to disregard the options presented by these trials. The Division added that the new analyses were not convincing enough to alter their original position on the NDAs' data.
12. Novartis asked if the Division still wanted to present these issues to an Advisory Committee. The Division noted that they would have to reflect on the actual role such a body would assume under these circumstances; generally, such a meeting would not be held if the Division had already concluded that the data did not support the safety and efficacy of the drug product in question. The Division added that the composition of the committee would depend on the specific questions that would be asked of them; for example, statisticians would be invited to speak about whether the normal rules of analysis could be abrogated under these circumstances. The applicant expressed their disagreement with the Division's position that the data did not support approval and were aware of past Advisory Committees that were convened under similar circumstances. Novartis was confident that they could provide convincing reasons for having such a meeting. The Division acknowledged the applicant's position and encouraged them to continue developing Certican<sup>®</sup>, especially Study 2411 for heart transplant recipients and perhaps something similar for kidney transplantation. (The Division noted their intention of providing feedback on the design of this trial in the very near future).
13. The applicant inquired about their inability to adequately prove that the patient populations treated in Studies A2306 and A2307 were comparable to those in Studies B201 and B251. The Division reiterated their concerns about the

unobserved covariates and non-randomization of treatment assignment, which undermined Novartis' cross-study comparisons. The applicant acknowledged this statement.

14. The Division noted that both sides entertained real differences in the interpretation of the data and the approach each would take to an Advisory Committee as a result. The Division asked Novartis to consider the comparative studies and whether they had really established the appropriate doses of Certican<sup>®</sup> and cyclosporine to be used in the transplantation setting.
15. The applicant estimated that they would need approximately 3 years (sometime in 2006) to complete Study 2411 and added that prolonging development in this way had not been discussed internally. When asked if there was a possibility that Study 2411 would not be conducted, Novartis stated that they were committed to doing so as part of their postmarketing plans, which were required by some of the European health authorities. The applicant acknowledged the Division's willingness to accept Study 2411 as further support for the use of Certican<sup>®</sup> in transplantation.

**ACTION ITEMS:**

1. Novartis agreed to provide a new, more detailed table of contents organized by discipline, which would enable a reviewer to locate specific data by organ type, and that contains accurate references to original NDA data.
2. Novartis agreed to provide new data tables reduced down to one row per subject as well as the statistical analysis plan for review.
3. Novartis agreed to provide a detailed table of contents (or index) of their February 27, 2004 resubmission organized by indication and review discipline.
4. Both sides agreed to schedule an additional teleconference to discuss the resubmission and the necessity of an Advisory Committee meeting.

Minutes Preparer: *{See appended electronic signature page}*

Meeting Chairperson: *{See appended electronic signature page}*

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Renata Albrecht  
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Office of Drug Evaluation IV**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: March 24, 2004**

<b>To:</b> Ron Van Valen Director, Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (862) 778-7646	<b>Phone number:</b> (301) 827-2127
<b>Subject:</b> Information request (NDAs 21-560 and 21-628)	

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**Total no. of pages including cover:** 4

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**Reviewers:** Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader/Arturo Hernandez, M.D., Medical Officer/Philip M. Colangelo, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader/Jang-Ik Lee, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer/Karen Higgins, Sc.D., Statistics Team Leader/Ruthanna Davi, M.S., Statistics Reviewer

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**NDA 21-560**  
**NDA 21-628**

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> (everolimus) Tablets and your resubmission of February 27, 2004, to these applications. Our reviewing clinical pharmacologist would like to request the following information. If it is already present in the resubmission, please direct us to the location(s) instead. The requests are listed in the order of urgency.

1. For Appendix 3 in the NDA Amendment and Final Safety Update, please provide electronically both SAS data and command files that generated the SAS outputs and graphs for the regression analyses (i.e., Cox regression, logistic regression, and assessment of interaction) so that we may fully understand the statistical models used for these analyses. Please also provide the mathematical formulas for the regression models with brief description.
2. For Appendix 3 of the NDA Amendment and Final Safety Update, for each of the two-dimensional probability plots of “event” vs. concentration, please clarify in writing whether the “event” used as the response parameter (y-axis) is the same as the “event” up to which concentration values were used to calculate the time-normalized mean concentrations (x-axis).
3. For Appendix 3 of the NDA Amendment and Final Safety Update, please provide the results of the regression analyses for azathioprine control group for each safety and efficacy event (i.e., probability of event as a function of cyclosporine exposure). Please provide raw data, SAS data files, SAS command files, SAS outputs, and graphs.
4. For Appendix 3 of the NDA Amendment and Final Safety Update, for the probability analyses and plots of 30% reduction in creatinine clearance (CrCL) vs. concentration, in addition to your analyses using the 1-month CrCL values as baseline, please perform similar analyses using CrCL values at a “median time” post transplant as baseline (y-axis) and the corresponding time-normalized drug concentrations starting at the “median time” to the time of the renal event (x-axis). The “median time” is the median time at which maximum CrCL values are determined post transplant. In our preliminary analysis, the median time to attain “maximum” CrCL appears to be 1 week or 2 weeks post transplant. Please provide raw data, SAS data files, SAS command files, SAS outputs, and graphs for both everolimus treatment and azathioprine control groups for this latter analysis.
5. For Section 8 of the NDA Amendment and Final Safety Update, please provide what concentration values (e.g., simple mean value calculated using concentrations measured up to 6 months or time-normalized mean value calculated using concentrations measured up to a specific event) was used in each figure and table.
6. For Study Report A2306 (Table 6-2 in Page 3231), please provide an explanation of why and how everolimus doses were reduced over time (i.e., from 1.5 mg at Day 1 to 1.2 mg at Month 12) in upper dose arm (1.5 mg bid). You provided in the report dose increase plan (i.e., to achieve everolimus trough concentration > 3 ng/mL) but no dose reduction plan. Furthermore, such dosage reduction is not reported in Study A2307.

Please provide us with the date(s) for the submission of this information.

NDA 21-560  
NDA 21-628

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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Matthew Bacho  
3/24/04 04:04:47 PM  
CSO  
NDAs 21-560 & 21-628



**NDA 21-560**  
**NDA 21-628**

Novartis Pharmaceuticals Corporation  
Attention: Ronald G. Van Valen  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

We acknowledge receipt of your February 27, 2004 resubmission to your new drug applications for Certican<sup>®</sup> Tablets (everolimus), 0.25, 0.50, 0.75, and 1.0 mg.

We consider this a complete, class 2 response to our October 20, 2003 action letter. Therefore, the user fee goal date is August 27, 2004.

If you have any questions, call me at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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NDAs 21-560 & 21-628



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Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: February 18, 2004**

<b>To:</b> Ron Van Valen, Director Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (973) 781-7646	<b>Phone number:</b> (301) 827-2127
<b>Subject:</b> Proposed NDA Amendment Statistical Analysis Plan (NDAs 21-560 and 21-628)	

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**Total no. of pages including cover:** 3

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**Reviewers:** Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader/Arturo Hernandez, M.D., Medical Officer/Karen Higgins, Sc.D., Statistics Team Leader/LaRee Tracy, M.A., Statistics Reviewer/Ruthanna Davi, M.S., Statistics Reviewer

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## NDA 21-560 and 21-628

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets as well as your February 11, 2004 statistical analysis plan analysis plan entitled, "Additional analyses bridging new studies A2306/A2307 to pivotal studies B201/B251/B253 and study B156 for Amendment to the original NDA." Our reviewing medical officer and statisticians would like to make the following comments:

1. Section 2.1 of the above referenced document seems to reflect your understanding that our concerns regarding the potential for systematic bias resulting from cross-study comparisons have been resolved. The issue of the validity of cross-study comparisons is a difficult one and will be addressed as part of the review of the NDA amendment. Please refer to the International Conference on Harmonization Harmonized Tripartite Guideline, "Choice of Control Group and Related Issues in Clinical Trials", (also titled E10) sections 1.2, 1.3, and 2.5 for discussion regarding the need for concurrently controlled trials.
2. Section 3.5 of the analysis plan proposes subgroup analyses by several factors (i.e., recipient race, donor type, and delayed graft function) we had mentioned during the November 25, 2003 teleconference. While we are appreciative of your efforts to examine these risk factors in detail, we wish to be clear that these particular covariates were mentioned as examples of how the populations from various studies may differ and were not intended to be an exhaustive list. Other factors affecting the validity of the cross-study comparisons may likely be identified as part of the review of the NDA amendment.
3. In multiple instances, the analysis plan proposes utilizing achieved exposures in the usual place of the randomized treatment assignment. This type of retrospective exposure-response analysis is considered by the Division to be exploratory, as the level of exposure achieved was not randomly assigned and is likely affected by numerous covariates. It is our opinion that this type of retrospective analyses of existing data will not adequately or conclusively delineate the effect of these covariates from the effect of the levels of exposure.
4. As part of the NDA amendment, please provide justification regarding the appropriateness of pooling studies B201 and B251.

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
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Matthew Bacho  
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NDAs 21-560 & 21-628



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Office of Drug Evaluation IV

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**DATE:** January 16, 2004

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Andrei E. Nabakowski Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (973) 781-7646	<b>Phone number:</b> (301) 827-2127

**Subject:** Clarification of requested  $t_{1/2}$  data for everolimus

**Total no. of pages including cover:** 3

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**NDA 21-560 & 21-628**  
**NDA 21-561 & 21-631**

Dear Mr. Van Valen:

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets, which were submitted on December 19, 2002, as well as NDAs 21-561 and 21-631 for Certican<sup>®</sup> Dispersible Tablets, which were submitted on January 31, 2003.

During our telecon of January 6, 2004, there was discussion regarding the  $t_{1/2}$  data from Studies W101 and B154. In order to clarify our position, the reviewing clinical pharmacologist would like to pass along the following recommendation:

Due to the apparent non-linearity in everolimus PK above doses of 2.5 mg, the Division highly recommends that Novartis provide the pooled  $t_{1/2}$  data from both studies at doses up to 2.5 mg, with particular emphasis on doses of 0.75 mg and 1.5 mg, if possible.

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Sincerely yours,

*{See appended electronic signature page}*

Andrei E. Nabakowski  
Regulatory Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Andrei Nabakowski

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CSO

Jan 16, 2004 Everolimus PK recommendation



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 15, 2004

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (862) 778-7646	<b>Phone number:</b> (301) 827-2127
<b>Subject:</b> Information request (NDAs 21-560 and 21-628)	

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**Total no. of pages including cover:** 4

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**Reviewers:** Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader/Arturo Hernandez, M.D., Medical Officer/Philip M. Colangelo, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader/Jang-Ik Lee, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer

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**NDA 21-560**  
**NDA 21-628**

Dear Mr. Van Valen:

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> (everolimus) Tablets, our memorandum of November 21, 2003, and the January 6, 2004 teleconference, during which the following was discussed.

(b) (4)

In the clinical pharmacology review of the exposure-response (E-R) data from Study B253 of the NDA, our exploratory analysis suggested that the incidence of nephrotoxicity is dependent, in part, upon everolimus trough concentrations.

1. In light of these findings, we request that you provide the raw data and the analyses demonstrating the effects of both everolimus and cyclosporine exposures on the efficacy and safety responses. Particularly, please provide the raw data and analyzed results obtained from Study B253 demonstrating that everolimus contributed to the rate of primary composite endpoints but not to the incidence of cyclosporine-induced nephrotoxicity. The results of the analyses should be such that our reviewers can easily reproduce. We recommend visualizing the effects of both everolimus and cyclosporine trough concentrations on the efficacy and safety responses in a 3-dimensional graph (e.g., x-axis = everolimus trough concentration, y-axis = cyclosporine trough concentration, and z-axis = % decrease, and/or incidence of  $\geq 30\%$  decrease, in calculated creatinine clearance from baseline)\* and, if possible, conducting relevant statistical analyses (e.g., logistic regression).
2. In the use of exposure parameters (i.e., trough concentrations), please develop criteria for when measured values should or should not be used. For example, as an everolimus exposure parameter, the trough concentration determined on Day 45 at the time of nephrotoxicity incidence (e.g., 10 ng/mL) should be used instead of the mean everolimus concentration calculated from all measured values for up to six months (e.g., 5 ng/ml). For another example, the mean concentration value (e.g., 3.3 ng/mL) adjusted for the time interval of observation (i.e., time-normalized mean concentration) should be used instead of the simple mean value (5 ng/mL) calculated from all values measured at Week 1 (9 ng/mL), Month 1 (3 ng/mL), and Month 6 (3 ng/mL) because the contribution of each concentration value to overall exposure is not equal. Of course, data obtained within a week post-transplant (non-steady state values) should not be used for the control as well as everolimus treatment groups.

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

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\* This suggestion was slightly altered from what was stated during the January 6, 2004 teleconference to reflect our reevaluation of this analysis. Our official minutes for this teleconference will of course accurately replicate what was discussed.

NDA 21-560  
NDA 21-628

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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Matthew Bacho  
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CSO  
NDAs 21-560 & 21-628

## MEMORANDUM OF TELECONFERENCE

**MEETING DATE:** January 6, 2004  
**TIME:** 8:45 AM  
**APPLICATION:** NDAs 21-560 and 21-628 [Certican<sup>®</sup> (everolimus) Tablets]

**BETWEEN:**

Kenneth Somberg, M.D.	Global Head of Clinical Research
Jonathan Jaffe, M.D.	Clinical Project Leader
John M. Kovarik, Ph.D.	Clinical Pharmacology
Chyi-Hung Hse, Ph.D.	Biostatistician
Heinz Schmidli, Ph.D.	Modeling Statistician
Ronald G. Van Valen	Drug Regulatory Affairs, International Project Team

Representing: Novartis Pharmaceuticals Corporation

**AND**

Marc Cavaille-Coll, M.D., Ph.D.	Medical Team Leader
Philip Colangelo, Pharm.D., Ph.D.	Clin. Pharmacology & Biopharm. Team Leader
Jang-Ik Lee, Pharm.D., Ph.D.	Clin. Pharmacology & Biopharm. Reviewer
Mark Seggel, Ph.D.	Chemistry Reviewer
Andrei Nabakowski, Pharm.D.	Regulatory Project Manager

Representing: Division of Special Pathogen and Immunologic Drug Products

**SUBJECT:** Novartis Pharmaceuticals Corporation (Novartis or applicant) requested a teleconference to discuss clinical pharmacology issues with NDAs 21-560 and 21-628 for Certican<sup>®</sup> (everolimus) Tablets.

**BACKGROUND:** Novartis' IND for everolimus was originally submitted to the FDA on November 15, 1996. Four pre-NDA meetings were conducted on December 3, 1999; January 27, 2000; February 6, 2001; and March 25, 2002 to discuss the applicant's proposed marketing applications for this drug product. Novartis subsequently submitted NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets on December 19, 2002, for which the Division issued an approvable letter on October 20, 2003. The Division responded to the applicant's meeting request of October 31, 2003, with a memorandum on November 21, 2003. A teleconference was held on November 25, 2003 to discuss the November 21, 2003 memorandum and proposed amendments to the application, during which it was decided that future discussions should be held on the pharmacokinetics of everolimus and a proposed everolimus therapeutic drug monitoring study. This

teleconference of January 6, 2004 was scheduled to discuss these pharmacokinetic issues.

### **DISCUSSION POINTS:**

After a brief introduction by the participants, Novartis indicated that everolimus had successfully completed the European mutual recognition process for approval after having been approved in Sweden. Novartis will submit the approved European labeling for FDA reference.

Four main points were identified by the division for discussion:

- 1) Everolimus clearance (CL/F), volume of distribution (V/F), and elimination half-life ( $t_{1/2}$ )
- 2) Drug interactions
- 3) Cyclosporine  $C_2$  vs  $C_{min}$  monitoring
- 4) Therapeutic index and therapeutic drug monitoring

### **Point #1: Clearance (CL/F), Volume of distribution (V/F), and Elimination half-life ( $t_{1/2}$ )**

The division is satisfied with the clearance issues, but has concern with the values provided for V/F and  $t_{1/2}$ . It appears that everolimus is a multi-compartment model drug, while the analysis submitted uses a one compartment model. A recent submission listed the V/F as (b) (4) while the proposed labeling (September 30, 2003 version) identified V/F as being (b) (4). Novartis said that the (b) (4) value was from an early formulation which was not to be marketed. The division then questioned if the sponsor had proven bioavailability or bioequivalence for the formulation. Novartis stated that when the volume is very large, the V/F is descriptive and not quantitative, and asked how precise must the value be for the product label. The division suggested that a range of V/F values observed in different studies might be more appropriate to present than one specific averaged value.

Study W101 enrolled 30 renal transplant patients who were administered everolimus doses ranging from 0.25 mg to 25 mg. The 0.25 mg dose produced undetectable blood concentrations, so the useful range was 0.75 mg to 25 mg, and provided a  $t_{1/2} = 28 \pm 7$  hours. The division stated that everolimus pharmacokinetics do not appear linear over the entire range of doses studied, there is a large difference in mean values between the two acceptable doses (0.75 mg and 2.5 mg), and that the number of patients was too small ( $n = 6$  per dose level). Furthermore, healthy volunteers showed a  $t_{1/2}$  of 40-50 hours, which is longer than the value seen in actual transplant patients, who received cyclosporine administration and would be expected to have a longer  $t_{1/2}$  than the healthy subjects. The division stated that a good measure of  $t_{1/2}$  was important in order to assist clinicians in dose adjustments. Novartis stated that clinicians often look at rough  $t_{1/2}$  values when making dose adjustments, but the division stated that if therapeutic drug monitoring is used, then a better idea of  $t_{1/2}$  is necessary. Novartis then suggested that the B154 study might be a good indicator for  $t_{1/2}$  values. The division agreed to review the study upon NDA resubmission and recommended that the  $t_{1/2}$  data be pooled between Studies B154 and W101 in order to provide a more adequate estimate of the  $t_{1/2}$ .

## Point #2: Drug Interactions

The division referred to the FDA guidances on *in vivo* and *in vitro* drug metabolism/drug interaction studies and stated that if a strong signal is seen (i.e. low  $IC_{50}$  and/or low  $K_i$ ) then *in vivo* studies should be performed to identify the magnitude of drug exposure. In order to make dose adjustments, we need to quantify what exactly will happen with everolimus exposure with concomitant drug therapy. This is an important issue- Rapamune<sup>®</sup> required about 15 drug interaction studies and we would expect a similar amount of effort to adequately address drug interaction issues. Preliminary recommendations for drug interaction studies included phenytoin, erythromycin, verapamil, and ketoconazole so that we know what may happen when these drugs are concomitantly administered with everolimus.

The division stated that the wording proposed by Novartis to address drug interactions in the label (i.e. (b) (4)

) is not very helpful. The magnitude of the effect may make a difference between contraindication versus a recommendation for increased monitoring of everolimus levels when such drug is started or stopped. Novartis stated that the individual magnitude of drug interactions can vary greatly between patients, and therapeutic drug monitoring with everolimus would allow detection and response in the individual patient rather than having to account for wide ranging populations. Those prescribers who would use everolimus would be knowledgeable in its use, and would know how to respond with their patients and their individual drug regimens. FDA pointed out that there was no mention of this in Novartis' table that described how the drug interactions could be handled. (b) (4)

While this could be an improvement, it remains a reviewable issue. FDA repeated its concern about the need to quantify the magnitude of strong drug interactions to decide whether these could be managed by TDM or contraindications in the label.

Novartis used rifampin in an *in vivo* study as an example of a strong inducer, and any moderate inducer would have an effect less than or up to the rifampin value. Novartis stated that anything over a 5-fold induction is strong, so if the result is 10- or 15-fold we already know that the effect will be great. Assays could be performed to measure the patient's levels, and Novartis states that same day results could be recorded with early delivery- if the sample is submitted by 10 AM, results could be had by 4 PM. The division noted that some patients may not have assays performed daily for any number of reasons, and that the treatment of these patients should also be considered.

The division then suggested that it may be preferable to have a representative study with ketoconazole (a strong CYP3A inhibitor) in order to characterize its magnitude of effect. Ketoconazole was studied for Rapamune<sup>®</sup> and it resulted in a contraindication. The division stated that the decision rests with Novartis, but the possibility exists that drugs such as rifampin, ketoconazole, and other strong inhibitors and inducers may be contraindicated in the labeling. Novartis agreed that further labeling consideration will be required. The division also believes that additional studies and data for drugs that affect p-glycoprotein mediated drug transport, for

example verapamil, are needed, with information on the ranges of change in patients as well as the average value.

Phenytoin was mentioned as a possible drug to be studied, but Novartis called attention to the small pool of transplant patients available who might be on phenytoin. Additionally, studies using single doses of phenytoin may not be useful so the proposal for phenytoin studies was dropped.

The division then recommended drug interaction studies with ketoconazole, erythromycin, and verapamil, and Novartis said that they would discuss this with their management. The possibility of conducting these studies as a Phase IV agreement was mentioned by Novartis. The division stated that if the efficacy and safety profiles of everolimus allow its administration as a fixed dose, then deferment of studies to Phase IV might be possible. If therapeutic drug monitoring is deemed to be necessary for the effective and safe use of everolimus, then these studies would be needed before full approval, otherwise an “approvable” might be an option with studies as a condition for full approval. Novartis stated that they do not believe that everolimus is a narrow therapeutic index drug. The division granted that while it may not intrinsically be a narrow therapeutic index drug, the circumstances in which it is used may require very careful use. Novartis pointed out that while sirolimus (Rapamune<sup>®</sup>) was used on a fixed dose and therefore required wide ranging drug interaction studies, everolimus would not need such studies due to their drug monitoring strategy. The division stated that Novartis needs a better handle on drug interactions. The division is dismayed at the apparent lack of diligence in pursuing drug interaction studies citing as example the number of drug interaction studies that had been conducted with the other drug in its class, sirolimus. (b) (4)

Ultimately, any decision to defer this issue to postmarketing would remain a review issue, meaning that it would be considered after looking at the totality of the data, but could still make the difference between an approvable vs. an approval when an action is taken.

### **Point #3: Cyclosporine $C_2$ vs. $C_{min}$ Monitoring**

The division stated that while  $C_2$  may potentially be a good measure, there are questions of reliably determining  $C_2$  due to the steep slope of the curve at that time point. Ten minutes of deviation in sampling could have a strong effect on the results, and some clinics may not adhere to a rigorous time schedule. This may potentially complicate therapeutic drug monitoring. Other medications such as Rapamune<sup>®</sup> and Prograf used  $C_{min}$  in their controlled studies, and the division would like to have  $C_{min}$  values. Novartis said that they used  $C_{min}$  values in the approved European labeling, and that they will provide  $C_{min}$  as well as  $C_2$  values in their submission to us. The Division agreed with this.

### **Point #4: Therapeutic Drug Monitoring**

In “role of therapeutic drug monitoring in everolimus use” in page 3 of Novartis’ response to Request 4b, it was claimed that everolimus is not a narrow therapeutic margin drug and that TDM is

not essential for the safe use of everolimus.

(b) (4)

In the clinical pharmacology review of the exposure-response (E-R) data from Study B253 of the NDA, our exploratory analysis suggested that the incidence of nephrotoxicity is dependent, in part, upon everolimus trough concentrations.

In light of these findings, we request that you provide the raw data and the analyses demonstrating the effects of both everolimus and cyclosporine exposures on the efficacy and safety responses. Particularly, please provide the raw data and analyzed results obtained from Study B253 demonstrating that everolimus contributed to the rate of primary composite endpoints but not to the incidence of cyclosporine-induced nephrotoxicity. The results of the analyses should be such that our reviewers can reproduce. We recommend visualizing the effects of both everolimus and cyclosporine trough concentrations on the efficacy and safety responses in a 3-dimensional graph (e.g.; x-axis = everolimus trough concentration, y-axis = cyclosporine trough concentration, and z-axis = incidence of  $\geq 30\%$  and/or  $\geq 50\%$  decrease in calculated creatinine clearance from baseline) and, if possible, conducting relevant statistical analyses (e.g., logistic regression).

In the use of exposure parameters (i.e., trough concentrations), please develop criteria for when measured values should or should not be used. For example, as an everolimus exposure parameter, the trough concentration determined on Day 45 at the time of nephrotoxicity incidence (e.g., 10 ng/mL) should be used instead of the mean everolimus concentration calculated from all measured values for up to six months (e.g., 5 ng/ml). For another example, the mean concentration value (e.g., 3.3 ng/mL) adjusted for the time interval of observation (i.e., time-normalized mean concentration) should be used instead of the simple mean value (5 ng/mL) calculated from all values measured at Week 1 (9 ng/mL), Month 1 (3 ng/mL), and Month 6 (3 ng/mL) because the contribution of each concentration value to overall exposure is not equal. Of course, data obtained within a week post transplant (non steady-state values) should not be used for the control as well as everolimus treatment groups.

#### ACTION ITEMS:

- 1) Novartis will submit the approved European labeling for FDA reference.
- 2) The division suggested that a range of V/F values observed in different studies might be more appropriate to present than one specific averaged value.
- 3) The Division agreed to review the pooled  $t_{1/2}$  data from Studies W101 and B154.  
[POST MEETING NOTE: Because of the apparent non-linearity in everolimus PK above doses of 2.5 mg, the Division highly recommends that Novartis provide the pooled  $t_{1/2}$  data from both studies at doses up to 2.5 mg, with particular emphasis on doses of 0.75 mg and 1.5 mg, if possible. This recommendation was transmitted to Novartis in our fax of January 16, 2004.]
- 4) The division recommends drug interaction studies with ketoconazole, erythromycin, and

verapamil. Novartis said that they would discuss this with their management.

5) Novartis will provide  $C_{\min}$  values for cyclosporine in their submission.

6) The division will forward Dr. Lee's comments on therapeutic drug monitoring to Novartis.  
[Transmitted on January 15, 2004]

Minutes Preparer: *{See appended electronic signature page}*

Meeting Chairperson: *{See appended electronic signature page}*

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NDA 21-560, 21-628 Minutes of January 6, 2004 telecon

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## FINAL CARCINOGENICITY STUDY EVALUATION

Executive CAC

Date of Meeting: December 2, 2003

Committee: David Jacobson-Kram, Ph.D., HFD-024, Chair  
Joseph Contrera, Ph.D., HFD-901, Member  
Abby Jacobs, Ph.D., HFD-024, Member  
Bob Osterberg, Ph.D., HFD-520, Alternate Member  
Stephen Hundley, Ph.D., HFD-590, Acting Team Leader  
Steven Kunder, Ph.D., HFD-590, Presenting Reviewer

Author of Draft: Steven Kunder

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21-560

Drug Name: certican (everolimus, SDZ RAD)

Sponsor: Novartis Pharmaceutical Corporation

Background: Certican is an immunosuppressant for prevention of organ transplantation rejection which binds to the immunophilin, FK binding protein 12 (FKBP-12), producing an immunosuppressive complex. This complex binds to and inhibits the activation of a kinase called the mammalian target of rapamycin (mTOR). Inhibition of mTOR by rapamycin suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle. Everolimus had no positive genotoxicity findings in the in vitro-bacterial reverse mutation, in vitro mammalian mouse lymphoma, V79 Chinese hamster cell mutation and in vivo mammalian micronucleus assays.

### Mouse Carcinogenicity Study

This study was acceptable to the executive CAC as the high dose group (males and females) had decreased weight gain (>10%) relative to the control groups at final necropsy. Exposure to drug can be considered adequate as more than 50% of mice were still alive at 89-90 weeks for both males and females. Sufficient numbers of mice survived to the terminal sacrifice to produce a valid study for statistical analysis. The protocol was previously judged to be possibly inadequate by the executive CAC, based on a 13-week dose-ranging study due to a possibly insufficiently high dose chosen by the sponsor, who had already begun the study. The study was conducted in accordance with the protocol and provided sufficient histopathological data from the designated organs and tissues to evaluate both the non-neoplastic and neoplastic effects of everolimus at all dose levels including the zero-level controls. Survival was approximately 55% in males

at 104 weeks and 42% of females after 101 weeks. Survival among treated mice was highest in the high dose groups correlating with lower bodyweight gain. Food consumption was unaffected by treatment. Histopathology findings included treatment-related changes in the thymus, testes, and epididymides. High dose females had thymic involution. Leukocytic infiltration of the renal cortex was reduced in mid- and high dose females. A similar effect was seen in the submandibular salivary gland in treated females and appears related to immunosuppression. Everolimus administration to mice for 104 weeks (males) or 101 weeks (females) provided immunosuppression-related pathologies and previously seen reproductive effects and no drug-related neoplastic findings. The high dose (0.9 mg/kg) group had an AUC of 1377.8 ng-hr/ml in males and 3084.2 ng-hr/ml in females (mean for both sexes= 2231 ng-hr/ml). The AUC for everolimus in patients after six days of treatment with 0.2 mg/kg was 81" 34 ng-hr/ml, which was exceeded by the mean exposure in mice receiving 0.9 mg/kg for 101-104 weeks.

#### Rat Carcinogenicity Study

This study was acceptable to the executive CAC as they concurred that the study achieved an MTD as the high dose group (males and females) had a >10% lower body weight relative to the bodyweight of the control groups at final necropsy. Weight gain was decreased by >10% in the high dose groups relative to the weight gain in control groups. Sufficient numbers of rats survived to the terminal sacrifice to produce a valid study for statistical analysis. The study was conducted in accordance with the protocol and provided sufficient histopathological data from the designated organs and tissues to evaluate both the non-neoplastic and neoplastic effects of everolimus at all dose levels including the zero-level controls. Survival was approximately 58% in males and 62% of females after 104 weeks. Survival among treated rats was highest in the mid and high dose groups correlating with lower bodyweight gain. Food consumption was slightly decreased in the high dose group; the rest of the groups were unaffected by treatment. Histopathology findings included treatment-related changes in the testes, epididymides, ovaries and uterus in the 0.9 mg/kg group. Immunosuppression-related changes included thymic atrophy, inflammatory changes in the Harderian glands, mesenteric lymph nodes, lachrymal glands, lungs, pancreas, skeletal muscle and submandibular gland. In the lung, increased incidence of alveolar macrophages was found, with eosinophilic deposition and pigment-laden macrophages. In the liver, age-related effects such as increased incidence of senile portal liver tract changes in males receiving 0.3 and 0.9 mg/kg appear treatment-related. Axonal degeneration of the sciatic nerve in females receiving 0.9 mg/kg was also treatment-related. Lens changes included anterior suture line opacity and increased incidence of lenticular degeneration in males at 0.9 mg/kg. Age-related effects of the adrenal cortex, focal hypertrophy, hyperplasia and fatty vacuolation, were reduced in treatment groups. Everolimus administration to rats for 104 weeks provided immunosuppression-related pathologies of the immune tissues and lungs, treatment-related effects on the lens, liver and adrenal gland and previously seen reproductive system effects with no neoplastic findings.

The high dose (0.9 mg/kg) group had an AUC of 138 ng-hr/ml in males and 42.9 ng-hr/ml in females (mean for both sexes=90 ng-hr/ml). The AUC for everolimus in patients after six days of treatment with 0.02 mg/kg was 81" 34 ng-hr/ml, approximating the mean exposure in rats receiving 0.9 mg/kg for 104 weeks.

#### Executive CAC Recommendations and Conclusions:

##### Mouse Study:

This study was acceptable to the committee, based on a >10% suppression of weight gain in the high dose groups relative to the control groups. The committee concurred that there were no drug-related tumor findings in this study.

##### Rat Study:

The committee concurred that the study reached an MTD, based on a >10% suppression of weight gain in the high dose groups relative to the control groups as well as a weight decrement of >10% in the high-dose groups compared to the mean weight of the control groups, that the study was therefore adequate and that there were no drug-related tumor findings in this study.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

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David Jacobson-Kram  
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## MEMORANDUM OF TELECONFERENCE

DATE: November 25, 2003

APPLICATION NUMBER: NDAs 21-560 & 21-628 [Certican<sup>®</sup> (everolimus) Tablets]

BETWEEN:

Name: Gilles Feutren, M.D., Global Head Development, Transplantation & Immunology  
Kenneth Somberg, M.D., Vice President, Clinical Research  
Jonathan Jaffe, M.D., Clinical Program Leader  
Yulan Li, Ph.D., Senior Project Biostatistician  
Monica Schnyder, Ph.D., Global Head DRA  
Ronald Van Valen, Director, DRA  
Mathias Hukkelhoven, Ph.D., Global Head Drug Regulatory Affairs  
Jonathan Kovarik, Ph.D., Clinical Pharmacology Expert  
Peter Marbach, Ph.D., Bioanalytical Expert  
Representing: Novartis Pharmaceuticals Corporation

AND

Name: Renata Albrecht, M.D., Director and Meeting Chairperson  
Steve Gitterman, M.D., Ph.D., Deputy Director  
Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader  
Arturo Hernandez, M.D., Medical Officer  
Ruthanna Davi, M.S., Statistics Reviewer  
LaRee Tracy, M.A., Statistics Reviewer  
Philip Colangelo, Pharm.D., Ph.D., Clin. Pharmacology & Biopharm. Team Leader  
Jang-Ik Lee, Pharm.D., Ph.D., Clin. Pharmacology & Biopharm. Reviewer  
Mark Seggel, Ph.D., Chemistry Reviewer  
Matthew A. Bacho, Regulatory Health Project Manager  
Representing: Division of Special Pathogen and Immunologic Drug Products

SUBJECT: Novartis Pharmaceuticals Corporation (Novartis or applicant) requested a teleconference to discuss their plan to amend NDAs 21-560 and 21-628 for Certican<sup>®</sup> (everolimus) Tablets.

BACKGROUND: Novartis' IND for everolimus was originally submitted to the FDA on November 15, 1996. Four pre-NDA meetings were conducted on December 3, 1999; January 27, 2000; February 6, 2001; and March 25, 2002 to discuss the applicant's proposed marketing applications for this drug product. Novartis subsequently submitted NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets on December 19, 2002, for which the Division issued an approvable letter on October 20, 2003. The Division responded to the applicant's meeting request of October 31, 2003, with a memorandum on November 21, 2003.

## DISCUSSION POINTS:

After a brief introduction from both sides, the applicant's proposals and Division's November 21, 2003 comments (italicized below) were discussed in detail.

1. *Proposal #1a: We propose to submit the completed 12-month clinical study reports from two (2) de novo renal transplant studies A2306 and A2307 to meet the Division's criteria and address your request '...for improved renal function while maintaining adequate protection against graft rejection, graft loss, or death in de novo renal transplantation.' Does the Division agree with this proposal?*

The Division noted that this proposal was acceptable. However, the Division expressed concerns regarding Studies A2306 and A2307, specifically the small number of subjects, the lack of an approved comparator, and the inherent difficulties to assessing biopsy-proven rejection due to the potential for bias in these open-label trials.\* Additionally, the Division stated that there were potential problems associated with cross-study comparisons when there were differences in the observed (e.g., relative differences in enrollment of black subjects, living-related donor grafts, and the number of patients with delayed graft function) and unobserved covariates between trials. Novartis acknowledged these statements and agreed that the cross study comparisons could be systematically biased; they then stressed how important it was for them to know whether their proposal fulfilled the requirement of the Division's approvable letter regarding alternative approaches.\*\* The Division stated their intention to be flexible on this issue by not arbitrarily discounting other types of data that might address the deficiencies, and from the perspective of *filing* the proposed amendment, the data from Studies A2306 and A2307 would be acceptable.

The Division added that while the drug regulations (specifically 21 CFR 314.126) outlined what the FDA considered to be "adequate and well-controlled studies" (including historical controls), they were also responsible for pointing out the data's weaknesses if there were any. The Division noted their willingness to consider whatever the applicant proposed, but there were types of data that could prove to be more challenging to review; and the Division also noted that after filing, they may identify issues and concerns that need further elucidation. The applicant stated their hope that the proposed amendment would "conceptually" address the deficiencies of the approvable letter because any other outcome would be counterproductive. The Division would not comment on the actual review or anticipate its outcome at that time and could only focus on the fileability of the proposed amendment. One of their goals, noted the Division, was to identify other useful data that could help determine the safety and efficacy of the drug product, and as long as Novartis provided the rationale that supports its inclusion, then the information would be seriously considered.

With respect to the data from Studies A2306 and A2307, the applicant asked if the Division had any suggestions regarding which deficiencies should be

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\* As previously communicated to Novartis on September 13, 2001, and March 25, 2002.

\*\* October 20, 2003 approvable letter: "An alternate approach would be to provide prospective analyses from completed, controlled studies evaluating lower exposures to cyclosporine in combination with everolimus and dosed according to a prospectively defined therapeutic drug monitoring scheme (TDM)."

addressed. In addition to what was stated above, the Division noted that these trials might not be able to exclude an unacceptable decrease in the rate of patient and graft survival; obviously, they would not make any assumptions about the trials' outcome but if the results were less than convincing, additional data would be necessary.

Novartis acknowledged the potential for bias inherent to cross-study comparisons but in terms of demographics and clinical practice over the last 5-6 years, there was very little difference between Studies A2306, A2307, and their other trials. The applicant acknowledged the low number of black subjects in A2306 and A2307 and suggested concentrating on non-black subjects for these comparisons. The Division noted that these issues should be addressed in the amendment; however, it was also noted that clinical practice had changed over the last few years since organs from living donors are much more common now than in the past, an important aspect that could affect outcome. The Division would have to complete their review of the proposed amendment within 6 months of its receipt and if Novartis could use their knowledge of the data to anticipate the Division's questions and analytical needs then the review would proceed more smoothly.

2. *Proposal #1b: We propose to initially recommend LCMS methodology as an example of a validated assay for everolimus blood concentrations as used in Studies A2306 and A2307 in order to support a successful monitoring schedule and dose adjustment range; supporting data demonstrating everolimus blood levels were managed by the investigators in A2306/7 will be provided. Study A2306 and A2307 will provide experience of a successful monitoring schedule and will demonstrate that a central laboratory-based monitoring method is capable of a rapid response time that can maintain patients within a desired therapeutic concentration range. In addition, Novartis is also working with (b) (4), an independent company, to develop and register an immunoassay kit for everolimus. While it is our intention to have the immunoassay kit available as soon as possible the timelines for approval from FDA/CDRH are not predictable. Does the Division accept our proposal to initially recommend LCMS methodology and a monitoring schedule based on Studies A2306/07?*

The applicant acknowledged the November 21, 2003 memorandum and asked if there were specific elements that the Division would like to see in these analytical reports. The Division asked Novartis to submit their proposal for review. The applicant added that there would be a parallel program (not involving (b) (4)) that included a central laboratory with a dedicated liquid chromatography-mass spectrometer and full-time employee. (The turnaround time would be 6 hours if a sample arrived by 10 a.m.) Novartis stated that proficiency testing would be completed before operation sometime in February 2004. (The applicant then noted that (b) (4) would be involved in the cross-validation required by the FDA.) The Division agreed with this plan and asked that it be documented in their amendment.

3. [REDACTED] (b) (4)

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6. *Proposal #2c: We propose to initially recommend LCMS methodology as an example of a validated assay for everolimus blood concentrations as used in Studies A2306 and A2307 in order to support a successful monitoring schedule and dose adjustment range. This methodology will also demonstrate that a laboratory-based TDM method is capable of a rapid response time that can maintain patients within a desired therapeutic concentration range. As indicated above (Novartis Response #2b) it is also our intention to have an everolimus immunoassay kit available for commercial use. Does the Division accept our proposal to initially recommend LCMS methodology and a monitoring schedule based on Studies A2306/07?*

Please refer to Proposal #1b above.

7. [REDACTED] (b) (4)  
n the  
c  
[REDACTED]

Novartis noted the Division's communication of November 21, 2003, and accepted the offer to discuss labeling after a substantial review of the amendment.

8. *Proposal #4: In addition to submitting A2306 and A2307 12-month completed clinical study reports in the amendment to the original NDA, Novartis would like to propose additional analyses to bridge the renal function and key efficacy results from these new trials to pivotal studies B201/B251/B156 and to B253 to further assist FDA's review:*

*In renal transplantation, PK/PD analyses will consist of bridging retrospective everolimus TDM results of B201/B251 to prospective everolimus TDM data of A2306 while renal function and key efficacy data analysis will include bridging of B201/B251 to A2306 to show improved renal function and comparable efficacy as well as bridging B156 to A2307 to show improved renal function and comparable efficacy.*

[REDACTED] (b) (4)

The Division agreed with these proposals while noting the caveats mentioned throughout this teleconference.

9. *Novartis Safety Update Proposal #2d: We propose to submit serious AEs on the use of Certican that is limited to other solid organ transplantation and includes lung transplantation (B159 and B152) and liver transplantation (B158). Does the Division accept our proposal?*

The Division accepted this proposal.

10. *Novartis Safety Update Proposal #4: We propose to submit CRFs and narratives for patients in Study 2306 and 2307 similar to that submitted for our core renal studies 201/251/156. As previously agreed with the Division, text narratives were submitted in the original NDA for the following events: death, except those which are clearly unrelated to study medication (e.g., elective surgery, surgical/technical events, etc.); graft losses; unexpected or life-threatening serious adverse events (SAE), including serious infections, unusually severe acute rejection episodes that are reported as SAEs and any malignancies; premature discontinuations of study medication for any reason except withdrawal of consent or administrative reasons (e.g., adverse events or abnormal laboratory values leading to premature discontinuation); all other life-threatening events, including overdose of study medication that prompts medical attention; and medically significant, unexpected SAEs. In addition, line listings were provided for the following events: notable laboratory abnormalities not included in text narratives that result in a SAE and all permanent discontinuations of study medication for administrative reasons or withdrawal of consent. Does the Division require the same information for this safety update? Will the Division accept CRFs and narratives only for deaths and dropouts due to serious adverse events?*

The applicant assured the Division that they would follow the memorandum of November 21, 2003, and asked if indeed all of the case report forms for Studies A2306 and A2307 should be submitted with the amendment. The Division confirmed their request for this information.

11. *Comment #4a from the Division's November 21, 2003 communication: Basic everolimus pharmacokinetic parameters were not adequately determined. Please provide adequately estimated values for the clearance (CL<sub>b</sub>/F), volume of distribution (V<sub>z,b</sub>/F), and elimination half-life (t<sub>1/2</sub>) of everolimus at the range of probable clinical doses following multiple (steady state) oral doses to targeted patients of interest using to-be-marketed Certican tablets or formulations that were tested for bioequivalence compared to the tablets.*

Novartis stated their belief that sufficient data to characterize the pharmacokinetics of everolimus had already been submitted for review and then inquired about the basis for this request. The Division noted that the drug product's basic pharmacokinetic parameters were not adequately determined: (a) Some studies were conducted using capsule formulations that were not tested for relative bioavailability to the to-be-marketed or clinical tablets; (b) Some studies did not include pharmacokinetic data at the proposed doses; (c) The elimination half-life could not be determined in some studies because the dosing interval was much shorter than the drug's half-life; and (d) Some studies were conducted in healthy subjects who were not taking cyclosporine that markedly decreases

everolimus clearance but increase elimination half-life. In summary, the Division did not have adequately determined values for the clearance, volume of distribution, and elimination half-life ( $t_{1/2}$ ) for the proposed steady-state clinical doses in targeted patients using the to-be-marketed tablets or formulations that were tested for bioequivalence to the tablets. The applicant noted that apart from the elimination half-life, clearance and volume of distribution of everolimus were calculated from a population pharmacokinetic analysis using pharmacokinetic data collected from Studies B201 and B251. Novartis added that those trials were conducted in a large number of targeted patients at the proposed clinical doses and at steady state. The Division noted that in terms of clearance, the estimated values in the population pharmacokinetic analysis were different from the values determined in other studies; in short, they did not know which values should be placed in the labeling for everolimus.\* Both sides agreed to discuss these issues at a future teleconference that included the Division's pharmacometrics reviewer.

12. *Comment #4b from Division's November 21, 2003 memorandum: In addition to the in vivo drug-drug interaction studies provided, please conduct additional in vivo interaction studies with other drugs/substrates that are known to affect CYP3A and/or P-glycoprotein and would be potentially coadministered with everolimus to transplant patients. Such drugs/substrates could include but are not limited to digoxin, erythromycin, glyburide, ketoconazole, nifedipine, phenytoin, ritonavir, and oral contraceptives. If it is determined that the TDM approach is necessary for this drug product to be used safely (e.g., a narrow therapeutic margin), you will need to provide us with more in vivo drug-drug interaction data prior to approval.*

Novartis believed that they had followed the FDA's clinical pharmacology guidance and the Division's advice in 1999 regarding the necessary drug-drug interaction data that would be required for their marketing applications. The Division noted that the applicant had changed the proposed regimen from one with a fixed dose of everolimus to TDM and they were concerned that certain drugs could interfere with a physician's attempt to achieve a specific concentration of everolimus and cyclosporine. This lack of data, added the Division, could present a challenge to labeling everolimus (although some of this could be addressed in the PRECAUTIONS and WARNINGS sections). The applicant stated that their exposure-effect analyses did not give them a lot to be concerned about except for the cytochrome P450 inducers. Novartis added that

(b) (4)

applicant also agreed to test all inducers of cytochrome P450. The Division stated that Novartis did not have to necessarily contraindicate some of these drugs if the labeling provided enough information about how to adequately adjust doses of

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\* Post-Meeting Note: The volume of distribution estimated in the population pharmacokinetic analysis did not provide the values of volume of distribution at the elimination phase. And before a future teleconference, please provide in which study or studies you reported adequately estimated values for the clearance (CL<sub>b/F</sub>), volume of distribution (V<sub>z,b/F</sub>), and elimination half-life ( $t_{1/2}$ ) of everolimus at the range of probable clinical doses following multiple (steady state) oral doses to targeted patients of interest using to-be-marketed Certican® tablets or formulations that were tested for bioequivalence compared to the tablets, and what the reported values of the parameters in the study were.

everolimus and cyclosporine. The applicant agreed to respond to this request in writing and discuss these issues with the Division at a future date. The Division concurred with this plan and noted the importance of considering this matter from a clinician's point of view: Which concomitant medications might increase or decrease the concentration of everolimus in my patient?

13. The Division inquired about Novartis' timeline for the proposed amendment. The applicant noted that it would have to be later than their original goal of December 2003. The Division stated their reluctance to lose any momentum regarding the discussion and eventual conduct of Novartis' proposed cardiac transplantation study utilizing everolimus TDM. The applicant agreed to discuss the design of this trial with the Division. The Division noted their willingness to consider Novartis' design proposals.

**ACTION ITEMS:** Both sides agreed to schedule a future teleconference to discuss the pharmacokinetics of everolimus. Both parties also confirmed their intention to discuss the proposed everolimus TDM study in cardiac transplant recipients.

Minutes Preparer: *{See appended electronic signature page}*

Meeting Chairperson: *{See appended electronic signature page}*

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/s/

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Matthew Bacho  
12/15/03 05:24:56 PM  
NDAs 21-560 & 21-628

Renata Albrecht  
12/16/03 12:53:35 PM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: November 21, 2003**

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (862) 778-7646	<b>Phone number:</b> (301) 827-2127

**Subject:** Response to Novartis' background material of October 31, 2003 (NDAs 21-560 and 21-628)

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**Total no. of pages including cover:** 5

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**Reviewers:** Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader/Arturo Hernandez, M.D., Medical Officer/Karen Higgins, Sc.D., Statistics Team Leader/Ruthanna Davi, M.S., Statistics Reviewer/LaRee Tracy, M.A., Statistics Reviewer/Philip M. Colangelo, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader/Jang-Ilk Lee, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer

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**Document to be mailed:** " YES  NO

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**NDA 21-560 & 21-628**

Dear Mr. Van Valen:

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> (everolimus) Tablets and your October 31, 2003 request for a Type A meeting, which will take place on November 25, 2003. In the interest of focusing our attention on the most important questions and issues next Tuesday, we would like to provide the following comments from our reviewing medical officer, statisticians, and clinical pharmacologist (the original comments and questions are italicized):

- 1. Novartis Proposal #1b: We propose to initially recommend LCMS methodology as an example of a validated assay for everolimus blood concentrations as used in Studies A2306 and A2307 in order to support a successful monitoring schedule and dose adjustment range; supporting data demonstrating everolimus blood levels were managed by the investigators in A2306/7 will be provided. Study A2306 and A2307 will provide experience of a successful monitoring schedule and will demonstrate that a central laboratory-based monitoring method is capable of a rapid response time that can maintain patients within a desired therapeutic concentration range. In addition, Novartis is also working with (b) (4), an independent company, to develop and register an immunoassay kit for everolimus. While it is our intention to have the immunoassay kit available as soon as possible the timelines for approval from FDA/CDRH are not predictable. Does the Division accept our proposal to initially recommend LCMS methodology and a monitoring schedule based on Studies A2306/07?*

A validated LC-MS method is acceptable until the (b) (4) assay kit is approved and available commercially. Please provide the analytical reports in Studies A2306 and A2307 for review. However, we ask that you to address whether the LC-MS method is applicable to the clinical settings other than the institutions that were involved in the everolimus trials for routine transplant patient care. Those settings may not have the comparable analytical capability and experience for this everolimus assay using the LC-MS method. Please also note that a switch from an LC-MS method to the (b) (4) assay in the future will need an adequate cross validation. (This also applies to Proposal #2c.)

- 2. (b) (4)*

We feel that it is premature to discuss the labeling for everolimus because not all of the data to support it has been submitted yet; presumably, the additional data you propose to submit in your amendment to NDAs 21-560 and 21-628 would enable us to address this issue after their review. However, if you believe there are critical aspects of labeling that should be addressed fairly soon, we are certainly amenable to such a conversation at a later time.

3. *Novartis Safety Update Proposal #4: We propose to submit CRFs and narratives for patients in Study 2306 and 2307 similar to that submitted for our core renal studies 201/251/156. As previously agreed with the Division, text narratives were submitted in the original NDA for the following events:*
- *Death, except those which are clearly unrelated to study medication (e.g., elective surgery, surgical/technical events, etc.),*
  - *Graft losses,*
  - *Unexpected or life-threatening serious adverse event (SAE), including serious infections, unusually severe acute rejections episodes that are reported as SAEs, and any malignancies,*
  - *Premature discontinuations of study medication for any reason except withdrawal of consent or administrative reasons (e.g., adverse events or abnormal laboratory values leading to premature discontinuation),*
  - *All other life-threatening events, including overdose of study medication that prompts medical attention,*
  - *Medically significant, unexpected SAEs.*

*In addition, line listings were provided for the following events:*

- *Notable laboratory abnormalities not included in text narratives that result in a SAE,*
- *All permanent discontinuations of study medication for administrative reasons or withdrawal of consent.*

*Does the Division require the same information for this safety update? Will the Division accept CRFs and narratives only for deaths and dropouts due to serious adverse events?*

We request that narratives for deaths as well as dropouts due to serious adverse events and abnormal laboratory values be included in your amendment. In addition, we request that CRFs be submitted for all patients.

4. We have the following concerns regarding your previous submission and recommend that you address these issues with your prospective submission. Otherwise, they may cause a delay in labeling negotiations at the time of approval or constitute requests for post-marketing commitments.
- a. Basic everolimus pharmacokinetic parameters were not adequately determined. Please provide adequately estimated values for the clearance (CL<sub>b/F</sub>), volume of distribution (V<sub>z,b/F</sub>), and elimination half-life (t<sub>1/2</sub>) of everolimus at the range of probable clinical doses following multiple (steady state) oral doses to targeted patients of interest using to-be-marketed Certican tablets or formulations that were tested for bioequivalence compared to the tablets.
  - b. In addition to the *in vivo* drug-drug interaction studies provided, please conduct additional *in vivo* interaction studies with other drugs/substrates that are known to affect CYP3A and/or P-glycoprotein and would be potentially coadministered with everolimus to transplant patients. Such drugs/substrates could include but are not limited to digoxin, erythromycin, glyburide, ketoconazole, nifedipine, phenytoin, ritonavir, and oral contraceptives. If it is determined that the TDM approach is necessary for this drug product to be used safely (e.g., a narrow therapeutic margin), you will need to provide us with more *in vivo* drug-drug interaction data prior to approval.

NDA 21-560 & 21-628

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Matthew Bacho  
11/21/03 06:19:47 PM  
CSO  
NDAs 21-560 & 21-628



**NDA 21-560**  
**NDA 21-628**

Novartis Pharmaceuticals Corporation  
Attention: Ronald G. Van Valen, Director of Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

We received your October 31, 2003 correspondence on November 5, 2003, requesting a teleconference to discuss your plans to amend NDAs 21-560 and 21-628 for Certican<sup>®</sup> (everolimus) Tablets. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You requested a Type A meeting. The teleconference has been scheduled for:

Date: November 25, 2003

Time: 8:45 a.m.

CDER participants: Edward Cox, M.D., M.P.H., ODE IV Acting Director  
Renata Albrecht, M.D., DSPIDP Director  
Steven Gitterman, M.D., DSPIDP Deputy Director  
Marc CavallJ-Coll, M.D., Ph.D., Medical Team Leader  
Arturo Hernandez, M.D., Medical Officer  
Philip Colangelo, Pharm.D., Ph.D., Clin. Pharm. & Biopharm. Team Leader  
Jang-Ik Lee, Pharm.D., Ph.D., Clin. Pharm. & Biopharm. Reviewer  
Karen Higgins, Sc.D., Statistics Team Leader  
Ruthanna Davi, M.S., Statistics Reviewer  
LaRee Tracy, M.A., Statistics Reviewer  
Matthew A. Bacho, Regulatory Health Project Manager

If you have any questions, call me at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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Matthew Bacho  
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NDAs 21-560 & 21-628



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**DATE: October 15, 2003**

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (862) 778-7646	<b>Phone number:</b> (301) 827-2127
<b>Subject:</b> CMC requests for information and recommendations (NDAs 21-560 and 21-628)	

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**Total no. of pages including cover:** 4

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**Reviewers:** Norman Schmuff, Ph.D., Chemistry Team Leader/Mark Seggel, Ph.D., Chemistry Reviewer

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11. [Redacted] (b) (4)

[Redacted]

[Redacted]

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[Redacted]

15. [Redacted] (b) (4)

[Redacted]

[Redacted]

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Sincerely yours,  
*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
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NDAs 21-560 & 21-628



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**DATE: October 8, 2003**

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (862) 778-7646	<b>Phone number:</b> (301) 827-2127
<b>Subject:</b> A request for information (NDAs 21-560; 21-628; 21-561; and 21-631)	

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**Total no. of pages including cover:** 3

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**Reviewers:** Steve Hundley, Ph.D., Acting Pharmacology-Toxicology Team Leader/Steve Kunder, Ph.D., Pharmacology-Toxicology Reviewer/Norman Schmuff, Ph.D., Chemistry Team Leader/Mark Seggel, Ph.D., Chemistry Reviewer

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**NDA 21-560 & 21-628**  
**NDA 21-561 & 21-631**

Dear Mr. Van Valen:

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets, which were submitted on December 19, 2002, as well as NDAs 21-561 and 21-631 for Certican<sup>®</sup> Tablets for Oral Suspension, which were submitted on January 31, 2003. Our reviewing toxicologist and chemist would like to request the following information:

[REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

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**DATE: October 3, 2003**

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (862) 778-7646	<b>Phone number:</b> (301) 827-2127
<b>Subject:</b> A request for information (NDAs 21-560; 21-628; 21-561; and 21-631)	

**Total no. of pages including cover:** 3

**Reviewers:** Philip M. Colangelo, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader/Seong Jang, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer/Norman Schmuff, Ph.D., Chemistry Team Leader/Mark Seggel, Ph.D., Chemistry Reviewer

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**NDA 21-560 & 21-628**  
**NDA 21-561 & 21-631**

Dear Mr. Van Valen:

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets, which were submitted on December 19, 2002, as well as NDAs 21-561 and 21-631 for Certican<sup>®</sup> Tablets for Oral Suspension, which were submitted on January 31, 2003. Our reviewing clinical pharmacologist and chemist would like to request the following information:

Please provide dissolution profiles for three batches of each strength of each dosage form by the proposed method. This information will allow us to further evaluate the suitability of the proposed acceptance criteria for the dissolution tests. Dissolution profiles for representative stability batches would also be useful.

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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Matthew Bacho  
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Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: September 12, 2003**

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (973) 781-7646	<b>Phone number:</b> (301) 827-2127
<b>Subject:</b> A request for information (NDAs 21-560; 21-628; 21-561; and 21-631)	

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**Total no. of pages including cover:** 3

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**Reviewers:** Marc CavailJ-Coll, M.D., Ph.D., Medical Team Leader/Arturo Hernandez, M.D., Medical Officer/Karen Higgins, Sc.D., Statistics Team Leader/LaRee Tracy, M.A., Statistics Reviewer/Ruthanna Davi, M.S., Statistics Reviewer

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**NDA 21-560 & 21-628**  
**NDA 21-561 & 21-631**

Dear Mr. Van Valen:

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets, which were submitted on December 19, 2002, as well as NDAs 21-561 and 21-631 for Certican<sup>®</sup> Tablets for Oral Suspension, which were submitted on January 31, 2003. Our reviewing medical officer and statisticians would like to make the following requests for information:

1. Appendix 5.1 (of report RAD001 B253) Statistical Methods (12 month analysis) refers to a "Master Analysis Plan." Please indicate the location of this document within the NDA submissions or, if not present, submit it for our review. Please indicate the date that the "Master Analysis Plan" became final.
2. In Section 3.3.4 of study protocol RAD B253, it states that, "...all patients prematurely discontinuing the study medication will be contacted at 3, 6, 12, and 24 months after the first dose of study medication to obtain follow up information..." Please clarify if protocol scheduled biopsies were to be obtained as part of this follow up (for patients who have prematurely discontinued study medication) and how missed biopsies were accounted for in the analyses.
3. Please refer to your submission dated August 7, 2003, Response to FDA Question #1, Table 1: RAD B253 Biopsy Compliance. Please further breakdown the reasons in the "Other (mainly due to missed visits or d/c study med.)" category contained under "Reason." Please also indicate how many of the subjects who did not receive a protocol-scheduled biopsy (for reasons other than death, loss to follow up, or graft loss) had experienced the primary event prior the indicated time point.
4. Please analyze the following composite endpoint; first occurrence of the primary endpoint or missed protocol scheduled biopsy, using the methods described in the B253 study report for the time-to-event analysis of the primary efficacy endpoint.

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Matthew Bacho  
9/12/03 09:53:29 AM  
CSO  
NDAs 21-560, 21-561, 21-628, and 21-631



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: June 24, 2003**

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (973) 781-7646	<b>Phone number:</b> (301) 827-2127
<b>Subject:</b> A request for information (NDAs 21-560; 21-628; 21-561; and 21-631)	

---

**Total no. of pages including cover:** 3

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**Reviewers:** Ekopimo Ibia, M.D., M.P.H., Acting Medical Team Leader/Arturo Hernandez, M.D., Medical Officer/Karen Higgins, Sc.D., Statistics Team Leader/LaRee Tracy, M.A., Statistics Reviewer/Ruthanna Davi, M.S., Statistics Reviewer

---

**Document to be mailed:**             YES             NO

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**NDA 21-560 & 21-628**  
**NDA 21-561 & 21-631**

Dear Mr. Van Valen:

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets, which were submitted on December 19, 2002, as well as NDAs 21-561 and 21-631 for Certican<sup>®</sup> Tablets for Oral Suspension, which were submitted on January 31, 2003. Our reviewing statisticians would like to request additional data relating to creatinine clearance and creatinine values for both the kidney and heart indications using the following variables:

1. Patient ID
2. Assigned Treatment
3. Baseline creatinine clearance and creatinine clearance (calculated using the Cockcroft-Gault formula for the heart indication and Nankivell formula for the kidney indication).
4. Creatinine clearance, creatinine, and acute rejection status (indicator value for whether or not acute rejection has occurred prior to creatinine measurement) at subsequent months.

[Note: Please provide average value(s) for creatinine and creatinine clearance if more than one assessment occurs during specified observation period and provide individual datasets for Studies B253, B201, B251 for both an ITT and an on-treatment population as well.]

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Health Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Matthew Bacho

6/24/03 10:17:00 AM

CSO

NDA's 21-560, 21-628, 21-561, and 21-631



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: June 3, 2004**

<b>To:</b> Ron Van Valen	<b>From:</b> Andrei Nabakowski
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> 301-827-2475
<b>Phone number:</b> (973) 781-7646	<b>Phone number:</b> 301-827-2127
<b>Subject:</b> Questions to be considered by Novartis panels on Certican	

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**NDA 21-560**  
**NDA 21-628**  
**NDA 21-561**  
**NDA 21-631**

Dear Mr. Van Valen,

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets, which were submitted on December 19, 2002, as well as NDAs 21-561 and 21-631 for Certican<sup>®</sup> Tablets for Oral Suspension, which were submitted on January 31, 2003. In order to facilitate your consultations with the expert panels, we would like to suggest that you consider including the following questions in your panel discussions, if you have not done so already. These questions reflect some of the issues and concerns raised during the review.

Please consider the following questions on heart transplantation that could be posed to your expert panel:

[Redacted text block] (b) (4)

[Redacted text block]

[Redacted text block] (b) (4)

Time permitting, you may also wish to consider asking questions regarding renal transplantation, C2 monitoring and risk management strategies:

### Renal Transplantation

- 1) Is it appropriate to use full dose cyclosporine with everolimus in *de novo* renal transplant recipients? These regimens were tested in studies B201 and B251, the only randomized, prospective, comparative trials evaluating everolimus for renal transplant recipients.
- 2) Is there sufficient information to support that everolimus, when used with full dose cyclosporine and corticosteroids, at the doses used in Study B201 and Study B251, is effective in preventing graft rejection in *de novo* renal transplant recipients, and is also safe?
- 3) If yes, which dose of everolimus should be recommended, 0.75 mg bid or 1.5 mg BID?
- 4) If no, what doses/regimens of everolimus and cyclosporine should be prospectively studied in *de novo* renal transplant recipients?
- 5) Studies A2306 and A2307 were non-comparative trials in which patients received everolimus in a cyclosporine modified regimen using a non-standardized method of C2 monitoring. The demographic characteristics of the populations studied showed the patient population was not comparable to either study B201 or B251. Therefore, given that no conclusions can be drawn regarding the efficacy and safety of the regimens used in comparison to other available or approved regimens, what should be the next steps in the evaluation of everolimus in renal transplant recipients.
- 6) Is there a population or subset of renal transplant patients for whom the regimens tested in B201 and B251 are appropriate? Can such a population be characterized and identified prospectively? If so, what are the characteristics of such a population?

### C2 monitoring in renal transplantation:

- 1) Is there sufficient information to support that cyclosporine dosing based on monitoring of cyclosporine whole blood concentrations two hours after dosing (C2 CsA

monitoring) is a standardized and validated procedure for effective and safe dosing of cyclosporine? Please consider whether there is successful experience in maintaining patients within targeted ranges of C2. Additionally, please consider the potential for variability and what subpopulations might be at risk for overdosing or underdosing when using C2 to monitor cyclosporine therapy.

### Risk Management

The use of mTOR inhibitors with full dose cyclosporine is associated with an increased risk of loss of renal function, which can be observed as early as during the first 3 months post transplantation.

- 1) Is there sufficient data to support a dose adjustment regimen for everolimus and cyclosporine that would reliably minimize renal toxicity while maintaining adequate protection against rejection in *de novo* renal transplant recipients? Could such a regimen be recommended without the need for further testing?
- 2) Is there sufficient data to support a dose adjustment regimen for everolimus and cyclosporine that would reliably minimize renal toxicity while maintaining adequate protection against rejection in *de novo* heart transplant recipients? Could such a regimen be recommended without the need for further testing?
- 3) What other risk management approaches would you recommend to minimize loss of renal function while maintaining adequate protection against rejection in transplant recipients receiving *de novo* immunosuppressive therapy?
- 4) What other risk management approaches would you recommend to minimize loss of renal function while maintaining adequate protection against rejection in transplant recipients receiving maintenance immunosuppressive therapy?

These questions address some of the Agency's concerns, and should provide beneficial and substantive discussion for your panels.

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

Sincerely yours,

*{See appended electronic signature page}*

Andrei Nabakowski, Pharm.D.  
Regulatory Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Andrei Nabakowski  
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CSO  
Questions for Certican panel



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: May 30, 2003**

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (973) 781-7646	<b>Phone number:</b> (301) 827-2127
<b>Subject:</b> A request for information (NDAs 21-560; 21-628; 21-561; and 21-631)	

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**Total no. of pages including cover:** 5

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**Reviewers:** Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader/Arturo Hernandez, M.D., Medical Officer/Karen Higgins, Sc.D., Statistics Team Leader/LaRee Tracy, M.A., Statistics Reviewer/Ruthanna Davi, M.S., Statistics Reviewer

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**NDA 21-560 & 21-628**  
**NDA 21-561 & 21-631**

Dear Mr. Van Valen:

Please refer to NDAs 21-560 and 21-628 for Certican<sup>®</sup> Tablets, which were submitted on December 19, 2002, as well as NDAs 21-561 and 21-631 for Certican<sup>®</sup> Dispersible Tablets, which were submitted on January 31, 2003. Our reviewing statistician and medical officer would like to request the following information regarding Study CRAD001 B253:

1. The protocol for Study CRAD001 B253 indicates that surveillance endomyocardial biopsy was to be performed for all subjects at each of the time points indicated in the attached table (Table 1: Biopsy Compliance). To evaluate compliance with this requirement, we request that you populate the referenced table.
2. We refer to "Table 1: Patient disposition for IVUS analysis (ITT population)" of Appendix 8.2 (IVUS) of the 24-month analysis of Study CRAD001 B253 (release date: November 6, 2002). You have provided the following reasons for not performing IVUS at baseline, 12 and 24 months:
  - a. No baseline/technical issues/administrative problems/not analyzable;
  - b. No consent;
  - c. Not done due to patient discontinuation, death, and AE;
  - d. Not done due to renal issues.

Please provide this tabulation with each of the above categories broken into single events. And please further categorize according to the specific type of event for the following: technical issues, administrative problems, and renal issues (e.g., technical issues may include machine not available, artery was not accessible, etc.).

3. In reference to the IVUS sub-analysis, we request an additional dataset containing the following parameters:
  - a. Patient ID
  - b. Treatment code
  - c. Study Center
  - d. Month 12 visit date
  - e. Month 24 visit date
  - f. Primary Efficacy Event for 12 month analysis (specify event, blank if not applicable)
  - g. Primary Efficacy Event for 24 month analysis (specify event, blank if not applicable)
  - h. Time to primary efficacy event from baseline for 12-month analysis
  - i. Time to primary efficacy event from baseline for 24-month analysis
  - j. Study medication discontinued for 12-month analysis
  - k. Study medication discontinued for 24-month analysis
  - l. Time to study medication discontinuation from baseline for 12-month analysis
  - m. Time to study medication discontinuation from baseline for 24-month analysis
  - n. Mean (per subject) of the maximal plaque thickness (i.e., PLQMAX) measured at baseline, 12 and 24 months
  - o. Maximum (per subject) of the maximal plaque thickness (i.e., PLQMAX) measured at baseline, 12 and 24 months

NDA 21-560 & 21-628  
NDA 21-561 & 21-631

- p. CMV disease for 12-month analysis (present/absent)
- q. CMV disease for 24-month analysis (present/absent)
- r. Baseline CMV status (donor and recipient)
- s. Acute rejection episode for 12-month analysis (include grade by ISHLT standardized endomyocardial biopsy grading scheme)
- t. Acute rejection episode for 24-month analysis (include grade by ISHLT standardized endomyocardial biopsy grading scheme)

This data set should consist of 211 rows (one row for each unique IVUS subject).

- 4. Please provide a summary of what treatment(s) patients received after discontinuing study medication and reason (i.e., from azathioprine to MMF, from RAD 1.5 mg to azathioprine, etc.). And please stratify by treatment arm.
- 5. Please provide the date the study was unblinded (per protocol amendment 3 dated November 29, 2001).
- 6. Please provide a summary of patients that received antibody therapy and specify the reason(s) (induction therapy, acute rejection treatment or both). Please stratify by study arm and study site.

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Table 1: Biopsy Compliance

	Day												Month									
	7			14			21			28			2			3			4			
	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A	
N (evaluable subjects**)																						
Number of subjects with biopsy*																						
Number of subjects without biopsy																						
Reason	Death																					
	Lost to follow up																					
	Missed visit																					
	Study Discontinuation																					
	Etc. (please describe additional reasons)																					
Reached primary efficacy endpoint <sup>#</sup>																						

	Month																	
	5			6			9			12			18			24		
	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A	R A D 1. 5	R A D 3	A Z A
N (evaluable subjects**)																		
Number of subjects with biopsy*																		
Number of subjects without biopsy																		
Reason	Death																	
	Lost to follow up																	
	Missed visit																	
	Study Discontinuation																	
	Etc. (please describe additional reasons)																	
Reached primary efficacy endpoint <sup>#</sup>																		

\* This row should contain the number of subjects who had the protocol defined biopsy at this time point. Please count each biopsy only once. For instance, if a subject had a biopsy between Day 7 and Day 14, this subject's biopsy should be counted at either Day 7 or Day 14.

# This row should contain the number of subjects who have reached the primary endpoint (acute rejection/graft loss/death) up to this time point. Patients who reach the endpoint based on the results of the biopsy should not be counted.

\*\*Evaluable subjects are all subjects with functioning graft (i.e., those who have not died or had graft loss, discontinued the study, or become lost-to-follow-up)

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/s/

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Matthew Bacho

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CSO

NDA's 21-560; 21-628; 21-561; and 21-631



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: May 21, 2003**

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (973) 781-7646	<b>Phone number:</b> (301) 827-2127

**Subject:** A request for information (NDAs 21-560, 21-628, 21-561, and 21-631)

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**Total no. of pages including cover:** 6

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**Reviewers:** Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader/Arturo Hernandez, M.D., Medical Officer/Philip M. Colangelo, Pharm.D., Ph.D., Acting Clinical Pharmacology & Biopharmaceutics Team Leader/Jang-Ik Lee, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer/Jenny J. Zheng, Ph.D., Pharmacometrics Reviewer/Karen Higgins, Sc.D., Statistics Team Leader/Ruthanna Davi, M.S., Statistics Reviewer

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**NDA 21-560 & 21-628**  
**NDA 21-561 & 21-631**

Dear Mr. Van Valen:

Please refer to NDAs 21-560 and 21-628 for Certican® Tablets, which were submitted on December 19, 2002, as well as NDAs 21-561 and 21-631 for Certican® Dispersible Tablets, which were submitted on January 31, 2003. Our reviewing clinical pharmacologist would like to request the following information:

1. For Studies B201, B251, and B253, please provide electronically all raw data used in the determination of everolimus exposure-response relationships, or provide the location if the data were already submitted. The raw data need to be in an analyzable format using SAS, S-Plus, and/or MS Excel. Please see the attachment for the type of information and format that we prefer.
2. For Studies B201, B251, and B253, please let us know whether you can conduct a Kaplan-Meier survival analysis for the primary composite efficacy variable (if this is not feasible, then rejection episode) stratifying the patients by the range of mean everolimus trough concentration rather than everolimus dose (please include MMF or azathioprine control). For this purpose, we recommend conducting a pilot survival analysis using the 6-month data in Study B253. To calculate a mean concentration, please include only the non-zero concentrations determined up to the time of efficacy/safety event. We also suggest that you extend the analysis to safety variables (e.g., the event of decrease in creatinine clearance by 30% of baseline value).
3. For Studies B201, B251, and B253, please recalculate all everolimus pharmacokinetic parameters after excluding all data sets in abbreviated concentration-time profiles in which everolimus concentration(s) at any sampling point(s) was/were missing, and in which blood sample(s) at any sampling points was/were presumably mislabeled. Please report both measured  $C_{0,b,ss}$  and predicted  $C_{12,b,ss}$  and conduct correlation analyses among  $C_{0,b,ss}$ ;  $C_{12,b,ss}$ ; and  $AUC_{\tau,b,ss}$  (3 pairs).
4. For Studies B201, B251, and B253; please provide spaghetti plots drawn in normal and log scales for abbreviated everolimus concentration-time profiles after stratifying by everolimus dose and study visit. Please exclude all data sets in which everolimus concentration(s) at any sampling point(s) was/were missing, and in which blood sample(s) at any sampling point(s) was/were presumably mislabeled.
5. For Study B157, please let us know whether the blood samples collected can be reanalyzed for everolimus concentrations using a more sensitive assay method (limit of quantitation < 0.5 ng/mL). If the reassay is possible, please update the study report using the new concentration values, particularly for the relationship between abbreviated and full everolimus concentration-time profile, and submit the updated report as soon as possible.
6. For all human pharmacokinetic studies submitted, please prepare a tabular summary to compare and contrast all analytical reports in terms of assay method and performance with respect to blood, urine, and other biological samples with respect to everolimus, everolimus metabolites, and drugs used in drug interaction studies. Specifically, for each

- site where each assay was conducted, please include information comparing the precision, accuracy, specificity, sensitivity, recovery, and linear range of calibration curve.
7. For Study W101, please provide the analytical report(s) containing the in-process performance of the assays used for the determination of whole blood concentrations of everolimus and cyclosporine, or the location if the report was submitted already.

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Attachment:

This is the preferable information and format for the raw data to determine everolimus exposure-response relationships. [Each (pair of) row in the following table actually represents each column in a patient's raw data set.]

Study #	
Patient #	
Age (year)	
Gender	M or F
Race	white, black, or other
Dosing Regimen	MMF or azathioprine control, 0.75 mg bid, or 1.5 mg bid
Everolimus C <sub>min</sub> (ng/mL)	Week 1 value
	Week 2 value
	Week 3 value
	Month 1 value
	Month 2 value
	Month 3 value
	Month 6 value
	Mean value
	Median value
	# of concentrations (n) used for mean and median
	Value used for exposure variable
	Cyclosporine C <sub>min</sub> (ng/mL)
Week 2 value	
Week 3 value	
Month 1 value	
Month 2 value	
Month 3 value	
Month 6 value	
Time to event of composite efficacy variable (days post-transplant)	Day of event posttransplant (blank for no event)
	Affected or unaffected? (Y, N)
Time to rejection (days posttransplant)	First episode
	Second episode
	Third episode
	Affected or unaffected? (Y, N)
Calculated creatinine clearance (mL/min) [Study B253 only, please report measured serum creatinine if creatinine clearance is not calculable]	Baseline value (immediately prior to transplant)
	Week 1 value
	Week 2 value
	Week 3 value
	Month 1 value
	Month 2 value
	Month 3 value
	Month 6 value
	Value used for decision
	Time point for decision (weeks or months post-transplant)
	Absolute difference (baseline – lowest value)
Affected or unaffected? (Y, N)	
Platelet Count	Week 1 value
	Week 2 value
	Week 3 value
	Month 1 value
	Month 2 value
	Month 3 value
	Month 6 value

	Count used for decision
	Time point for decision (weeks or months post-transplant)
	Affected or unaffected? (Y, N)
Leukocyte Count	Week 1 value
	Week 2 value
	Week 3 value
	Month 1 value
	Month 2 value
	Month 3 value
	Month 6 value
	Count used for decision
	Time point for decision (weeks or months post-transplant)
	Affected or unaffected? (Y, N)
Serum Hemoglobin [alternatively Hematocrit]	Week 1 value
	Week 2 value
	Week 3 value
	Month 1 value
	Month 2 value
	Month 3 value
	Month 6 value
	Value used for decision
	Time point for decision (weeks or months post-transplant)
	Affected or unaffected? (Y, N)
Serum Triglyceride	Week 1 value
	Week 2 value
	Week 3 value
	Month 1 value
	Month 2 value
	Month 3 value
	Month 6 value
	Value used for decision
	Time point for decision (weeks or months post-transplant)
	Affected or unaffected? (Y, N)
Serum Cholesterol	Week 1 value
	Week 2 value
	Week 3 value
	Month 1 value
	Month 2 value
	Month 3 value
	Month 6 value
	Value used for decision
	Time point for decision (weeks or months post-transplant)
	Affected or unaffected? (Y, N)
Time to lipid lowering therapy initiation (days post-transplant)	

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/s/

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Matthew Bacho

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CSO

NDA 21-560, 21-628, 21-561, and 21-631



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/s/

-----  
Matthew Bacho  
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**FILING REVIEW ISSUES IDENTIFIED**

**NDA 21-560**  
**NDA 21-628**

Novartis Pharmaceuticals Corporation  
Attention: Ronald G. Van Valen  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

Please refer to your December 19, 2002 new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Certican™ (everolimus) Tablets, 0.25, 0.50, 0.75, and 1.0 mg.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications have been filed under section 505(b) of the Act on February 18, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

- We do not agree with your proposal to [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] The detailed chemistry, manufacturing and controls for sirolimus should be documented in either the NDA or in DMF 15720.
- We are unable to confirm that the non-proprietary name, everolimus, has been adopted by the USAN Council. Please provide documentation of its adoption by the USAN Council. If the USAN Council has not adopted the name, you should apply to the USAN Council for adoption of a name that will comply with that section of the Act as provided by 21 CFR 299.4(e). They can be reached at the following address:

Secretary  
United States Adopted Names (USAN) Council  
c/o American Medical Association  
P.O. Box 10790

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the applications and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the applications.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Renata Albrecht  
3/3/03 05:20:37 PM



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: February 3, 2003**

<b>To:</b> Ron Van Valen Associate Director of Drug Regulatory Affairs	<b>From:</b> Matthew A. Bacho Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corp.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
<b>Fax number:</b> (973) 781-8364	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (973) 781-7646	<b>Phone number:</b> (301) 827-2127

**Subject:** A request for information (NDA 21-560)

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**Total no. of pages including cover:** 3

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**Reviewers:** Gene Holbert, Ph.D., Acting Chemistry Team Leader/Mark Seggel, Ph.D., Chemistry Reviewer/Philip M. Colangelo, Pharm.D., Ph.D., Acting Clinical Pharmacology & Biopharmaceutics Team Leader/Jang-Ik Lee, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer/Shukal Bala, Ph.D., Microbiology Team Leader

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**Document to be mailed:**             YES             NO

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**NDA 21-560**

Dear Mr. Van Valen:

Please refer to NDA 21-560 for Certican™ Tablets. Our reviewing chemist, microbiologist, and clinical pharmacologist would like to request the following information:

1. Please submit a desk copy of Item #4, the Chemistry section, and confirm whether or not the proposed manufacturing sites are ready for inspection.
2. Please submit desk copies (in paper) of the Mechanism of Action section (probably Volumes 2, 4, 5, and 72) from the Nonclinical Pharmacology and Toxicology section (Item #5) for this NDA.
3. Please submit the location of all final study reports for each of the following: *in vitro* pharmacokinetic studies, *in vitro* metabolism studies, analytical validations, and dissolution studies.

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

Sincerely yours,

*{See appended electronic signature page}*

Matthew A. Bacho  
Regulatory Project Manager  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Matthew Bacho  
2/3/03 03:55:51 PM  
CSO  
NDA 21-560



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 31, 2003

<b>To:</b> Mr. Ronald G. Van Valen	<b>From:</b> Ms. Diana M. Willard
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
<b>Fax Number:</b> 973-781-8364	<b>Fax Number:</b> 301-827-2475
<b>Phone Number:</b> 973-781-7646	<b>Phone Number:</b> 301-827-2485

**Subject:** NDA 21-560

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**Total no. of pages including cover: 3**

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Regarding your December 19, 2002 submission of NDA 21-560, we request that you populate the attached table with information from the two pivotal studies in renal transplantation.

Please contact Diana Willard at (301) 827-2485 if you have any questions regarding this facsimile transmission.

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Diana M. Willard, Regulatory Project Manager  
Division of Special Pathogen and Immunologic Drug Products



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/s/

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Diana Willard  
1/31/03 02:19:17 PM  
CSO



NDA 21-560

Novartis Pharmaceuticals Corporation  
Attention: Ronald Van Valen  
Director, Drug Regulatory Affairs  
One Health Plaza  
Eat Hanover, NJ 07936-1080

Dear Mr. Van Valen:

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

Name of Drug Product: Certican (everolimus) Tablets, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg

Review Priority Classification: Standard (S)

Date of Application: December 19, 2002

Date of Receipt: December 20, 2002

Our Reference Number: NDA 21-560

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 20, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:  
Center for Drug Evaluation and Research  
Division of Special Pathogen and Immunologic Drug Products  
Attention: Division Document Room, HFD-590  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 21-560

Page 2

Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Special Pathogen and Immunologic Drug Products, HFD-590

Attention: Document Room

9201 Corporate Boulevard

Rockville, Maryland 20850

If you have any questions, call Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Ellen Frank  
1/13/03 04:14:21 PM  
NDA 21-560