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RESEARCH**

*APPLICATION NUMBER:*  
**21-560**

**OTHER ACTION LETTERS**



NDA 021560

**COMPLETE 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:

Please refer to your new drug application (NDA) dated December 19, 2002 and received December 20, 2002 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zortress (everolimus) Tablets, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg.

We acknowledge receipt of your amendments dated:

August 31, 2004	August 21, 2008 (2)	August 28, 2009	November 3, 2009 (3)
September 3, 2004	October 23, 2008	August 31, 2009 (2)	November 5, 2009
September 23, 2004	March 19, 2009	September 3, 2009	November 6, 2009
November 10, 2004	March 20, 2009	September 10, 2009 (2)	November 9, 2009
January 25, 2005	April 1, 2009	September 17, 2009	November 10, 2009
July 6, 2006	April 3, 2009	October 5, 2009	November 18, 2009 (2)
March 8, 2007	June 30, 2009 (3)	October 7, 2009	November 23, 2009
November 27, 2007	July 23, 2009	October 19, 2009	November 25, 2009
December 6, 2007	August 4, 2009	October 21, 2009	December 1, 2009
May 8, 2008	August 24, 2009	October 22, 2009	December 4, 2009
		November 2, 2009	December 11, 2009 (2)

One of the June 30, 2009 amendments constituted a complete response to our August 27, 2004 action letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Zortess (everolimus) to ensure that the benefits of the drug outweigh the risks of wound healing complications, hyperlipidemia, proteinuria, and graft thromboses, as well as nephrotoxicity when co-administered with standard doses of cyclosporine. The REMS, once approved, will create enforceable obligations.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Zortess (everolimus) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zortess (everolimus). FDA has determined that Zortess (everolimus) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Zortess (everolimus).

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed everolimus.

**Communication Plan:** We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Zortess (everolimus) will support implementation of the elements of your REMS and should be implemented at the time of product launch. The communication plan must provide for the dissemination of information about wound healing complications, hyperlipidemia, proteinuria, and nephrotoxicity when co-administered with standard doses of cyclosporine, and graft thromboses. The communication plan must include, at minimum, the following:

- Dear Healthcare Professional Letter
- Dear Pharmacist Letter
- Dear Professional Association Letter

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that 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.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include additional information in the

template that is specific to your proposed REMS for Zortress (everolimus). Additionally, all relevant proposed REMS materials including communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include:

- a. An evaluation of patients' understanding of the serious risks of Zortress (everolimus)
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 021560  
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 021560  
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

## **LABELING**

Please submit draft labeling in the physician labeling rule (PLR) format that includes the revisions proposed in the Zortress (everolimus) draft package insert attached as

Appendix C to this letter.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

In addition, please update the information in the proposed Medication Guide to reflect the information summarized in the package insert.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

### **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

We have determined that, if NDA 021560 is approved, you will be required to assess the long-term safety profile of Zortress (everolimus), including wound healing complications, hyperlipidemia, proteinuria, and graft thromboses, as well as nephrotoxicity when co-administered with standard doses of cyclosporine, and other adverse events as described in your proposed labeling. Specifically, we have determined that, if NDA 021560 is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to:

1. Submit the final report for Trial A2309 which contains the 24-month follow-up safety and efficacy data on all patients enrolled in the trial.

The specific details of this postmarketing requirement and other postmarketing studies and trials that may be required will be described more fully in the approval letter for this application, if it is approved.

### **OTHER**

We have listed below several issues that are not deficiencies that need to be addressed before the application is resubmitted, but are issues we would like you to consider as you continue to develop everolimus for the indication of prevention of rejection in *de novo* kidney transplant patients.

1. Please provide the results from any pre-testing of the proposed communication materials for the required REMS. This should include explanation of how the materials were modified based on the results.

### **Everolimus Assay**

2. We encourage you to work with diagnostic companies developing everolimus assays, particularly those using the same technology as the assays used in trial A2309 (see item 3, below). As we noted previously, the most straightforward comparison for any new assay would be for the new assay to measure samples from the Novartis trial (A2309) and compare their new analytical results with the analytical results obtained during the trial. This recommendation assumes the samples are completely stable over the time period/conditions stored. If this is not the case and/or if sufficient samples from the trial

are not available, we recommend that the diagnostic assay manufacturer compare clinical sample results obtained with their new assay to results obtained from the assay/laboratory used during the Novartis clinical trial A2309. We appreciate any assistance you can provide to device manufacturers regarding provision of information or materials to facilitate their studies for supporting an FDA submission.

3. Tests using different measurement technologies are often not directly comparable. Immunoassays, for example, often have significant cross-reactivities with metabolites that can bias test results. Given the narrow therapeutic range of 3-8 ng/mL which appears to be critical to use of everolimus as currently understood, we strongly encourage you to collaborate with manufacturers developing LCMSMS assays, specifically. Cross-reactivity likely to be present in immunoassays can lead, not only to bias, but also to unpredictable variability between samples due to variations in metabolite accumulation either between individual patients, or within individual patients over time.
4. The specific assay used during your clinical trial could be submitted to FDA's Center for Devices and Radiological Health as a 510(k). Please note that manufacturing of such an assay to be marketed for clinical use must follow the Quality System Regulation (21 CFR Part 820).

### **Advertising**

5. We request that you voluntarily submit the proposed advertising and launch material that you propose to use with Zortress (everolimus).

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jacquelyn Smith, M.S., Regulatory Project Manager,  
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: Appendix A: REMS Template  
Appendix B: REMS Supporting Document  
Appendix C: Draft Zortress (everolimus) Package Insert

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

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

/s/  
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RENATA ALBRECHT  
12/23/2009



NDA 21-560  
NDA 21-628

Novartis Pharmaceuticals Corporation  
Attention: Ronald Van Valen  
Director, Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936

Dear Mr. Van Valen:

Please refer to your new drug applications dated December 19, 2002, received December 20, 2002, 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 acknowledge receipt of your submissions dated:

October 17, 2003 (3)	October 30, 2003	October 31, 2003
November 14, 2003	January 22, 2004	February 11, 2004
March 1, 2004	March 19, 2004	April 14, 2004
April 28, 2004	June 24, 2004	July 7, 2004
July 16, 2004	July 22, 2004	

Your February 27, 2004 submission constituted a complete response to our October 20, 2003 action letter.

We have completed the review of these applications, as amended, and they are approvable. Although you have demonstrated your product is efficacious, you have yet to show a sufficiently safe regimen for everolimus when used with cyclosporine. Before these applications may be approved, safe and effective dosing regimens of everolimus and cyclosporine for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients must be established. Therefore, before the applications may be approved, it will be necessary for you to:

1. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal function impairment while maintaining adequate protection against graft rejection, graft loss, or death in *de novo* renal transplantation. In order to do this, we believe that it will be necessary for you to provide data from an adequate and well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* renal transplant recipients, which would support therapeutic drug monitoring (TDM) schemes for everolimus and cyclosporine.

2.

(b) (4)

At present, we are unable to identify another approach to provide the necessary data to support the safety and efficacy of your products. Should you have an alternative to conducting such a study or studies, we strongly encourage you to discuss the study design with the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) prior to its initiation.

If a non-inferiority study design is chosen, the active control should represent an approved comparator regimen. Target concentration ranges over time for both everolimus and cyclosporine should be prospectively defined, and then demonstrated to be safe and effective in both early stages post transplantation and during the maintenance phase.

A primary analysis at 6 months after the last protocol specified change in target everolimus and cyclosporine concentration ranges (i.e., 6 months into maintenance phase) could support a resubmission of the NDAs for these indications, providing there were a commitment to provide follow-up outcome and safety data (including renal function, rejection, graft loss, and death) at 12, 24, and 36 months post transplantation.

To demonstrate the safety and efficacy of the proposed everolimus-cyclosporine combination regimens, you need to adequately determine a starting dose and a target trough concentration ( $C_{min}$ ) range (upper and lower limits) for both everolimus and cyclosporine for each indication. A safe and effective TDM regimen for everolimus, used in combination with cyclosporine, would also require a validated assay for everolimus blood concentrations and need to be supported by experience with a successful monitoring schedule and dose adjustment scheme proven capable of maintaining patients within the proposed therapeutic concentration range.

If the proposed regimen(s) would require doses and blood concentrations of everolimus that are higher than those observed in studies previously submitted to the NDA, additional safety data of similar duration in an adequate number of subjects would be needed to support approval of the recommended regimen(s). A minimum of 300 transplant patients should have been observed for at least 12 months at the proposed recommended exposure of everolimus with cyclosporine. This might be achieved by simultaneous submission of data from an adequate well-controlled study in *de novo* renal transplantation and an adequate well-controlled study in *de novo* cardiac transplantation, as described in items 1 and 2 above.

You are encouraged to communicate with DSPIDP regarding the option(s) you plan to select before resubmitting your applications. The ultimate suitability of the proposed approaches can only be determined after review of the relevant data.

Although not a condition of approval, we strongly recommend that you continue to adequately determine the terminal  $t_{1/2}$  of everolimus in the target patient population following the administration of the proposed everolimus-cyclosporine regimen. This everolimus  $t_{1/2}$  should be determined at the range of proposed clinical doses and/or concentrations of everolimus and cyclosporine following multiple dose (steady state) administration of the proposed everolimus-cyclosporine combination regimen to transplant patients.

We note that *in vivo* drug interaction studies with everolimus are ongoing; we anticipate continued progress and cooperation in identifying significant drug interactions with everolimus.

In addition, it will be necessary for you to submit draft labeling revised to reflect the additional information provided.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
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  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend these applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. If you do

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not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with DSPIDP to discuss what steps need to be taken before the application may be approved.

The drug products may not be legally marketed until you have been notified in writing that the applications are approved.

If you have any questions, call Andrei Nabakowski, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

Mark J. Goldberger, M.D., M.P.H.  
Director  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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

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Edward Cox  
8/27/04 04:39:23 PM  
for Mark J. Goldberger, MD MPH



**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 new drug applications dated December 19, 2002, received December 20, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Certican<sup>®</sup> (everolimus) Tablets, 0.25, 0.50, 0.75, and 1.0 mg.

We acknowledge receipt of your submissions dated:

October 4, 2002	February 5, 2003	February 14, 2003
February 21, 2003	March 3, 2003	May 2, 2003
May 30, 2003	June 10, 2003	July 9, 2003
July 18, 2003	August 1, 2003	August 6, 2003
August 7, 2003	August 12, 2003	August 28, 2003
September 26, 2003	October 3, 2003	October 13, 2003

We also acknowledge receipt of your submissions dated September 23, 2003, and October 17, 2003. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of these applications, as amended, and they are approvable. Although you have demonstrated your product to be efficacious, as studied in your clinical trials, you have yet to show a sufficiently safe regimen for everolimus when used with cyclosporine. Before these applications may be approved, you must establish a dosing regimen of everolimus and cyclosporine that is both safe and effective for the prophylaxis of organ rejection in allogeneic renal and cardiac transplant patients. Therefore, it will be necessary for you to:

1. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal function impairment while maintaining adequate protection against graft rejection, graft loss or death in *de novo* renal transplantation.
  - One approach would be to provide data from an adequate and well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* renal transplant recipients, which would support therapeutic dose monitoring (TDM) schemes for everolimus and cyclosporine.
  - 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).

- Other approaches that may support the definition of a safe and effective regimen for everolimus in the prevention of graft rejection in *de novo* renal transplantation should be discussed with the Division.

The data and analyses that support a therapeutic concentration range in *de novo* renal transplantation need to identify a clinically efficacious and safe concentration range of everolimus (upper as well as lower limits) when used with the proposed cyclosporine concentration range. A safe and effective TDM regimen for everolimus, used in combination with cyclosporine, would also require a validated assay for everolimus blood levels, and need to be supported by experience with a successful monitoring schedule and dose adjustment scheme, proven capable of maintaining patients within the proposed therapeutic concentration range.

2. [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

3. Have adequately addressed by Sandoz [formerly Biochemie and the holder of Drug Master File (DMF) 15720] the deficiencies that were communicated to Sandoz's U.S. Agent, Geneva Pharmaceuticals, Inc. DMF 15720 describes the manufacture of sirolimus by fermentation at Kundl, Austria.

You are encouraged to communicate with the Division regarding the option(s) you plan to select before resubmitting your applications. The ultimate suitability of the proposed approaches can only be determined after review of the relevant data.

In addition, it will be necessary for you to submit draft labeling revised to reflect the additional information provided.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw these applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before these applications may be approved.

The drug product may not be legally marketed until you have been notified in writing that these applications are approved.

If you have any questions, call Matthew A. Bacho, Regulatory Health Project Manager, at (301)

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NDA 21-628  
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827-2127

Sincerely,

*{See appended electronic signature page}*

Mark J. Goldberger, M.D., M.P.H.  
Director  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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

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Mark Goldberger  
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NDA 21-560 & NDA 21-628