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APPLICATION NUMBER:

21-995

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-995

Merck & Co., Inc.
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
UG2CD-48
P.O. Box 1000
North Wales, PA 19454-1099

Dear Dr. Aurecchia:

Please refer to your new drug application (NDA) dated December 16, 2006, received December 16, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Januvia (sitagliptin phosphate) Tablets, 25 mg, 50 mg, and 100 mg.

We acknowledge receipt of your submissions dated December 16, 2005, and January 26 and 30, February 16 and 17, March 1, 3, 13, 22, and 30, April 5 and 25, May 4 and 10, June 13, 21, and 23, July 7, 18, and 20, August 2, 14, 15, and 24, September 21, and October 12, 13 and 16 (2), 2006.

This new drug application provides for the use of Januvia (sitagliptin phosphate) Tablets as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus as monotherapy and in combination with metformin or a PPARγ agonist (e.g., thiazolidinediones) when diet and exercise plus the single agent do not provide adequate glycemic control.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for package insert and text for the patient product information submitted on October 16, 2006, immediate container and carton labels submitted on December 16, 2005, and sample carton and container labels submitted on March 1, 2006.) Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit either an electronic version or 20 paper copies of the FPL as soon as it is available (no more than 30 days after it is printed). If paper copies are submitted, individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-995**." Approval of this submission by FDA is not required before the labeling is used.

We acknowledge your October 16, 2006, agreement to revise by January 31, 2007, all of the labeling pieces to reflect that the dosage amount shown in the labeling refers to the drug base rather than the drug salt. At that time, you should again submit either an electronic version or 20 paper copies of the FPL as soon as it is available (no more than 30 days after it is printed). If paper copies are submitted, individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-995**." Approval of this submission by FDA is not required before the labeling is used. Revised content of labeling in SPL format should also be submitted at that time.

The agreed-upon dissolution method and acceptance criterion are as follows:

Apparatus	[redacted]
In vitro dissolution medium	
Volume of dissolution medium	
Medium temperature	
Stirring speed	
Acceptance criterion	[redacted]

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages birth to 10 years, inclusive, and deferring pediatric studies for ages 11 to 16 years, inclusive, for this application.

Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of type 2 diabetes in pediatric patients ages 11 to 16, inclusive.

   Protocol Submission: by March 31, 2008
   Study Start: by June 30, 2008
   Final Report Submission: by December 31, 2010

For administrative purposes, all submissions related to this pediatric postmarketing study commitment should be clearly designated "**Required Pediatric Study Commitment**".

We remind you of your postmarketing study commitments in your submission dated October 16, 2006. These commitments are listed below.

2. Clinical safety and efficacy study of sitagliptin as add-on therapy to insulin.

   Protocol Submission: by March 31, 2007
   Study Start: by June 30, 2007
   Final Report Submission: by March 31, 2009

3. Clinical safety and efficacy study of sitagliptin as add-on therapy to sulfonylureas. (A study protocol was previously submitted and the study recently completed.)

   Final Report Submission: by March 31, 2007

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

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolism and Endocrinology Products and two copies of both the promotional materials and the package insert directly to:

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

As indicated in our Information Request letter dated September 7, 2006, and teleconference on October 13, 2006, your proposed Chemistry, Manufacturing, and Controls (CMC) Regulatory Agreement submitted as part of the CMC Pilot Program is under review. Your proposal outlines the regulatory mechanisms for managing changes related to process design and control spaces post-approval. While a mutually accepted CMC Agreement is not a condition for the approval of this application, it will have implications for post-approval changes. Therefore, you are reminded that, until the CMC Agreement is approved, the existing regulations and guidances should be followed, as appropriate, for the post-approval CMC changes.

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

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

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

If you have any questions, call Lina AlJuburi, Pharm.D., M.S., Regulatory Project Manager, at (301) 796-1168.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Package Insert, Patient Product Information, Carton Labels, Container Labels, Sample Carton and Container Labels

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