DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201280

NDA APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Maureen Oakes, Pharm.D.
Associate Director, Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Oakes:

Please refer to your New Drug Application (NDA) dated and received July 2, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tradjenta (linagliptin) tablets, 5 mg.

We acknowledge receipt of your amendments dated July 7 and 9, August 2, 3, and 25, September 2, 23, and 30, October 8 and 28, November 1, 12, and 19, and December 1, 17, and 21, 2010; and January 6, 27 (2), 28, and 31, February 4, 7, 11 (2), 14, 16 (2), and 18, March 1 (2), 14, 17, 25, and 29, and April 18, 20, and 29, and May 2, 2011.

This new drug application provides for the use of Tradjenta (linagliptin) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate-container labels submitted on March 25, 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 201280**." Approval of this submission by FDA is not required before the labeling is used.

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

ADVISORY COMMITTEE

Your application for Tradjenta (linagliptin) tablets was not referred to an FDA advisory committee because:

- this drug is not a first-in-class anti-diabetic therapy (two other DPP4-inhibitors are currently marketed);
- the indication sought is based on a well-established efficacy endpoint relied upon for approval of other drugs across the 11 classes of anti-diabetic therapies;
- clinical trials assessing efficacy and safety are typical of diabetes programs evaluated by FDA for approval of other anti-diabetic therapies; and
- no unexpected safety concerns were identified in the nonclinical or clinical development program.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because the necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric studies for ages 10 to 16 years (inclusive) for this application because this product is ready for approval for use in adults and pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

PMR 1766-1: A randomized, placebo-controlled, dose-finding study under PREA evaluating at least two doses of linagliptin as monotherapy in pediatric patients ages 10 to 16 years (inclusive).

Final Protocol Submission:	by November 30, 2011
Trial Completion:	by February 28, 2014
Final Report Submission:	by August 31, 2014

PMR 1766-2: Deferred randomized and controlled pediatric study under PREA to evaluate efficacy, safety, and pharmacokinetics of linagliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years (inclusive) as monotherapy and when added to metformin therapy.

Final Protocol Submission:	by June 30, 2014
Trial Completion:	by March 31, 2017
Final Report Submission:	by September 30, 2017

Submit the protocols to your IND 070963, with a cross-reference letter to this NDA. Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s)**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

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 either a signal of a serious risk of cardiovascular events or a serious risk of hypersensitivity reactions associated with Tradjenta (linagliptin) tablets treatment.

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

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

PMR 1766-3 An epidemiologic study to compare the risk of severe hypersensitivity and severe cutaneous reactions in type 2 diabetics exposed to linagliptin to the risk in type 2 diabetics exposed to other antidiabetic medications.

The timetable you submitted on April 28, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	by May 30, 2012
Study Completion:	by November 30, 2018
Final Report Submission:	by June 30, 2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events with anti-diabetic medications, including Tradjenta (linagliptin) tablets, to definitively exclude unacceptable cardiovascular toxicity.

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

PMR 1766-4 A randomized, double-blind, placebo-controlled trial evaluating the effect of Tradjenta (linagliptin) tablets on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus.

> The primary objective of this trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with Tradjenta (linagliptin) tablets to that observed in the control group is less than 1.3. Secondary objectives must include an assessment of the long-term effects of Tradjenta (linagliptin) tablets on immunological and , hypersensitivity reactions (including serious skin and/or mucosal reactions), neoplasms, serious hypoglycemia, pancreatitis, and renal safety. For hypersensitivity reactions, especially angioedema, reports should include detailed information on concomitant use of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker. For cases of pancreatitis, serum amylase and/or lipase concentrations with accompanying normal ranges and any imaging reports should be included in the narratives.

The timetable you submitted on April 20, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	by June 30, 2012
Trial Completion:	by October 31, 2018
Final Report Submission:	by May 31, 2019

Submit the protocol to your IND 070963, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically

report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

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

PROMOTIONAL MATERIALS

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

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instructions on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

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

and program description details at
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Raymond Chiang, M.S., Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
- Package Insert
- Patient Package Insert
- Container Label – 30-tablet bottle
- Container Label – 90-tablet bottle
- Container Label – 1000-tablet bottle
- Container Label – 7-tablet blister card (sample)
- Carton Label – 7 tablet (sample)

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

/s/

CURTIS J ROSEBRAUGH
05/02/2011