DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-350

NDA APPROVAL

Bristol-Myers Squibb Company
Attention: Pamela Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your new drug application (NDA) dated and received on June 30, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Onglyza (saxagliptin) Tablets, 2.5 mg and 5 mg.

We acknowledge receipt of your submissions dated June 30, August 28, September 26, October 15, 24, 28, and 29, November 3, 14, 19, and 24, and December 2, 15, 16, 23, and 24, 2008, and January 21(2), 22, 23, and 26, February 3, 19(2), 24, and 26, March 12 and 16, April 2, 6, 15, 20, and 23, May 19 and 27, June 3, 17, and 22, and July 6, 17 (2), 22 (3), 27, 28, and 30 (3), 2009.

This new drug application provides for the use of Onglyza (saxagliptin) Tablets, 2.5 mg and 5 mg, 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, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm , that is identical to the enclosed labeling text for the package insert and patient package insert submitted July 30, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-350**."

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 June 30, 2008 and July 6 and 17, 2009, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-350**." 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.

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 (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 the pediatric studies have not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

PMR 1493-1: Deferred randomized and controlled pediatric study under PREA to evaluate efficacy, safety, and pharmacokinetics of saxagliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years.

Final Report Submission: by June 30, 2015

Submit all final reports to this NDA. Use the following designator to prominently label all submissions:

Required Pediatric Assessment(s)

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) 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 (section 505(o)(3)(A)).

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 a serious risk of embryofetal toxicity observed in a previously submitted study of saxagliptin plus metformin in rats, a signal of a serious risk of cardiovascular events, and the serious risks of severe hepatic events and hypersensitivity reactions associated with saxagliptin treatment.

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.

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

PMR 1493-2 Embryofetal development study of saxagliptin and metformin in combination in rats. Include saxagliptin monotherapy and metformin monotherapy treatment arms.

The timetable you submitted via email on June 29, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by July 31, 2010
Study Completion:	by September 30, 2010
Final Report Submission:	by April 30, 2011

PMR 1493-3 Embryofetal development study with of saxagliptin and metformin in combination in rabbits. Include saxagliptin monotherapy and metformin monotherapy treatment arms.

The timetable you submitted via email on June 29, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by July 31, 2010
Study Completion:	by September 30, 2010
Final Report Submission:	by April 30, 2011

PMR 1493-4 An epidemiologic study to compare the risk of severe hepatic events among patients with type 2 diabetes exposed to saxagliptin to the risk in patients exposed to other antidiabetic medications.

The timetable you submitted by email on July 22, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by January 31, 2010
Study Completion:	by May 30, 2015
Final Report Submission:	by November 30, 2015

PMR 1493-5 An epidemiologic study to compare severe hypersensitivity and severe cutaneous reactions among patients with type 2 diabetes exposed to saxagliptin and those exposed to other antidiabetic medications.

The timetable you submitted by email on July 22, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by January 31, 2010
Study Completion:	by November 30, 2016
Final Report Submission:	by June 30, 2017

Finally, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes and available data have not definitively excluded the potential for this serious risk with saxagliptin. 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 saxagliptin, to definitively exclude unacceptable cardiovascular toxicity. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1493-6 A randomized, double-blind, controlled trial evaluating the effect of saxagliptin 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 saxagliptin to that observed in the control group is less than 1.3. Secondary objectives must include an assessment of the long-term effects of saxagliptin on lymphocyte counts, infections, hypersensitivity reactions, liver, bone fracture, pancreatitis, skin reactions, 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 study reports should be included in the narratives.

Because renal impairment is an important complication of diabetes, you must ensure that there is a minimum of 1 year of exposure for at least 200 saxagliptin-treated patients with moderate renal impairment and at least 100 saxagliptin-treated patients with severe renal impairment.

The timetable you submitted on July 15, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	by November 30, 2009
Study Completion:	by July 31, 2015
Final Report Submission:	by January 31, 2016

Submit the protocols to your IND, 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(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing,

Advertising, and Communications (DDMAC), see
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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

In addition to the standard reporting requirements for an approved NDA, we request that you submit as 15-day expedited reports, all postmarketing cases of (1) liver test abnormalities accompanied by jaundice or hyperbilirubinemia, (2) opportunistic infections associated with the use of saxagliptin, and (3) pancreatitis, regardless of whether these reports are classified as serious or unexpected.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

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 – 2.5mg, 30 tablet bottle
Container Label – 2.5mg, 90 tablet bottle
Container Label – 5mg, 10 tablet blister card
Container Label – 5mg, 30 tablet bottle
Container Label – 5mg, 30 tablet bottle (sample)
Container Label – 5mg, 90 tablet bottle
Container Label – 5mg, 500 tablet bottle
Carton Label – 5mg, 28 tablet, contains 4 of the 7 tablet wallets (sample)
Carton Label – 5mg, 30 tablet bottle (sample)
Carton Label – 5mg, 100 tablet, 10 blister cards with 10 tablets each
Container/Carton Label – 5mg, 7 tablet wallet (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
07/31/2009