



NDA 200678/S-003
NDA 200678/S-004

SUPPLEMENT APPROVAL

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

Dear Dr. Smith:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received on May 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kombiglyze XR (saxagliptin/metformin hydrochloride extended-release) tablets 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg.

We acknowledge receipt of your amendments dated September 14 (2) (S-003), October 14 (S-003 and S-004), December 16 (S-003 and S-004), 2011 and January 31 (S-003 and S-004), 2012. We also acknowledge receipt of your email dated March 1, 2012, that includes the agreed-upon labeling.

The “Prior Approval” supplemental new drug applications provide for modifications to the Medication Guide, changes to the **RECENT MAJOR CHANGES, INDICATIONS AND USAGE, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS** sections of the Highlights of Prescribing Information section, and changes to the **INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY AND CLINICAL STUDIES** sections of the Full Prescribing Information section of the Kombiglyze XR package insert.

These changes are based on the safety and efficacy results from study CV181057, entitled “A multicenter, randomized, double-blind, phase 3 trial to evaluate the efficacy and safety of saxagliptin added to insulin monotherapy or to insulin in combination with metformin in subjects with type 2 diabetes who have inadequate glycemic control on insulin alone or on insulin in combination with metformin” (S-003), study CV181067, entitled “The effect of saxagliptin on the pharmacokinetics of the active moiety of a combined oral contraceptive containing ethinyl estradiol and norgestimate in healthy female subjects” (S-004), and study CV181054, entitled “A 52 week, randomized, double-blind, active-comparator controlled, phase 3b study to evaluate the efficacy and safety of saxagliptin in combination with metformin compared with a sulfonylurea (SU) in combination with metformin in adults with type 2 diabetes who have inadequate glycemic control on metformin therapy alone” (S-004). All three studies included in these

submissions have been previously reviewed under the saxagliptin NDA and are already labeled for saxagliptin.

We have completed our review of the supplemental applications, as amended. They are 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 Medication Guide), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. 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 provide appropriate annotations, including supplement number(s) and annual report date(s).

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), 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).

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

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Package Insert
Medication Guide

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

/s/

MARY H PARKS
03/07/2012