DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021178/S-015

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Ana Cibrian
Director, Global Regulatory and Safety Sciences
Mature Products, Metabolics, CV and CNS
P.O. Box 4000
Princeton, NJ 08543

Dear Ms. Cibrian:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 6, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Glucovance (Glyburide and Metformin HCl) tablets, 1.25 mg/250 mg, 2.5 mg/500 mg, and 5 mg/500 mg.

We also refer to our Prior Approval Supplement Request letter dated March 7, 2013, requesting additional revisions to the label for Glucovance.

Supplemental new drug application, S-015, provides for the following revisions to the labeling for Glucovance. Additions are noted by underline.

Under **CONTRAINDICATIONS**:

GLUCOVANCE is contraindicated in patients with:
4. Concomitant administration of bosentan

Under **PRECAUTIONS**, **Drug Interactions**, **Glyburide**, after the first paragraph:

An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore concomitant administration of GLUCOVANCE and bosentan is contraindicated.

Under **PRECAUTIONS**, **Drug Interactions**, **Glyburide,** after the last paragraph:

Colesevelam: Concomitant administration of colesevelam and glyburide resulted in reductions in glyburide AUC and C_{max} of 32% and 47%, respectively. The reductions in glyburide AUC and C_{max} were 20% and 15%, respectively when administered 1 hour before, and not significantly changed (-7% and 4%, respectively) when administered 4 hours before colesevelam.

Under **DOSAGE AND ADMINISTRATION**, after the section **Addition of Thiazolidinediones to GLUCOVANCE Therapy**:

Patients Receiving Colesevelam: When colesevelam is coadministered with glyburide, maximum plasma concentration and total exposure to glyburide is reduced. Therefore, GLUCOVANCE should be administered at least 4 hours prior to colesevelam.

In **Patient Information About Glucovance (Glyburide and Metformin HCl) Tablets,** under Q14. **Can I take GLUCOVANCE with other medications?**

Do not take GLUCOVANCE if you are taking bosentan used for pulmonary arterial hypertension (PAH), which is high blood pressure in the vessels of the lungs.

APPROVAL & LABELING

We have completed our review of this supplemental application. 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, text for the patient package insert,), with the addition of any labeling changes in pending "Changes Being Effected" (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 that includes labeling changes 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.

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, contact Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

AMY G EGAN
10/15/2013