DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 017532/S-034

SUPPLEMENT APPROVAL

Sanofi-aventis U.S. LLC
Attention: Doris Sincak, MS
US Regulatory Affairs Marketed Products
55 Corporate Drive
Bridgewater, NJ 08807

Dear Ms. Sincak:

Please refer to your Supplemental New Drug Application (sNDA) dated and received January 23, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Diabeta (glyburide) tablets 1.5 mg, 2.5 mg, and 5 mg.

We acknowledge receipt of your amendments dated April 24 and June 18, 2013.

We also refer to our letter dated March 7, 2013, requesting additional revisions to the label for Diabeta, to be submitted as a prior approval supplement, or as an amendment to a pending prior approval supplement.

Supplemental new drug application, S-034, provides for the addition of information regarding the involvement of cytochrome P450 enzyme in glyburide metabolism and interaction of glyburide with colesevelam in the PRECAUTIONS, Drug Interactions section of the Diaßeta prescribing information.

The agreed upon changes to the language are as follows (additions are noted by underline).

Under **PRECAUTIONS**, **Drug Interactions**, moved the following statement to after the first paragraph of the section, and modified as follows:

An increased incidence of elevated liver enzymes was observed in patients receiving glyburide concomitantly with bosentan. Therefore concomitant administration of Diaβeta and bosentan is contraindicated (See CONTRAINDICATIONS).

Under **PRECAUTIONS**, **Drug Interactions**, 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. When glyburide was administered 1 hour before colesevelam, the reductions in glyburide AUC and C_{max} were 20% and 15%, respectively, and not significantly changed (-7% and 4%, respectively) when administered 4

hours before colesevelam. Therefore, glyburide should be administered at least 4 hours prior to colesevelam.

Glyburide is mainly metabolized by CYP 2C9 and to a lesser extent by CYP 3A4. There is a potential for drug-drug interaction when glyburide is coadministered with inducers or inhibitors of CYP 2C9, which should be taken into account when considering concomitant therapy.

Under **DOSAGE AND ADMINISTRATION**, **Usual Starting Dose**, after the last paragraph,

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

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revision listed below.

Revised ~~XXXX~~ October 2013

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),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, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

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:
Package Insert

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