DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839/S-023

Sanofi-Synthelabo, Inc.
Attention: Nancy Barone Kribbs, Ph.D.
Associated Director, Regulatory Affairs
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Kribbs:

Please refer to your supplemental new drug application received December 11, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75mg Tablets.

We acknowledge receipt of your submission dated August 3, 2004. This submission constituted a complete response to our July 28, 2004 action letter.

This supplemental new drug application provides for labeling revisions to the package insert as follows:

1. Under the **CLINICAL STUDIES** section, Figure 3 was changed to include the box-and-whisker plots for age, race and gender.

2. Under the **PRECAUTIONS, General** section**,** the phrase, "As with other antiplatelet agents," was added to the front of the sentence reading,

   "Plavix prolongs the bleeding time and therefore should be used with caution in patients who may at risk of increased bleeding from traumas, surgery, or other pathological conditions (particularly gastrointestinal and intraoccular)."

3. Under **PRECAUTIONS, Information for Patients,** the section was changed to read,

   "Patients should be told that they may bleed more easily and it may take them longer than usual to stop bleeding when they take Plavix or Plavix combined with aspirin, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking Plavix and/or any other product known to effect bleeding before any surgery is scheduled and before any new drug is taken. If bleeding potential is a concern, patients should be encouraged to use a lower dose of aspirin with Plavix."

4. Under **PRECAUTIONS,** a **Geriatric Use** section was added that reads,

   "Of the total number of subjects in controlled clinical studies, approximately 50% of patients treated with Plavix were 65 years of age and over. Approximately 16% of patients treated with Plavix were 75 years of age and over.

   The observed difference in risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Figure 3 (see **CLINICAL STUDIES**). The observed difference in risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Table 3 (see **ADVERSE REACTIONS**). If bleeding potential is a concern, elderly patients should be encouraged to use a lower dose of aspirin with Plavix."

5. Per Agency request in the March 26, 2004 teleconference, under **ADVERSE REACTIONS**, Table 3 added footnotes to include bleeding event rate information about the standard age categories (under 65, 65 to 75, and 75 and over).

6. Also, per Agency request, the final sentences in the **PRECAUTIONS, Information for Patients** section, and in the **PRECAUTIONS, Geriatric Use** section, reading, "If bleeding potential is a concern, elderly patients should be encouraged to use a lower dose of aspirin with Plavix" were deleted.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on August 3, 2004.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Ms. Meg Pease-Fye, M.S., Regulatory Project Manager, at (301) 594-5327.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.
Acting Director,
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center For Drug Evaluation and Research

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

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/s/

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Norman Stockbridge

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