DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839/S-021 and S-024

Sanofi-Synthelabo, Inc.
Attention: Janine Masi, Pharm.D.
90 Park Avenue
New York, NY 10016

Dear Dr. Masi:

Please refer to your supplemental new drug applications dated September 4, 2003, received September 8, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix, (clopidogrel bisulfate) 75 mg Tablets.

We acknowledge receipt of your submissions dated July 17, 2003 and September 4, 2003. Your submissions of September 4, 2003 constituted a complete response to our July 9, 2003 action letter.

These supplemental new drug applications provide for the following changes to the package insert:

S-021

1. Under **CLINICAL PHARMACOLOGY, Mechanism of Action,** the word, "cardiovascular" was added just before "atherosclerotic" in the second sentence.

2. Under **CLINICAL PHARMACOLOGY, Special Populations,** *Renally Impaired Patients,* the final sentence, "No dosage adjustment is needed in renally impaired patients" was deleted.

3. Under **CLINICAL STUDIES**, in the paragraph under Table 1, the overall risk reduction percentages were changed from 9.78% and 10.64% to 9.8% and 10.6%.

4. In the 1st sentence of the 3rd paragraph under the Figure 1 in the **CLINICAL STUDIES** section, the word "atherothrombotic" was replaced with "thrombotic."

5. In the 5th paragraph under the Figure 1 in the **CLINICAL STUDIES** section, the sentence was changed from,

   "Patients also received aspirin (75-325 mg once daily) and other standard therapies such as heparin, but the use of GPIIb/IIIa inhibitors was prohibited during the initial hospitalization."

   To read,

   "Patients also received aspirin (75-325 mg once daily) and other standard therapies such as heparin. The use of GPIIb/IIIa inhibitors was not permitted for three days prior to randomization."

6. In Table 2 under **CLINICAL STUDIES,** a column heading changed from, "Relative Risk" to "Relative Risk Reduction."

7. In the paragraph directly under Figure 2 under **CLINICAL STUDIES**, the words, "(clopidogrel bisulfate tablets)" were added after "PLAVIX."

8. In the **INDICATIONS AND USAGE** section, the first sentence reading,

   "Plavix is indicated for the reduction of artherosclerotic events as follows…"

   Was changed to read,

   "Plavix is indicated for the reduction of thrombotic events as follows…"

9. Under the **PRECAUTIONS, General** section**,** the sentence,

   "As with other antiplatelet agents, Plavix should be used with caution in patients who may at risk of increased bleeding from traumas, surgery, or other pathological conditions."

   Was changed to read,

   "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)."

10. Also, under **PRECAUTIONS, general,** a second paragraph was added just underneath the heading which reads:

    "Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see **ADVERSE REACTIONS**)."

11. Under **PRECAUTIONS, General,** *GI Bleeding*, the first sentence reading, "Plavix prolongs bleeding time" was deleted.

12. Under **PRECAUTIONS, General,** *Use in Renally Impaired Patients,* section was added. It reads, "Experience is limited in patients with severe renal impairment. Plavix should be used with caution in this population."

13. Under **ADVERSE REACTIONS, Postmarketing Experience,** subsection changed from,

    The following events have been reported spontaneously from worldwide marketing experience: fever, very rare cases of hypersensitivity reactions including angioedema, bronchospasms, and anphylactoid reactions. Suspected thrombotic thrombocytopenic purpura (TTP) has been reported as part of the world-wide postmarketing experience, see **WARNINGS.**

    To read,

    The following events have been reported spontaneously from worldwide marketing experience:

    - *Body as a whole:*

- hypersensitivity reactions, anaphylactoid reactions
- *Central and Peripheral Nervous System disorders:*
  - confusion, hallucinations, taste disorders
- *Liver and Biliary system disorders:*
  - abnormal liver function test, hepatitis (non-infectious)
- *Platelet, Bleeding and Clotting disorders:*
  - cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retoperitoneal hemorrhage)
  - agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura(TTP) – see WARNINGS.
  - conjunctival , ocular and retinal bleeding
- *Respiratory system disorders:*
  - bronchospasm
- *Skin and Appendage disorders:*
  - angioedema, erythema mulitforme
- *Urinary system disorders:*
  - Glomerulopathy, abnormal creatinine levels

14. Under **DOSAGE AND ADMINISTRATION, Acute Coronary Syndrome**, the first sentence was changed from,

"For patients with acute coronary syndrome, Plavix should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily."

To read,

"For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), Plavix should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily."

S-024

1. Under **PRECAUTIONS, Drug Interactions,** *Warfarin,* the wording was changed from,

"The safety of the coadministration of Plavix with warfarin has not been established. Consequently, concomitant administration of these two agents should be undertaken with caution."

To read,

Because of the increased risk of bleeding, the concomitant administration of warfarin with Plavix should be undertaken with caution."

2. Under **ADVERSE EVENTS, Postmarketing Experience**, two additions were made:

- *Collagen disorders:*
  - vasculitis
- *Gastrointestinal disorders:*
  - colitis (including ulcerative or lymphocytic colitis)

We have completed our review of this supplemental new drug application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on September 8, 2003.

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, call Meg Pease-Fye, Regulatory Project Manager, at (301) 594-5312.

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doug Throckmorton

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