DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839/S-035

Sanofi-Aventis Inc.
Attention: Mr. Christopher Graham
300 Somerset Corporate Boulevard
P.O. Box 6977
Bridgewater, NJ, 08807

Dear Mr. Graham:

Please refer to your supplemental new drug application dated February 14, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

This supplemental new drug application provides for revisions to the **WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS** sections of the package insert. In our letter dated January 10, 2006, we requested you make the following changes to the labeling:

1. **Replace**

WARNINGS Thrombotic thrombocytopenic purpura (TTP): TTP has been reported rarely following use of Plavix, sometimes after a short exposure (< 2 weeks). TTP is a serious condition and requires urgent referral to a hematologist for prompt treatment. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. (b)(4)

(b)(4)

(b)(4)

With

WARNINGS Thrombotic thrombocytopenic purpura (TTP): TTP has been reported rarely following use of Plavix, sometimes after a short exposure (< 2 weeks). TTP is a serious condition that can be fatal in the absence of urgent treatment with plasmapheresis. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. (b)(4)

(b)(4)

(b)(4)

2. **Replace**

Post-marketing Experience

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

- *Body as a whole:*
  - hypersensitivity reactions, anaphylactoid reactions, serum sickness
- *Central and Peripheral Nervous System disorders:*
  - confusion, hallucinations, taste disorders
- *Hepato-biliary disorders:*
  - abnormal liver function test, hepatitis (non-infectious), acute liver failure
- *Platelet, Bleeding and Clotting disorders:*

- cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage)
- agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP) – some cases with fatal outcome- (see **WARNINGS)**.
- conjunctival, ocular and retinal bleeding

• *Respiratory, thoracic and mediastinal disorders:*
- bronchospasm, interstitial pneumonitis

• *Skin and subcutaneous tissue disorders:*
- angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus

• *Renal and urinary disorders:*
- glomerulopathy, increased creatinine levels

• *Vascular disorders:*
- vasculitis, hypotension

• *Gastrointestinal disorders:*
- colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis

• *Musculoskeletal, connective tissue and bone disorders:*
- myalgia

With

Post-marketing Experience

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

• *Body as a whole:*
- hypersensitivity reactions, anaphylactoid reactions, serum sickness

• *Central and Peripheral Nervous System disorders:*
- confusion, hallucinations, taste disorders

• *Hepato-biliary disorders:*
- abnormal liver function test, hepatitis (non-infectious), acute liver failure

• *Platelet, Bleeding and Clotting disorders:*
- cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage)
- thrombotic thrombocytopenic purpura (TTP) – some cases with fatal outcome- (see **WARNINGS)**.
- agranulocytosis, aplastic anemia/pancytopenia
- conjunctival, ocular and retinal bleeding

• *Respiratory, thoracic and mediastinal disorders:*
- bronchospasm, interstitial pneumonitis

• *Skin and subcutaneous tissue disorders:*
- angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus

• *Renal and urinary disorders:*
- glomerulopathy, increased creatinine levels

• *Vascular disorders:*
- vasculitis, hypotension

• *Gastrointestinal disorders:*
- colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis

• *Musculoskeletal, connective tissue and bone disorders:*
- myalgia

3. **Replace**

Information for Patients

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 affect bleeding before any surgery is scheduled and before any new drug is taken.

With

Information for Patients

Patients should be told that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they take Plavix or Plavix combined with aspirin, and that they should report any unusual (b)(4) bleeding to their physician (b)(4). Patients should inform physicians and dentists that they are taking Plavix and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.

In response to the above request for changes, you proposed the following:

1. **WARNINGS**

Thrombotic thrombocytopenic purpura (TTP):

TTP has been reported rarely following use of Plavix, sometimes after a short exposure (< 2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. (See **ADVERSE REACTIONS**.)

2. The **ADVERSE REACTIONS, Postmarketing Experience** section was changed to match the recommended wording from the Division's letter.

3. **PRECAUTIONS**

Information for Patients

Patients should be told that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily 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 affect bleeding before any surgery is scheduled and before any new drug is taken.

We have completed our review of this supplemental new drug application. It is are approved, effective on the date of this letter, for use as recommended in the electronic final printed labeling (FPL) submitted on February 14, 2006.

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
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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
(301) 796-1130

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: approved labeling

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

/s/

Norman Stockbridge

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