



NDA 20-839/S-037

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 15, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We also acknowledge your submission dated February 27, 2007.

This supplemental new drug application provides for revisions requested in our August 17, 2006 approval letter for supplement 034 in which we requested changes to the **CLINICAL STUDIES** section of the package insert. You proposed the following changes:

1. In the **CLINICAL STUDIES** section of the package insert, the following paragraph was revised:

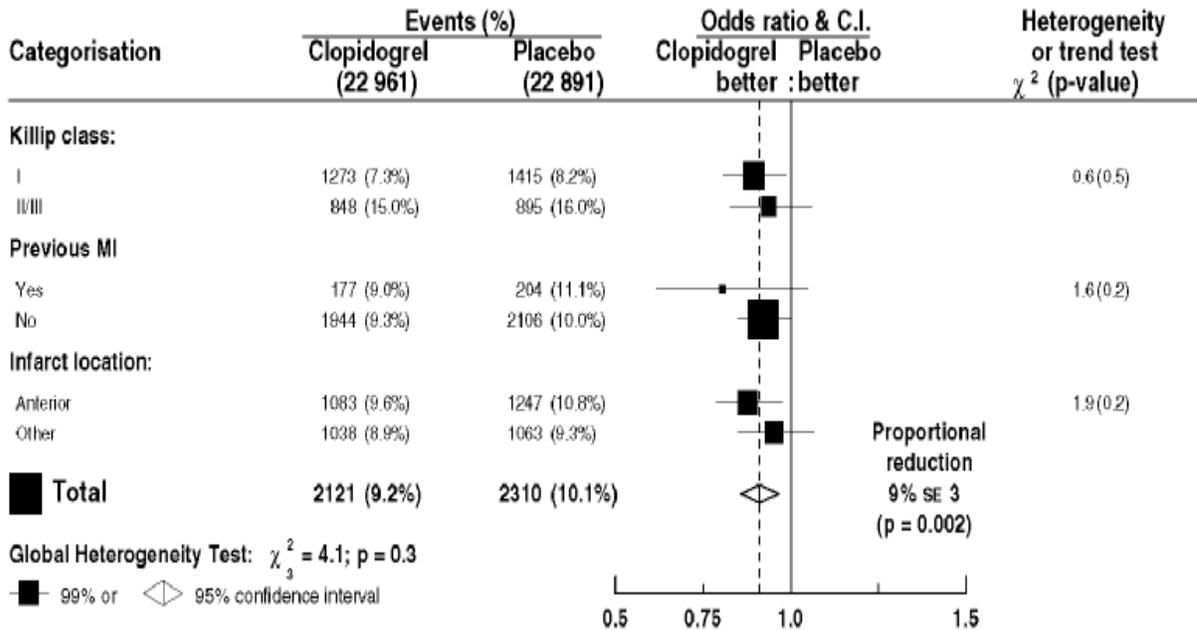
“The clinical evidence for the efficacy of Plavix is derived from four double-blind trials involving 81,090 patients: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of Plavix to aspirin, and the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction) and the COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial / Second Chinese Cardiac Study) studies comparing Plavix to placebo, both given in combination with aspirin and other standard therapy.”

To read:

“The clinical evidence for the efficacy of Plavix is derived from four double-blind trials involving 81,090 patients: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of Plavix to aspirin, and the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), the COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial / Second Chinese Cardiac Study) studies comparing Plavix to placebo, both given in combination with aspirin and other standard therapy and CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction).”

2. The following figure was added (Figure 7) to the **CLINICAL STUDIES** section:

Figure 7: Effects of Adding PLAVIX to Aspirin in the Non-Prespecified Subgroups in the COMMIT Study



- Under the **WARNINGS, Thrombotic thrombocytopenic purpura (TTP)** subsection, the paragraph approved on August 4, 2006 (SLR 035) was changed from:

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. TTP was not seen during clopidogrel’s clinical trials, which included over 17,500 clopidogrel-treated patients. In worldwide post-marketing experience, however, TTP has been reported. (See **ADVERSE REACTIONS**.)

To read:

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**.)

- Under **PRECAUTIONS, Information for Patients**, the paragraph approved on August 4, 2006 (SLR 035) was changed from:

“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 bruising or 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.”

To read:

“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.”

5. Other revisions reflect updates in the figure numbers as required by the additional figure 7.

We recommend the following changes be made to the **ADVERSE REACTIONS** sections in order to have more consistent ordering of terms:

Under *Autonomic Nervous System Disorders*, “Cramps legs” should read “leg cramps”

Under Heart rate and rhythm disorder, “Fibrillation atrial” should read “atrial fibrillation”

Under Body as a whole, “necrosis ischemic” should read “ischemic necrosis”

Under Cardiovascular disorders, “Edema generalized” should read “Generalized edema”

Under *Gastrointestinal system disorders*,

- “gastric ulcer perforated” should read “perforated gastric ulcer”
- “gastritis hemorrhagic” should read “hemorrhagic gastritis”
- “upper GI ulcer hemorrhagic” should read hemorrhagic upper GI ulcer

Under *Liver and Biliary system disorders*,

- “hepatitis infectious” should read “infectious hepatitis”
- “liver fatty” should read “fatty liver”

Under *Platelet, bleeding and clotting disorders*,

- “hemorrhage intracranial” should read “intracranial hemorrhage”
- “hemorrhage retroperitoneal” should read “retroperitoneal hemorrhage”
- “hemorrhage of operative wound” should read “operative wound hemorrhage”
- “purpura allergic” should read “allergic purpura”

Under *Red blood cell disorders*,

- “Anemia aplastic” should read “aplastic anemia”
- “anemia hypochromic” should read hypochromic anemia”

Under *Skin and appendage disorders*,

- “rash erythematous” should read “erythematous rash”
- “rash maculopapular” should read “maculopapular rash”

We have completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted electronically on February 15, 2007.

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
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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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