



NDA 20-839/S-030/S-031

Sanofi-Synthelabo Inc.  
Attention: Mr. Christopher Graham  
90 Park Avenue, 5<sup>th</sup> Floor  
New York, NY 10016

Dear Mr. Graham:

Please refer to your supplemental new drug applications dated October 22, 2004 (S-030) and October 29, 2004 (S-031), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix, (clopidogrel bisulfate) 75 mg Tablets.

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

**S-030**

1. Under the **INDICATIONS AND USAGE** and in the 3<sup>rd</sup> paragraph under the Figure 1 of the **CLINICAL STUDIES** section, the term “thrombotic” was changed to “atherothrombotic.”

**S-031**

1. Under the **DESCRIPTION** section, the phrase, “hydroxypropyl methylcellulose 2910” was replaced with, “hypromellose 2910.”
2. The **WARNINGS** section was revised to be more consistent with the **ADVERSE REACTIONS** and **PRECAUTIONS** sections for information about drug induced TTP treatment. Under **WARNINGS**, the 2<sup>nd</sup> sentence, “TTP is a serious condition requiring prompt treatment” has been revised to read, “TTP is a serious condition and requires urgent referral to a hematologist for prompt treatment.” In addition, the phrase, “(see **ADVERSE REACTIONS**)” was added to the end of the last sentence of the **WARNINGS** section.
3. Under **ADVERSE REACTIONS; Post-marketing Experience**, the System Organ Class headings were revised to be inline with the MedDRA dictionary. Also, the terms hypotension, lichen planus, pancreatitis, Stevens Johnson syndrome, and myalgia were added.

The section was revised to read as follows:

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

- *Body as a whole:*
  - hypersensitivity reactions, anaphylactoid reactions
- *Central and Peripheral Nervous System disorders:*

- confusion, hallucinations, taste disorders
- *Hepato-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 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
- *Skin and subcutaneous tissue disorders:*
  - angioedema, erythema multiforme, Stevens-Johnson syndrome, lichen planus
- *Renal and urinary disorders:*
  - glomerulopathy, increased creatinine levels
- *Vascular disorders:*
  - vasculitis, hypotension
- *Gastrointestinal disorders:*
  - colitis (including ulcerative or lymphocytic colitis) , pancreatitis
- *Musculoskeletal, connective tissue and bone disorders:*
  - myalgia”

4. The 1<sup>st</sup> paragraph in the **OVERDOSE** section was revised from:

“One case of deliberate overdosage with Plavix was reported in the large, CAPRIE controlled clinical study. A 34-year-old woman took a single 1,050 mg dose of Plavix (equivalent to 14 standard 75-mg tablets). There were no associated adverse events. No special therapy was instituted, and she recovered without sequelae. No adverse events were reported after single oral administration of 600 mg (equivalent to 8 standard 75-mg tablets) of Plavix in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75 mg of Plavix per day.”

To read as follows:

“Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these

submissions "**FPL for approved supplement NDA 20-839/S-030/S-031.**" Approval of these submissions by FDA is not required before the labeling is used.

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 Meg Pease-Fye, 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

Enclosure: approved labeling

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/s/

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