

026-839- S-009

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER(S)**

**NDA 20-839/S-009**

**Trade Name:** Plavix Tablets

**Generic Name(s):** (clopidogrel bisulfate)

**Sponsor:** Sanofi-Synthelabo, Inc.  
**Agent:**

**Approval Date:** July 25, 2000

**Indication:** Provides for manufacturing controls

NDA 20-839/S-009

7/25/00

Sanofi-Synthelabo, Inc.  
Attention: Mr. John Purpura  
90 Park Avenue  
New York, NY 10016

Dear Mr. Purpura:

Please refer to your supplemental new drug application dated March 31, 2000, received April 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) Tablets.

We acknowledge receipt of your submission dated June 20, 2000.

This supplemental new drug application provides for reformulation of the drug product using clopidogrel bisulfate — that is manufactured at Sanofi Chimie, Aramon, France. Sanofi Winthrop Industrie in Ambares, France will manufacture the drug product containing clopidogrel bisulfate — The expiration period for the drug product shall be — in blister packaging and — in bottles.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the last approved labeling (submitted June 2, 2000, acknowledged July 5, 2000 for SLR-008), except that the last paragraph of the **DESCRIPTION** section of the package insert should be revised as proposed in your March 31, 2000 submission.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-839/S-009." Approval of this submission by FDA is not required before the labeling is used.

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If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
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. Colleen LoCicero  
Regulatory Health Project Manager  
(301) 594-5334

Sincerely,

/S/

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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cc:

Archival NDA 20-839

HFD-110/Div. Files

HFD-110/cil

HFD-110/Reviewers and Team Leaders

HF-2/MedWatch (with labeling)

HFD-002/ORM (with labeling)

HFD-101/ADRA (with labeling)

HFD-42/DDMAC (with labeling)

HFI-20/Press Office (with labeling)

HFD-400/OPDRA (with labeling)

HFD-613/OGD (with labeling)

HFD-095/DDMS-IMT (with labeling)

HFD-810/DNDC Division Director

DISTRICT OFFICE

Drafted by: cil/July 20, 2000

Initialed by: F Zielinski/7/20/00

K Srinivasachar/7/20/00

G Robbie/7/21/00

P Marroum/7/20/00

N Morgenstern/7/24/00

Final: asb/7/24/00

Filename: 20-839s009(ap).doc

APPROVAL (AP)

RHPM Review of Final Printed Labeling  
NDA 20-839/SCF-009

Date labeling submitted: September 6, 2000  
Date labeling reviewed: September 22, 2000  
Product: Plavix (clopidogrel bisulfate) Tablets  
Sponsor: Sanofi-Synthelabo Inc.

**Background**

This supplemental application provides for a reformulation of the drug product using clopidogrel bisulfate. The original supplemental application included data to support the change and the **DESCRIPTION** section of the package insert revised to reflect the formulation change. The Agency issued an approval letter for this application on July 25, 2000. The letter requested that the sponsor submit final printed labeling identical to the last approved labeling (submitted June 2, 2000, acknowledged July 5, 2000 for SLR-008), with the exception of the last paragraph of the **DESCRIPTION** section, which should be revised as proposed in the March 31, 2000 submission.

**Evaluation**

I reviewed the submitted final printed package insert in its entirety and found it to be exactly as requested in the July 25, 2000 approval letter with a few minor exceptions. In several places throughout the text, the generic name has been added or removed following the brand name. Additionally, in the first paragraph of the *Neutropenia/agranulocytosis/ADVERSE REACTIONS* subsection, "Clinical Trials" is no longer printed in bold font.

**Recommendation**

I recommend that the Division issue an acknowledge and retain letter for the submitted final printed labeling.

/s/

Colleen Locicero, RHPM

cc: orig NDA 20-839/S-009  
HFD-110  
HFD-110/Blount  
HFD-110/LoCicero

NDA 20-839/S-009

Sanofi-Synthelabo Inc.  
Attention: Mr. Kenneth R. Palmer  
90 Park Avenue  
New York, NY 10016

Dear Mr. Palmer:

We acknowledge the receipt of your September 6, 2000 submission containing final printed labeling in response to our July 25, 2000 letter approving your supplemental new drug application for Plavix (clopidogrel bisulfate) Tablets.

We have reviewed the labeling that you submitted in accordance with our July 25, 2000 letter, and we find it acceptable.

If you have any questions, please call:

Ms. Colleen LoCicero  
Regulatory Health Project Manager  
(301) 594-5334

Sincerely,

A handwritten signature in black ink, appearing to be 'R. Lipicky', written over a faint, stylized 'S' or similar mark.

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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cc:

Archival NDA 20-839

HFD-110/Div. Files

HFD-110/C.LoCicero

HFD-110/Reviewers and Team Leaders

HF-2/Medwatch (with labeling)

HFD-101/ADRA (with labeling)

HFD-40/DDMAC (with labeling)

HFD-093/DDMS-IST (with labeling)

HFD-613/OGD (with labeling)

HFD-735/OPDRA (with labeling)

DISTRICT OFFICE

Drafted by: cll/September 22, 2000

Initialed by: F Zielinski/9/22/00

K Srinivasachar/9/25/00

G Robbie/9/25/00

P Marroum/9/25/00

N Morgenstern/10/4/00

Final: asb/10/5/00

Filename: 20-839s009(ar).doc

ACKNOWLEDGE AND RETAIN (AR)



RHPM Review of Draft Labeling  
NDA 20-839/SCF-009

Date of supplement:	March 31, 2000
Date of amendments:	June 20, 2000
Date of review:	July 20, 2000
Product:	Plavix (clopidogrel bisulfate) Tablets
Sponsor:	Sanofi-Synthelabo Inc.

### Background

This supplemental application provides for a change in the formulation of Plavix 75 mg tablets as a consequence of the use of clopidogrel bisulfate — drug substance. The submission includes data to support the change, including data from a bioequivalence study comparing the current formulation with the proposed formulation. Also included in the submission are proposed changes to the **DESCRIPTION** section of the package insert that reflect the formulation change.

### Evaluation

With respect to labeling in this submission, the sponsor has only included a revised **DESCRIPTION** section of the package insert. The changes to the **DESCRIPTION** section reflect the proposed formulation change and are limited to the last paragraph of this section. This paragraph has been changed from the following:

Each tablet contains anhydrous lactose, hydrogenated castor oil, microcrystalline cellulose, polyethylene glycol 6000 and pregelatinized starch as inactive ingredients. The pink film coating contains ferric oxide (red), hydroxypropyl methylcellulose 2910, polyethylene glycol 6000 and titanium dioxide.  
The tablets are polished with Carnauba wax.

to the following:

Each tablet contains hydrogenated castor oil, hydroxypropyl cellulose, mannitol, microcrystalline cellulose and polyethylene glycol 6000 as inactive ingredients. The pink film coating contains ferric oxide, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide and triacetin. The tablets are polished with Carnauba wax.

### *Clinical Pharmacology/Biopharmaceutics Review*

In his May 4, 2000 review of the bioequivalency study report included in this submission, Dr. Robbie states that the — batches of clopidogrel, the batch containing — and the batch containing — are bioequivalent.

In his June 20, 2000 review of the comparative dissolution of the proposed and currently marketed clopidogrel tablets, Dr. Robbie recommends that the dissolution specification be revised to a specification of not less than — (Q) dissolved in 30 min at pH 2.0 at a paddle speed of 50 rpm. This message was conveyed to the sponsor in a June 20, 2000 teleconference between representatives of Sanofi and Drs. Zielinski and Marroum. The sponsor accepted the Agency's recommendation and amended this supplement, submission dated June 20, 2000, to replace the originally proposed dissolution specifications with the specifications recommended by Dr. Robbie (Q= —% in 30 minutes at 50 RPM).

*Chemistry Review*

In his July 20, 2000 review of this supplement, Dr. Zielinski indicates that the data and information provided in these submissions support the proposed formulation change. He recommends approval of the supplement.

**Recommendation**

I recommend that the Division issue an approval letter for this supplement, in accordance with 21 CFR 314.70 (b)(2)(i). The approval letter should request that the sponsor submit a final printed package insert with the last paragraph of the **DESCRIPTION** section revised as proposed in their March 31, 2000 submission. The letter should state further that the remainder of the text should be identical to the last approved labeling (final printed labeling for SLR-008, submitted June 2, 2000 and acknowledged July 5, 2000).

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Colleen LoCicero, RHPM

cc: orig NDA 20-839  
HFD-110  
HFD-110/Blount  
HFD-110/LoCicero