

020839\_5-006

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER(S)**

**NDA 20-839/S-006**

**Trade Name:** Plavix Tablets

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

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

**Approval Date:** February 22, 2000

**Indication:** Provides for labeling revision

2-22-00

NDA 20-839/S-006

Sanofi-Synthelabo Inc.  
Attention: Ms. Allyson Chambers  
90 Park Avenue  
New York, NY 10016

Dear Ms. Chambers:

Please refer to your supplemental new drug application dated January 7, 2000, received January 10, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) Tablets.

This "Changes Being Effected" supplemental new drug application provides for labeling revised by the addition of a **Postmarketing Experience** subsection to the **ADVERSE REACTIONS** section. The new subsection has been added at the end of the **ADVERSE REACTIONS** section and immediately precedes the **OVERDOSAGE** section. The proposed text reads as follows:

**Postmarketing Experience:**

The following events have been reported spontaneously from worldwide postmarketing experience: very rare cases of hypersensitivity reactions including angioedema, bronchospasms, and anaphylactoid reactions.

We have completed the review of this supplemental application 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 submitted labeling (package insert submitted January 7, 2000). Accordingly, the supplemental application is approved effective on the date of this letter.

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

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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 contact:

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

Sincerely yours,

A stylized handwritten signature, possibly reading 'R. Lipicky', written in black ink.

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/LoCicero

HFD-110/Reviewers and Team Leaders

HF-2/MedWatch (with labeling)

HFD-002/ORM (with labeling)

HFD-101/ADRA (with labeling)

HFD-40/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: cll/February 8, 2000

Initialed by: F Zielinski/2/9/00

A DeFelice/2/10/00

S Rodin/2/10/00

A Karkowsky/2/10/00

N Morgenstern/2/17/00

Final: asb/2/17/00

Filename: 20-839s006(ap).doc

APPROVAL (AP)

RHPC Review of Draft Labeling  
NDA 20-839/S-006

Date of Supplement:	January 7, 2000
Date of Review:	February 4, 2000
Product:	Plavix (clopidogrel bisulfate) Tablets
Sponsor:	Sanofi-Synthelabo Inc.
Evaluation:	

This "Changes Being Effected" supplement provides for the addition of a **Postmarketing Experience** subsection to the **ADVERSE REACTIONS** section of the package insert. The new subsection has been added at the end of the **ADVERSE REACTIONS** section and immediately precedes the **OVERDOSAGE** section. The proposed text reads as follows:

**Postmarketing Experience:**

The following events have been reported spontaneously from worldwide postmarketing experience: very rare cases of hypersensitivity reactions including angioedema, bronchospasms, and anaphylactoid reactions.

The sponsor states that this change will be implemented at the next printing, and should be incorporated into commercial product no later than February 29, 2000.

I reviewed the proposed labeling in its entirety and found that besides the addition of the **Postmarketing Experience** subsection, the following changes from the last approved package insert (submitted January 8, 1998 and acknowledged March 31, 1998) have been made:

1. The generic name (clopidogrel bisulfate) has been added to follow the brand name (PLAVIX) in certain parts of the text and removed from following the brand name in other parts of the text.
2. The description of the tablet in the **HOW SUPPLIED** section has been changed from the following:

PLAVIX (clopidogrel bisulfate) is available as a pink, round, biconvex, film-coated tablet engraved with "75" on one side.

to the following:

PLAVIX (clopidogrel bisulfate) is available as a pink, round, biconvex, film-coated tablet debossed with "75" on one side and "1171" on the other.

The addition of "1171" to the unmarked side of the tablet was made in accordance with the sponsor's commitment, as noted in the November 17, 1997 approval letter for this application, to investigate further possibilities for additional code imprint to

the tablet so that the tablet could be more easily identified. The sponsor notes the change to the tablet in the **Chemistry, Manufacturing, and Controls Changes** section of their 1999 Annual Report (Y-002, dated January 18, 2000). This change is also reflected in the revised package insert submitted with the 1999 Annual Report. However, the sponsor does not note the change to the package insert in the **Labeling Changes** section of the 1999 Annual Report.

3. The **HOW SUPPLIED** section has been further revised to add 30- and 90-count bottle descriptions and delete the 100-count bottle description. These changes were included in the sponsor's first Annual Report (Y-001, dated January 15, 1999). The 30-tablet bottle was approved in a prior CMC supplement (S-002, submitted December 19, 1997 and approved May 21, 1998). According to Dr. James Short's December 10, 1999 review of this Annual Report, the 90-tablet bottle was provided for in the original NDA submission, but not implemented at the time of approval. Dr. Short found these changes to be satisfactory (see his December 10, 1999 review of this Annual Report).
4. The "Caution: Federal law prohibits dispensing without a prescription" statement has been deleted. It has not been replaced with the "Rx only" statement as, under 21 CFR 201.57, this statement is not required to be included in the package insert (see Guidance for Industry, Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997—Elimination of Certain Labeling Requirements, Revised July 1998).
5. "Sanofi" has been replaced throughout with "Sanofi-Synthelabo Inc." to reflect the change in sponsor name.

The submitted package insert, which the sponsor refers to as final printed labeling, is actually a copy of the package insert. In light of the fact that we are currently accepting electronic labeling as final printed labeling, I believe this to be acceptable.

**Recommendation:**

This supplement provides for the addition of adverse reactions to labeling. I recommend that the Division issue an approval letter for this supplement, in accordance with 21 CFR 314.70(c)(2)(i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction].

/S/

Colleen LoCicero, RHPC

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