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## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER
## 20-839/SE1-019

# Administrative Documents

sanofi~synthelabo

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Center for Drug Evaluation and Research
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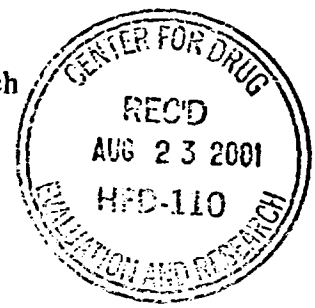
Rockville, Maryland 20857




ORIGINAL AMENDMENT
N-X P

Re: Patent Information for PLAVIX® (clopidogrel bisulfate)
Supplemental New Drug Application 20-839 for the Use of Clopidogrel Bisulfate in Patients With Acute Coronary Syndrome Without ST Segment Elevation (Unstable Angina or Non-Q-Wave MI)

Gentlemen:

Under the provisions of 21 U.S.C. 355(b)(1) and 21 CFR 314.53, submitted herewith is the information on each patent that claims the drug clopidogrel bisulfate or a method of using said drug that is the subject of the above-identified supplemental new drug application (sNDA) and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug.

| U.S. Patent No. | Expiration Date | Type of Patent | Patent Owner |
|---|---|---|---|
| 4,529,596 | July 5, 2003 | Drug<br>Drug Product<br>Method of Use | Sanofi-Synthelabo |
| 4,847,265 | November 17, 2011 | Drug<br>Drug Product | Sanofi-Synthelabo |
| 5,576,328 | January 31, 2014 | Method of Use | Sanofi-Synthelabo |

The following party is authorized to receive on behalf of the patent owner notice of patent certification under 21 U.S.C. 355(b)(3) and (j)(2)(B), and 21 CFR 314.52 and 314.95.

Sanofi-Synthelabo, Inc.
Patent Counsel
9 Great Valley Parkway
Malvern, PA 19355

Pursuant to 21 CFR 314.53(D)(2)(ii), the undersigned certifies that U.S. Patents Nos. 4,529,596; 4,847,265 and 5,576,328, information for which was previously submitted in NDA 20-839, claim the drug, drug product and method of use which are the subject of this sNDA.

This letter is submitted in duplicate.

Respectfully submitted,

Paul E. Dupont
Sr. Director of Patents

## PATENT INFORMATION

Pursuant to 21 CFR 314.53(d)(4) the patent information for this supplement is being submitted concurrently herewith by separate letter addressed to the Central Document Room.

## REQUEST FOR EXCLUSIVITY

Pursuant to 21 U.S.C. 355(c)(3)(D)(iv) and (j)(4)(D)(iv), and under the provisions of 21 CFR 314.108(b)(5), applicant hereby claims a period of exclusivity of three years from the date of approval of this supplemental application (sNDA) for the use of clopidogrel bisulfate for the reduction of atherothrombotic events in patients with acute coronary syndrome without ST segment elevation (unstable angina or non-Q-wave MI).

In support of the instant sNDA, applicant has conducted a clinical investigation (the CURE study) under investigational new drug application IND 34,663 and certifies that, to the best of its knowledge, said clinical investigation is a new clinical investigation, the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

Applicant further certifies that a thorough search of the scientific literature has been conducted for all published studies or publicly available reports of clinical investigations relevant to the use of clopidogrel bisulfate for the reduction of atherothrombotic events in patients with acute coronary syndrome without ST segment elevation (unstable angina or non-Q-wave MI) and that no relevant studies or reports were found. Accordingly, in applicant's opinion and to the best of its knowledge no publicly available information exists to support the approval of the use of clopidogrel bisulfate in the indication for which applicant is seeking approval except for the new clinical investigation included in the instant sNDA. The new clinical investigation is therefore essential to approval of this sNDA.

**EXCLUSIVITY SUMMARY for NDA #: 20-839 SUPPL #: 019**

**Trade Name: Plavix Generic Name: clopidogrel bisulfate**

**Applicant Name: Sanofi-Synthelabo Inc. HFD-110**

**Approval Date: February 27, 2002**

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-839, Plavix

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # EFC3307, CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (OASIS-4))

Investigation #2, Study # N/A

Investigation #3, Study # N/A

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more

investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency tc support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # EFC3307 (CURE)

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial

support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

| | |
|---|---|
| Investigation #1 | |
| IND # 34,663 YES /_X_/ | NO /___/ Explain: |
| Investigation #2 | |
| IND # _____ YES /___/ | NO /___/ Explain: |

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | |
| YES /___/ Explain _____ | NO /___/ Explain _____ |
| _____ | _____ |
| _____ | _____ |
| Investigation #2 | |
| YES /___/ Explain _____ | NO /___/ Explain _____ |
| _____ | _____ |
| _____ | _____ |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

Colleen LoCicero 2/28/02
Signature of Preparer Date
Title: Regulatory Health Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Colleen LoCicero
3/1/02 11:58:48 AM

Doug Throckmorton
3/1/02 12:26:28 PM

# PEDIATRIC PAGE

## (Complete for all APPROVED original applications and efficacy supplements)

**NDA # :** 20-839 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 019

**Stamp Date:** 8/21/02 **Action Date:** February 27, 2002 (approval)

**HFD-**110 **Trade and generic names/dosage form:** Plavix (clopidogrel bisulfate) Tablets

**Applicant:** Sanofi-Synthelabo Inc. **Therapeutic Class:** anti-platelet

**Indication(s) previously approved:** Plavix (clopidogrel bisulfate) is indicated for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease.

*In addition to the addition of the new indication, the original indication is modified to the following:*

Plavix is indicated for the reduction of atherosclerotic events, as follows:

**Recent MI, Recent Stroke or Established Peripheral Arterial Disease**
For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, PLAVIX has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

### Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

**Number of indications for this application(s):** 1

**Indication #1:**

PLAVIX (clopidogrel bisulfate) is indicated for the reduction of atherosclerotic events, as follows:

**Acute Coronary Syndrome**
For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, PLAVIX has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

**Is there a full waiver for this indication (check one)?**

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
**NOTE: More than one may apply**
**Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason(s) for full waiver:**

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
X **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

*f studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

| | | | | |
|---|---|---|---|---|
| **Min____** | **kg____** | **mo.____** | **yr.____** | **Tanner Stage____** |
| **Max____** | **kg____** | **mo.____** | **yr.____** | **Tanner Stage____** |

**Reason(s) for partial waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

| | | | | |
|---|---|---|---|---|
| **Min____** | **kg____** | **mo.____** | **yr.____** | **Tanner Stage____** |
| **Max____** | **kg____** | **mo.____** | **yr.____** | **Tanner Stage____** |

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

**Other:**_____

**Date studies are due (mm/dd/yy):** _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

| | | | | |
|---|---|---|---|---|
| **Min____** | **kg____** | **mo.____** | **yr.____** | **Tanner Stage____** |
| **Max____** | **kg____** | **mo.____** | **yr.____** | **Tanner Stage____** |

**Comments:**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

*{See appended electronic signature page}*

**Regulatory Project Manager**

**cc: NDA**
**HFD-960/ Terrie Crescenzi**
**(revised 1-18-02)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960**
**301-594-7337**

## Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** _____

**Is there a full waiver for this indication (check one)?**

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  **NOTE: More than one may apply**
  **Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason(s) for full waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |

**Reason(s) for partial waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

**Min_____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

**Date studies are due (mm/dd/yy):** _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

**Min_____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Comments:**

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.***

**This page was completed by:**

*{See appended electronic signature page}*

_____
**Regulatory Project Manager**

**cc: NDA**
**HFD-960/ Terrie Crescenzi**
**(revised 1-18-02)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960**
**301-594-7337**

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

/s/

Colleen LoCicero
3/4/02 09:20:13 AM
CSO

## Item 16. Debarment Certification

Sanofi-Synthelabo, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Nancy Barone Kribbs, Ph.D.
Associate Director
Regulatory Affairs
Sanofi-Synthelabo, Inc.

**RHPM Overview**

Date:

| | |
|---|---|
| Application: | NDA 20-839/SE1-019<br>Plavix (clopidogrel bisulfate) Tablets |
| Applicant: | Sanofi-Synthelabo Inc. |
| Classification: | Priority |
| User Feel Goal Date: | February 21, 2002 |

**Background**

This supplemental application proposes a new indication for Plavix in patients with Acute Coronary Syndrome, based on the findings of the CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (OASIS-4)) study.

In an effort to expedite the submission of this supplemental application due to the potential clinical importance of the CURE study findings and as agreed to by the Division, the Sponsor submitted an abbreviated supplemental application. The details of the application, i.e., the items essential for an adequate review of the application, were discussed and agreed upon at the March 27, 2001 pre-sNDA meeting for this supplemental application (minutes of this meeting can be found in the "Minutes of Meetings" section of the Action Package). Additionally, the Division designated this application a priority review.

The application was submitted in electronic format, with only those documents requiring an original signature provided in paper.

User Fee

The user fee for this application was paid in full prior to the submission of the application.

Labeling

The original submission contains proposed draft labeling revised to include the new indication as well as changes to other sections of the package insert that reflect the findings of the CURE study. The RHPM review of the Sponsor's proposed labeling is attached to this overview and included in the *Labeling* Section of the Action Package.

In his review of this application, Dr. Hung recommends that the results of the unspecified endpoints reported in the New England Journal of Medicine (NEJM) article not be included in labeling.

Dr. Throckmorton's labeling recommendations are appended to his review (Appendix 4). He also provided a complete marked-up draft of the Sponsor's proposed labeling that is included in the *Labeling* section of the Action Package. Dr. Andrew Haffer of DDMAC collaborated with Dr. Throckmorton on the labeling recommendations and marked-up draft of the proposed labeling. Because of this collaboration, which was managed via telephone and electronic mail communication between Drs. Haffer and Throckmorton, Dr. Haffer did not write a formal review for this supplemental application.

Dr. Lipicky found Dr. Throckmorton/Haffer's proposed marked-up labeling acceptable, with the exception of the **DOSAGE AND ADMINISTRATION** and **INDICATIONS AND USAGE** sections. He revised these sections of the labeling. Following his review of Dr. Lipicky's proposed language, Dr. Haffer revised Dr. Lipicky's **DOSAGE AND ADMINISTRATION** section and forwarded this to the Division. Dr. Throckmorton found Dr. Lipicky's **INDICATIONS AND USAGE** section and Dr. Haffer's **DOSAGE AND ADMINISTRATION** section acceptable. Dr. Lipicky recommended that the **INDICATIONS AND USAGE** section of the marked-up draft be replaced with his language and the **DOSAGE AND ADMINISTRATION** section with Dr. Haffer's language and, subsequently, the marked-up draft labeling be faxed to the Sponsor for consideration. He suggested that the Sponsor review the labeling, decide which of our changes they would accept, incorporate these changes into the labeling, and submit the revised labeling (as draft) to the sNDA.

The Division's marked-up draft labeling was faxed to the Sponsor on February 14, 2002. The Sponsor submitted revised draft labeling on February 15, 2002 that incorporated most of the changes the Division proposed. The Division made a few minor changes to this labeling in the **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION** sections. Dr. Lipicky decided that the Division would issue an approvable letter for this supplemental application, requesting final printed labeling identical to this version (the Sponsor's February 15, 2002 submitted draft labeling with a few minor changes) of marked-up draft labeling.

Patent

The patent information for this supplemental application was submitted separately from the supplemental application on August 21, 2001 and was forwarded to Ms. MaryAnn Holovac on September 7, 2001.

The Sponsor has requested three years exclusivity for the proposed new indication in acute coronary syndrome.

The exclusivity summary for this application can be found in the *Exclusivity Checklist* section of the Action Package.

Financial Disclosure

Financial disclosure information for the CURE study was included in this submission. In his January 30, 2002 memorandum regarding the CURE financial disclosure information, Dr. Throckmorton states that the Sponsor asserts that neither they nor Bristol-Myers Squibb have entered into any financial arrangement with any of the CURE clinical investigators as defined under 21 CFR 54. He continues that, according to the Sponsor, 63 investigators from 28 sites (out of 428 sites that enrolled patients) did not submit the required financial disclosure information to the Sponsor. He further notes that only one of these 63 investigators was a principle investigator. Dr. Throckmorton concludes that there is no evidence suggesting inappropriate or suspicious financial arrangements between the Sponsor and investigators of the CURE study. He notes that the sites with investigators who did not submit the required financial information represent only a small percent of the investigators who contributed to the CURE study enrollment.

Secondary Review/Division Director Memo

Following his review of Drs. Throckmorton and Hung's reviews, Dr. Lipicky concluded that a secondary review of this application would not be needed.

Medical Review

In his February 6, 2002 review of this supplemental application, Dr. Throckmorton states that in the setting and patient population studied, clopidogrel significantly reduced the incidence of the two pre-specified primary endpoints of the study. He notes that clopidogrel's effect in this setting was seen across a broad range of patient demographics. He adds that the major safety concern identified was an increase in bleeding adverse events in patients on clopidogrel. He concludes that the CURE study supports the approval of clopidogrel to reduce the occurrence of cardiovascular death, non-fatal myocardial infarction, strokes, and refractory ischemia, as defined in the protocol.

Dr. Throckmorton's labeling recommendations are appended to his review (Appendix 4). Additionally, he provided a complete marked-up draft of the Sponsor's proposed labeling that is located in the *Labeling* section of the Action Package.

Safety Update

Per Dr. Nancy Kribbs of Sanofi-Synthelabo, all the safety information from the CURE study that Sanofi-Synthelabo has in its possession was included in the original sNDA, with the exception, perhaps, of some follow-up safety (adverse event) reports. She could not say with certainty whether there are any follow-up reports that were not included in the original application, but speculates that if there are, they are few. Additionally, these reports would have been submitted to the IND as follow-up safety reports and reviewed by the IND medical reviewer (Dr. Throckmorton). Dr. Throckmorton concluded that

because there is no significant new safety information from the CURE study, a safety update is not needed for this supplemental application.

Pediatric Information

The Sponsor requested and was granted a full waiver of the pediatric study requirement for this supplemental application. The waiver letter and electronic mail message from Dr. Lipicky concerning the waiver can be found in the *Pediatric Page* section of the Action Package.

Statistical Review

Dr. Hung concludes that the rate of the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or stroke and the rate of the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or refractory ischemia are significantly lower in the clopidogrel group. He notes that clopidogrel's effect appears to be constant throughout the duration of the study. He notes further that there is no noticeable inconsistency in the results over the subgroups or evidence that US results differ from non-US results. Additionally, he notes that major and minor bleeding were more common in the clopidogrel group. Finally, he recommends that the results of the unspecified endpoints reported in the NEJM article not be included in labeling.

DSI

It was decided at the filing meeting that a DSI audit of the CURE study would not be necessary, as CURE was a large, multi-center study for which no single investigator enrolled enough subjects to significantly affect the outcome of the study. See the Filing Summary/Minutes in the *Minutes of Meetings* section of the Action Package for additional detail.

Environmental Assessment Review/Categorical Exemption

Finding of No Significant Impact (FONSI) recommended.

In the February 15, 2002 review of the Environmental Assessment provided for this supplemental application, the Office of New Drug Chemistry concludes that "this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared."

RHPM Summary

All primary and secondary reviews are completed. To my knowledge, there are no outstanding issues that would preclude acting on this application. At Dr. Lipicky's recommendation, an approvable (on enclosed marked-up draft labeling) letter will be prepared for his signature.

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

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/s/

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Colleen LoCicero
2/22/02 10:09:05 AM
CSO

RHPM Review of Draft Labeling
NDA 20-839/SE1-019

| | |
|---|---|
| Date labeling submitted: | August 21, 2001 |
| Date labeling reviewed: | January 9, 2002 |
| Product: | Plavix (clopidogrel bisulfate) Tablets |
| Sponsor: | Sanofi-Synthelabo Inc. |

**Evaluation**

This supplemental application proposes labeling changes that reflect the findings of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) study. I reviewed the proposed revised draft package insert in its entirety and found changes to the **CLINICAL PHARMACOLOGY, CLINICAL STUDIES, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE,** and **DOSAGE AND ADMINISTRATION** sections from the last approved package insert (for S-018, submitted July 2, 2001 and approved January 28, 2002), as follows:

1. The second sentence in the **CLINICAL PHARMACOLOGY/Mechanism of Action** subsection has been revised from the following:

to the following:

> A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with atherothrombosis as evidenced by stroke or transient ischemic attacks, myocardial infarction, angina (stable and unstable), peripheral arterial disease or need for vascular bypass or angioplasty.

2. The first sentence in the first paragraph of the **CLINICAL STUDIES** section has been revised from the following:

to the following:

> The clinical evidence for the efficacy of PLAVIX is derived from two double-blind trials: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of PLAVIX to aspirin, and the CURE study

(Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), a comparison of PLAVIX to placebo, both given in combination with aspirin and other standard therapy.

3. The second sentence of the first paragraph of the **CLINICAL STUDIES** section has become the first sentence of the second paragraph of the section and has been revised from the following:

\

to the following:

The CAPRIE trial was a 19,185-patient, 304-center, international, randomized, double-blind, parallel-group study comparing PLAVIX (75 mg daily) to aspirin (325 mg daily).

4. The heading of the first table in the **CLINICAL STUDIES** section has been revised from the following:

\

to the following:

Table 1: Outcome Events in the CAPRIE Primary Analysis

5. The first sentence in the paragraph preceding the first figure in the **CLINICAL STUDIES** section has been revised from the following:

\

to the following:

The curves showing the overall event rate are shown in Figure 1.

6. The following heading has been added to immediately precede the first figure in the **CLINICAL STUDIES** section:

Figure 1: Fatal or Non-Fatal Vascular Events in the CAPRIE Study

7. The second sentence in the second paragraph following the first figure in the **CLINICAL STUDIES** section has been revised from the following:

\

to the following:

> The efficacy of PLAVIX relative to aspirin was heterogeneous across the randomized subgroups (P-0.043).

8. A description of the CURE study findings that includes a table and two figures has been added to follow the description of the CAPRIE study findings in the **CLINICAL STUDIES** section.

9. The **INDICATIONS AND USAGE** section has been revised from the following:

to the following:

> PLAVIX (clopidogrel bisulfate) is indicated for the early and long-term reduction of atherothrombotic events.
>
> - **Recent MI, Recent Stroke or Established Peripheral Arterial Disease**
> PLAVIX is indicated for the reduction of atherothrombotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease.
>
> - **Acute Coronary Syndrome**
> PLAVIX is indicated for the reduction of atherothrombotic events (myocardial infarction, stroke, cardiovascular death, and refractory ischemia), in combination with aspirin in patients with acute coronary syndrome (unstable angina or non-Q-wave MI) whether or not they undergo cardiac revascularization (surgical or PCI, with or without stent).
>
> Plavix can be used in these patients independent of their risk of ischemic events and in addition to other needed treatment for cardiovascular disease (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid-lowering drugs, beta blockers, and ACEIs).

10. The number of clopidogrel-treated patients in the fourth sentence of the **WARNINGS/***Thrombotic thrombocytopenic purpura (TTP)* subsection has been revised from [redacted] to 17,500.

11. In the first paragraph of the **PRECAUTIONS/General** subsection, the number of days PLAVIX should be discontinued prior to surgery has been revised from [redacted] to 5.

12. The following sentence has been inserted between the second and third sentences in the **PRECAUTIONS/General/***GI Bleeding* subsection:

    In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs 0.7% (PLAVIX + aspirin vs placebo + aspirin, respectively.)

13. The last sentence of the **PRECAUTIONS/General/***GI Bleeding* subsection has been revised from the following:

\

to the following:

    Drugs that might induce such lesions should be used with caution in patients taking PLAVIX.

14. The last sentence of the **PRECAUTIONS/Drug Interactions/***Aspirin* subsection has been revised from the following:

\

to the following:

    PLAVIX and aspirin have been administered together for up to one year.

15. The following sentence has been deleted from the **PRECAUTIONS/Drug Interactions/***Heparin* subsection:

    The safety of this combination has not been established, however, and concomitant use should be undertaken with caution.

16. The last sentence of the **PRECAUTIONS/Drug Interactions** subsection has been revised from the following:

\

to the following:

In addition to the above specific interaction studies, patients entered into clinical trials with PLAVIX received a variety of concomitant medications including **diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents** (including **insulin**), **antiepileptic agents, hormone replacement therapy**, and **GPIIb/IIIa antagonists** without evidence of clinically significant adverse interactions.

17. The first sentence of the **ADVERSE REACTIONS** section has been revised from the following:

to the following:

PLAVIX has been evaluated for safety in more than 17,500 patients, including over 9,000 patients treated for 1 year or more.

18. The text "in CAPRIE" was added to the second sentence in the first paragraph of the **ADVERSE REACTIONS** section.

19. The last sentence of the first paragraph of the **ADVERSE REACTIONS** section has been revised from the following:

to the following:

The clinically important adverse events observed in CAPRIE and CURE are discussed below.

20. The first sentence in the **ADVERSE REACTIONS**/*Hemorrhagic* subsection has been revised from the following:

to the following:

In CAPRIE patients receiving PLAVIX, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%.

21. The following text and table was added to the **ADVERSE REACTIONS**/*Hemorrhagic* subsection:

In CURE, PLAVIX, when given with aspirin, was not associated with an increase in life-threatening or fatal bleeds, compared to placebo with aspirin (see Table 3). The incidence of intracranial hemorrhage was 0.1% in both groups. There was an excess in major bleeds, primarily gastrointestinal and at puncture sites.

In patients receiving both PLAVIX and aspirin in CURE, the incidence of bleeding is described in Table 3.

Table 3: CURE Incidence of bleeding complications (% patients)

| Event | PLAVIX (+ aspirin)* (n=6259) | Placebo (+ aspirin)* (n=6303) | P-value |
|---|---|---|---|
| Major bleeding † | 3.7 ‡ | 2.7 § | 0.001 |
| Life-threatening bleeding | 2.2 | 1.8 | 0.13 |
| Fatal | 0.2 | 0.2 | |
| 5 g/dL hemoglobin drop | 0.9 | 0.9 | |
| Requiring surgical intervention | 0.7 | 0.7 | |
| Hemorrhagic strokes | 0.1 | 0.1 | |
| Requiring inotropes | 0.5 | 0.5 | |
| Requiring transfusion (≥4 units) | 1.2 | 1.0 | |
| Other major bleeding | 1.6 | 1.0 | 0.005 |
| Significantly disabling | 0.4 | 0.3 | |
| Intraocular bleeding with significant loss of vision | 0.05 | 0.03 | |
| Requiring 2-3 units of blood | 1.3 | 0.9 | |
| Minor bleeding ¶ | 5.1 | 2.4 | < 0.001 |

* Other standard therapies were used as appropriate.
† Life threatening and other major bleeding.
‡ Major bleeding event rate for PLAVIX + aspirin was dose-dependent on aspirin: <100mg=2.6%; 100-200mg= 3.5%; >200mg=4.9%
§ Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100mg=2.0%; 100-200mg= 2.3%; >200mg=4.0%
¶ Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin/LMWH, and the rate of bleeding in these patients was similar to the overall results.

There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.4% PLAVIX + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for PLAVIX + aspirin, and 6.3% for placebo + aspirin.

22. The following sentence has been deleted from the **ADVERSE REACTIONS**/*Neutropenia/agranulocytosis* subsection:

    Patients in CAPRIE (see Clinical Trials) were intensively monitored for neutropenia.

23. The text "In CAPRIE" has been added at the beginning of what is now the second sentence in the first paragraph of the **ADVERSE REACTIONS**/*Neutropenia/agranulocytosis* subsection, as follows:

    In CAPRIE severe neutropenia was observed in six patients, four on PLAVIX and two on aspirin.

24. The first sentence in the second paragraph of the **ADVERSE REACTIONS**/*Neutropenia/agranulocytosis* subsection is now the fourth sentence in the first paragraph of this subsection and has been revised to include the text "in CAPRIE" as follows:

    One of the four PLAVIX patients in CAPRIE was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with PLAVIX (clopidogrel bisulfate).

25. The following sentence has been added as the last sentence of the first paragraph of the **ADVERSE REACTIONS**/*Neutropenia/agranulocytosis* subsection:

    In CURE, the numbers of patients with thrombocytopenia (19 PLAVIX + aspirin vs 24 placebo + aspirin) or neutropenia (3 vs 3) were similar.

26. The text "in the CAPRIE trial" has been added to the end of the first sentence in the first paragraph of the **ADVERSE REACTIONS**/*Gastrointestinal subsection.*

27. The following sentence has been added as the last sentence of the first paragraph of the **ADVERSE REACTIONS**/*Gastrointestinal* subsection:

    In the CURE trial the incidence of these gastrointestinal events for patients receiving PLAVIX + aspirin was 11.7% compared to 12.5% for those receiving placebo + aspirin.

28. The text "in the CAPRIE trial" has been added to the first sentence of the second, third, and fourth paragraphs in the **ADVERSE REACTIONS**/*Gastrointestinal* subsection.

29. The following sentence has been added at the end of the second paragraph in the **ADVERSE REACTIONS**/*Gastrointestinal* subsection:

In the CURE trial the incidence of peptic, gastric or duodenal ulcers was 0.4% for PLAVIX + aspirin and 0.3% for placebo + aspirin.

30. The following sentence has been added at the end of the third paragraph in the **ADVERSE REACTIONS**/*Gastrointestinal* subsection:

    In the CURE trial, the incidence of diarrhea for patients receiving PLAVIX + aspirin was 2.1% compared to 2.2% for those receiving placebo + aspirin.

31. The following sentence has been added at the end of the fourth paragraph in the **ADVERSE REACTIONS**/*Gastrointestinal* subsection:

    In the CURE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 0.9% for PLAVIX + aspirin compared with 0.8% for placebo + aspirin.

32. The text "In the CAPRIE trial" has been added to the first sentences in the first and second paragraphs of the **ADVERSE REACTIONS**/*Rash and Other Skin Disorders* subsection.

33. The following sentence has been added to the end of the first paragraph of the **ADVERSE REACTIONS**/*Rash and Other Skin Disorders* subsection:

    In the CURE trial the incidence of rash or other skin disorders in patients receiving PLAVIX + aspirin was 4.0% compared to 3.5% for those receiving placebo + aspirin.

34. The following sentence has been added to the end of the second paragraph of the **ADVERSE REACTIONS**/*Rash and Other Skin Disorders* subsection:

    In the CURE trial, the incidence of patients withdrawing because of skin and appendage disorders adverse reactions was 0.7% for PLAVIX + aspirin compared with 0.3% for placebo + aspirin.

35. The heading of the table in the **ADVERSE REACTIONS** section of adverse events occurring in $\geq$ 2.5% of PLAVIX patients in CAPRIE has been revised to include the text "Table 4" and "in CAPRIE".

36. The second entry under *Body as a Whole-general disorders* in the first table of adverse events in the **ADVERSE REACTIONS** section (Table 4) has been changed from the following:

to the following:

Accidental/Inflicted Injury

37. The following text and table have been added following the CAPRIE adverse event table (Table 4) in the **ADVERSE REACTIONS** section:

Adverse events occurring in ≥2.0% of patients on PLAVIX in the CURE controlled clinical trial are shown below regardless of relationship to PLAVIX.

**Table 5: Adverse Events Occurring in ≥2.0% of PLAVIX Patients in CURE**

| | % Incidence (% Discontinuation) | |
|---|---|---|
| ***Body System*** | **PLAVIX (+ aspirin)* [n=6259]** | **Placebo (+ aspirin)* [n=6303]** |
| **Event** | | |
| *Body as a Whole– general disorders* | | |
| Chest Pain | 2.7 (<0.1) | 2.8 (0.0) |
| *Central & peripheral nervous system disorders* | | |
| Headache | 3.1 (0.1) | 3.2 (0.1) |
| Dizziness | 2.4 (0.1) | 2.0 (<0.1) |
| *Gastrointestinal system disorders* | | |
| Abdominal pain | 2.3 (0.3) | 2.8 (0.3) |
| Dyspepsia | 2.0 (0.1) | 1.9 (<0.1) |
| Diarrhea | 2.1 (0.1) | 2.2 (0.1) |

*Other standard therapies were used as appropriate.

38. The paragraph immediately preceding the list of adverse events occurring in 1 to 2.5% of patients in the **ADVERSE REACTIONS** section has been revised from the following:

to the following:

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving PLAVIX (clopidogrel bisulfate) in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).

39. "Fever" has been added to the events in the *Body as a whole-general disorders* section of the paragraph that lists adverse events occurring in 1% to 2.5% of patients in the **ADVERSE REACTIONS** section.

40. The paragraph in the **ADVERSE REACTIONS** section preceding the list of adverse events occurring in less than 1% of patients has been revised from the following:

to the following:

> Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received PLAVIX in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).

41. Urinary system disorders have been added to the list of adverse events occurring in less than 1% of patients in the **ADVERSE REACTIONS** section, as follows:

> *Urinary system disorders*: Abnormal renal function, acute renal failure.

42. The first sentence in the **OVERDOSAGE** section has been revised to include the word "CAPRIE', as follows:

> One case of deliberate overdosage with PLAVIX was reported in the large, CAPRIE controlled clinical study.

43. The **DOSAGE AND ADMINISTRATION** section has been revised from the following:

to the following:

> The recommended dose of PLAVIX is 75 mg once daily long term.

For patients with acute coronary syndrome without ST segment elevation, PLAVIX should be initiated with a 300 mg loading dose and then continued long term at 75 mg once a day (with aspirin 75 mg-325 mg daily).

PLAVIX can be administered with or without food.

No dosage adjustment is necessary for elderly patients or patients with renal disease. (See **Clinical Pharmacology**: Special **Populations**.)

44. The italics surrounding the numbers in the **HOW SUPPLIED** section have been replaced with "»".

**Reviewer Labeling Recommendations**

*Statistical*

Dr. Hung's only labeling recommendation is that the results of the unspecified endpoints reported in the New England Journal of Medicine article on the CURE study not be included in labeling.

*DDMAC*

Dr. Haffer collaborated with Dr. Throckmorton on the labeling recommendations and marked-up draft of the Sponsor's proposed labeling. Because this collaboration was done via telephone and electronic message communication between Drs. Throckmorton and Haffer, Dr. Haffer did not write a formal review of the proposed labeling.

*Medical*

Dr. Throckmorton's labeling recommendations are appended to his review (Appendix 4). Additionally, he provided a marked-up draft of the Sponsor's proposed labeling on which he and Dr. Haffer collaborated.

Dr. Lipicky found Drs. Throckmorton and Haffer's marked-up draft acceptable, except for the **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections, which he revised. Following his review of Dr. Lipicky's proposed language, Dr. Haffer revised Dr. Lipicky's **DOSAGE AND ADMINISTRATION** section and forwarded it to the Division. Dr. Throckmorton found Dr. Lipicky's **INDICATIONS and USAGE** section and Dr. Haffer's **DOSAGE AND ADMINISTRATION** section acceptable. Dr. Lipicky found Dr. Haffer's **DOSAGE AND ADMINISTRATION** section acceptable, as well. He recommended that the original marked-up draft be revised to include his **INDICATIONS AND USAGE** section and Dr. Haffer's **DOSAGE AND ADMINISTRATION** section and faxed to the Sponsor for their consideration. The Division's marked-up draft was faxed to the Sponsor on February 14, 2002. The Sponsor responded with a submission of revised draft labeling

on February 15, 2002 in which they incorporated most of the Division's changes. The Division found the Sponsor's February 15, 2002 submitted draft labeling acceptable with a few exceptions.

**Conclusion**

As recommended by Dr. Lipicky, I will attach the Sponsor's February 15, 2002 submitted draft marked-up labeling, with a few minor changes to the **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION** section, to the approvable letter for Dr. Lipicky's signature. The letter will state that in order for the supplemental application to be approved, the Sponsor must submit final printed labeling identical to the enclosed marked-up draft.

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/s/

Colleen LoCicero
2/22/02 10:14:34 AM
CSO

# RHPM review of February 21, 2002 submitted final printed labeling

RHPM Review of Final Printed Labeling
NDA 20-839/S-019

| | |
|---|---|
| Product: | Plavix (clopidogrel bisulfate) Tablets |
| Sponsor: | Sanofi-Synthelabo Inc. |
| Date labeling submitted: | February 21, 2002 |
| Date labeling reviewed: | February 25, 2002 |

**Background**

This final printed labeling was submitted in response to the Agency's February 20, 2002 approvable letter for this supplemental application. The approvable letter specified that final printed labeling, identical to the marked-up draft labeling that accompanied the letter, must be submitted prior to approval. Prior to this submission, Dr. Nancy Kribbs of Sanofi-Synthelabo Inc. discussed with me the addition of the definition of acute coronary syndrome to the **DOSAGE AND ADMINISTRATION** section. Dr. Lipicky found this proposal acceptable and I informed Dr. Kribbs in a February 20, 2002 telephone conversation that it would be acceptable to include this definition in the **DOSAGE AND ADMINISTRATION** section of the final printed labeling.

**Evaluation**

This labeling was submitted entirely in electronic format. In the cover letter of the submission, the Sponsor notes that the labeling is not yet typeset so as to avoid review and approval delays. I reviewed the submitted final printed labeling in its entirety, comparing it to the marked-up labeling that accompanied the February 20, 2002 approvable letter, and noted the following changes:

1. The fifth paragraph following Figure 1 in the **CLINICAL STUDIES** section has been revised from the following:

to the following:

> Patients were randomized to receive PLAVIX (300 mg loading dose followed by 75 mg/day) or placebo, and were treated for up to a year. Patients also received aspirin (75-325 mg once daily) and other standard therapies such as heparin. The use of GPIIb/IIIa inhibitors was not permitted for three days prior to randomization.

*The Sponsor noted this change in the cover letter of the submission, indicating that they made the change to more accurately reflect the conduct of the CURE study. Both Drs. Lipicky and Throckmorton find the change acceptable.*

2. Relative risk values have been added to the last column in Table 2 in the **CLINICAL STUDIES** section. Additionally, the heading of this column has been changed from [redacted] to "Relative Risk Reduction (%) (95% CI)."

*This column was left blank in the labeling that accompanied the approvable letter so that the Sponsor could complete it with the appropriate values. Drs. Lipicky and Throckmorton find these changes acceptable.*

3. The first sentence in the **DOSAGE AND ADMINISTRATION/Acute Coronary Syndrome** subsection has been revised to include the definition of acute coronary syndrome, as follows:

   For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), PLAVIX should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily.

*As mentioned in the **Background** above, prior to the submission of this final printed labeling, the Agency agreed with the Sponsor's proposal to add this definition to the **DOSAGE AND ADMINISTRATION** section, recommending that the Sponsor include this in the final printed labeling.*

**Evaluation**

Drs. Lipicky and Throckmorton find the above changes acceptable. At Dr. Lipicky's recommendation, I will draft an approval (acceptable final printed labeling submitted) letter for this supplemental application for his signature.

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/s/

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Colleen LoCicero
2/28/02 12:15:15 PM
CSO

96 pages redacted from this section of the approval package consisted of draft labeling

Record of a Telephone Conversation

| | |
|---|---|
| Date: | April 7, 1999 |
| IND#: | 34,663 |
| Product: | Plavix (clopidogrel) Tablet |
| Sponsor: | Sanofi Pharmaceuticals, Inc. |
| Contact: | Nancy Krybbs, Ph.D. |
| Phone#: | (610) 889-6425 |

APR - 7 1999

Dr. Ganley completed his review of Sanofi's October 14, 1998 submission containing Protocol EFC3307, "CURE: Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (OASIS-4)- A phase 3 randomized, double-blind, parallel-group clinical trial of clopidogrel versus placebo in patients with an acute coronary syndrome (unstable angina or myocardial infarction without ST segment elevation)" and a response to FDA request for information regarding the proposed myocardial assessment process for the CURE study. As recommended by Dr. Ganley, I contacted Dr. Krybbs at Sanofi to convey to her the clarifications Dr. Ganley requested in his review.

I informed Dr. Krybbs that Dr. Ganley states in his review that the sponsor should clarify the following points regarding the CURE study:

1. Will the Operations Committee be provided efficacy outcome data?
2. Will any members of the Steering Committee have access to unblinded or blinded data of analyses during the conduct of the clinical trial?

I further noted that Dr. Ganley believes a FDA statistician should review the proposed statistical analysis plan and that I will be forwarding the submission to the statistician for review. If, upon completion of his review, the statistician has additional comments regarding this submission, they will be communicated to Sanofi at that time.

Dr. Krybbs will communicate Sanofi's responses to Dr. Ganley's questions by telephone (to either Dr. Ganley or me) or a written submission to the IND.

/s/

Colleen LoCicero, CSO

cc: orig IND 34,663
HFD-110
HFD-110/LoCicero

**Minutes of a meeting**

| | |
|---|---|
| Date of meeting: | March 27, 2001 |
| Application: | IND 34,663 |
| Product: | Plavix (clopidogrel bisulfate) Tablets |
| Sponsor: | Sanofi-Synthelabo Inc. |
| Purpose: | pre-sNDA |
| Meeting Chair: | Douglas Throckmorton, M.D. |
| Meeting Recorder: | Colleen LoCicero |
| Participants: | |
| FDA | |
| Douglas Throckmorton, M.D. | Deputy Director, Division of Cardio-Renal Drug Products (HFD-110) |
| Norman Stockbridge, M.D., Ph.D. | Team Leader, Medical, HFD-110 |
| James Hung, Ph.D. | Team Leader, Statistical, Division of Biometrics (HFD-710) |
| John Lawrence, Ph.D. | Statistician, HFD-710 |
| Colleen LoCicero | Regulatory Health Project Manager, HFD-110 |
| Sanofi-Synthelabo Inc. | |
| Alex Boddy, M.S. | Biostatistics |
| Deborah Dukovic, M.A.S. | Biostatistics |
| William Friggle, M.S. | Scientific Information Systems |
| Thomas Guinter | Clinical Information Management |
| Richard Gural, Ph.D. | Regulatory Affairs |
| Nancy Kribbs, Ph.D. | Regulatory Affairs |
| Gina Schmidt | Regulatory Operations |

**Background**

The sponsor requested this meeting to discuss their anticipated supplemental application for a new indication for clopidogrel in unstable angina, based on the findings of the CURE study (Protocol EFC3307: Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (OASIS-4) – A phase 3 randomized, double-blind, parallel group clinical study of clopidogrel versus placebo in patients with an acute coronary syndrome (unstable angina or myocardial infarction without ST segment elevation)).

**The meeting**

The Division started the meeting by acknowledging the sponsor's request for an expedited review of this supplemental application, in light of the clinical significance of the CURE findings.

Discussion Point #1: Basic elements needed in sNDA submission

The Division identified the following elements as necessary for an adequate review of this application:

1. Case report forms for all CURE subjects as previously identified by the Division in our response to the sponsor's previous proposal regarding this supplemental application. (*Post-meeting note: The sponsor's previous proposal is a February 23, 2001 proposal on patient narratives, case report forms, etc. to be included in the CURE supplemental application. The Division's response to this proposal was communicated to Dr. Kribbs by Ms. LoCicero on March 14, 2001.*)

2. The raw data in SAS (version 6.12) transport files, including the SAS code for the primary analysis. The sponsor should verify that these files can be imported into JMP.

3. A copy of the CURE protocol and amendments, including the dates of the amendments.

4. A copy of the New England Journal of Medicine pre-print on the CURE study.

5. An annotated case report form.

6. Information on the CURE interim analyses. (*Post-meeting Note: This information should include the timing and results of the interim analyses and the datasets supporting the interim analyses.*)

7. Copies of the DSMB meeting minutes.

8. A revised annotated package insert reflecting the sponsor's proposed labeling changes.

Following some discussion, the Division clarified that the application will need to include case report forms for all clopidogrel-treated subjects from the CURE study who died or discontinued study due to an adverse event. No additional case report forms will be needed for the initial submission, although the sponsor agreed to provide within one week any additional case report forms the Division might request once the review is started. It will not be necessary for the sponsor to include any narratives in this application.

Discussion Point #2: Safety information from ongoing/completed studies

For the safety information from other completed and ongoing studies, the sponsor proposed the following:

1. To provide safety information from ongoing clinical studies in the manner in which such information is provided in the IND Annual Reports, i.e., a list of adverse events, etc.

2. To provide a synopses only of other completed studies

The Division found this proposal acceptable.

Discussion Point #3: Adequacy of follow-up for the CURE study

As the CURE study is reported to have demonstrated a mortality effect, the Division will be concerned with the adequacy of subject follow-up. The sponsor assured the Division that the percent of follow-up exceeded 99%, noting that one of the major criteria for this study was adequate follow-up. The Division found this acceptable.

Discussion Point #4: Presentation of CURE data

The Division does not wish to see a presentation of the CURE data prior to the sponsor's submission of the supplemental application.

Discussion Point #5: Full electronic submission

The Division will accept a full electronic submission (i.e., no paper copies), although we may request paper copies once we start our review.

Discussion Point #6: CURE adverse events in labeling

For the labeling of the CURE adverse events, the sponsor proposed to add a table of adverse events for the CURE study only that will include those adverse events that occurred at a frequency of two percent or greater (with the exception of some clinically relevant events that will be included irrespective of incidence). Although the Division does not discuss labeling issues prior to reviewing the data typically, we believed this proposal would probably be acceptable.

Signature, Minutes Preparer: /S/ ___Colleen LoCicero

Concurrence, Meeting Chair: /S/ ___Douglas Throckmorton, M.D.

drafted: 4/4/01 finaled: 4/5/01

initialed by:
Hung/4/4/01
Lawrence/4/4/01
Stockbridge/4/5/01
Throckmorton/4/5/01

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**
**FOOD AND DRUG ADMINISTRATION**

AUG - 3 1998

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Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | (610) 889-6901 |
| **Attention:** | Ann Hards |
| **Company Name:** | Sanofi |
| **Phone:** | (610) 889-8521 |
| **Subject:** | 6/25 meeting minutes |
| **Date:** | 8/3/98 |
| **Pages including this sheet:** | 6 |

**From:** **Colleen Locicero**
**Phone:** **301-594-5312**
**Fax:** **301-594-5494**

Dr. Hards,

Attached are the minutes from our June 25, 1998 meeting regarding IND 34,663. Please let me know that you have received this fax.

Sincerely,
Colleen LoCicero

cc: orig IND
HFD-110
HFD-110/CLoCicero

JUL 24 1998

**Minutes of a Meeting**

| | |
|---|---|
| Date of Meeting: | June 25, 1998 |
| Application: | IND 34,663<br>Plavix (clopidogrel) tablets |
| Sponsor: | Sanofi |
| Purpose: | to discuss the development of Plavix in the treatment of acute coronary syndrome |
| Meeting Chair: | Robert Temple, M.D. |
| Meeting Recorder: | Colleen LoCicero |

Participants

FDA

| | |
|---|---|
| Robert Temple, M.D. | Director, Office of Drug Evaluation I |
| Rachel Behrman, M.D. | Deputy Director, Office of Drug Evaluation I |
| Robert Fenichel, M.D., Ph.D. | Deputy Director, Division of Cardio-Renal Drug Products (HFD-110) |
| Stephen Fredd, M.D. | Deputy Director, Division of Cardio-Renal Drug Products (HFD-110) |
| Charles Ganley, M.D. | Team Leader, Medical, HFD-110 |
| Isaac Hammond, M.D., Ph.D. | Medical Officer, HFD-110 |
| Walid Nuri, Ph.D. | Statistician, Division of Biometrics I (HFD-710) |
| Aleka Kapatou, Ph.D. | Statistician, HFD-710 |
| Colleen LoCicero | Consumer Safety Officer, HFD-110 |

Sanofi

| | |
|---|---|
| Daniel Beaumont, M.D. | Vice President, Cardiovascular Portfolio |
| Alex Boddy, M.S. | Biostatistics |
| Ann Hards, Ph.D. | Associate Director, Drug Regulatory Affairs |
| Richard Gural, Ph.D. | Vice President, Regulatory Affairs |
| Jean Bouthier, M.D. | Clinical Research, Cardio-Thrombosis Products |
| Professor Salim Yusuf, FRCP | Chairman of CURE Steering Committee |

## Background

Plavix (clopidogrel) is currently approved under NDA 20-839 for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease.

Sanofi requested this meeting to discuss the development of an additional indication for Plavix in the reduction of atherosclerotic events in patients with acute coronary syndrome without ST segment elevation.

Along with the draft phase 3 protocol, Operations Manual and sample Contact Form, a list of questions for review by the Division was included in the meeting package. These questions were to serve as the primary discussion points for this meeting.

**The meeting**

Discussion Point #1: Patient Population

In response to concerns expressed by the FDA regarding the second group described in the study population (patients with chest pain above the age of 60 who do not have ECG changes, but in which there is a high degree of certainty that the presenting chest pain is due to myocardial ischemia), Sanofi explained that the chest pain required for inclusion in this group would be the same chest pain as that required for inclusion in the first group. The FDA requested that Sanofi rewrite the description of the criteria for the second group to include the same definition of chest pain as is currently in the description of the criteria for the first group. Once this clarification is made to the protocol, the FDA believed the study population would support the additional draft indication.

Discussion Point #2: Appropriateness of the primary efficacy outcome (cardiovascular death, myocardial infarction or stroke) to support the additional indication

The FDA asked Sanofi how troponins would be used in the assessment of myocardial infarction (MI). Sanofi explained that elevation of any one of the three enzymes (CK, CK-MB, or troponins) would qualify as criteria for the assessment of an MI. The FDA was concerned that post-PTCA elevations in CK levels would be used to assess MIs. Sanofi will have their adjudicating committee define their process for assessing MIs and submit it to the IND prior to initiation of the study so that the Medical Officers can determine if this is an issue.

The FDA recommended that Sanofi use total death rather than cardiovascular death as the component in their primary outcome. A large number of non-cardiovascular deaths could significantly affect the credibility of the study results, if cardiovascular deaths are used. The FDA further noted that when a patient dies of, e.g., cancer, one frequently cannot be sure that the patient did not actually die of an MI or other event.

Dr. Yusuf explained that there would be a bias toward counting deaths as cardiovascular; that is, deaths would be classified as cardiovascular unless it was very clearly known that the patient died of something else. He would prefer the use of cardiovascular deaths to total deaths as biologically more plausible, and because total deaths could add noise and, to a small extent, obscure the treatment effect.

It was noted that, of late, the Cardio-Renal Advisory Committee has favored, but not insisted upon, total death rather than cardiovascular death. The FDA would favor, but not insist upon this, as well. The FDA noted that if Sanofi uses cardiovascular death and the number of non-cardiovascular deaths in the active drug arm is significantly higher than that of the placebo arm, the FDA will look at the totality of the data, and, despite a statistically significant positive result, may not perceive this as favorable.

Discussion Point #3: Duration of patient treatment and follow-up

The FDA agreed that the duration of patient treatment and follow-up described in the phase III protocol is sufficient to support chronic administration of Plavix.

Discussion Point #4: Support of indication by single study

The FDA stated that this was result dependent, but agreed that this single study, if it achieves statistical significance at conventional levels and has no important problems, may be sufficient to support the proposed additional indication because other data in similar populations would provide substantiating support. The FDA cautioned, however, that statistical significance for the primary efficacy outcome alone would not guarantee approval. All of the data would be examined, and, for example, a high incidence of non-cardiovascular deaths may not be perceived as favorable and may result in nonapproval.

Discussion Point #5: Use of the secondary outcome (death, MI, plus refractory ischemia) to support a claim if the primary outcome fails to reach statistical significance

The FDA would prefer the use of urgent intervention to refractory ischemia as a component of the secondary outcome, and reminded the sponsor of the hazard of using a combined endpoint consisting of both "hard" and "soft" endpoints, such as urgent intervention or refractory ischemia, and the possibility of obtaining a statistically significant positive combined endpoint that is carried by a strongly positive result from the "soft" component, while the results from the "hard" components are negative. Such a result would require interpretation by the FDA, and may not be perceived as positive.

The FDA also suggested the use of co-primary endpoints, rather than a primary and secondary endpoint, and suggested splitting the alpha between the 2 endpoints, allotting more of the alpha for the first endpoint. This would, the FDA believed, be worth investigating, as the penalty may be minimal. Dr. Temple suggested that Sanofi come up with a proposal for the use of co-primary endpoints and submit it to the agency for review.

Discussion Point #6: The reporting of efficacy outcomes on study outcomes form versus as a serious adverse event

The FDA agreed that the primary and secondary outcomes could be reported on the study outcomes form and not reported as serious adverse events and will send Sanofi a letter granting them permission to do this.

Discussion Point #7: Definition of a completed patient

The FDA agreed that the protocol definition of a completed patient is acceptable, and reminded the sponsor that every effort should be made to minimize the number of patients lost-to-follow-up.

Discussion Point #8: Contact Form

Dr. Ganley distributed the Contact Form that he developed as an alternate to the Contact Form submitted in the meeting package . Dr. Ganley's Contact Form changed question number 6 to consist of a list of several questions that would preclude the need for Investigator judgment. His form (see attached) was accepted by Sanofi and will replace their proposed Contact Form.

Discussion Point #9: Concurrent medical and surgical intervention during the trial

The FDA noted that Sanofi was allowing the use of currently available medical treatment (e.g., 2b/3a antagonists, antithrombins, other antiplatelet agents, etc.) and/or surgical intervention (PTCA, CABG, etc.) during the trial, if deemed necessary by the Investigator. For patients requiring administration of medical treatment, administration of the study drug would be held until completion and/or discontinuation of the medical treatment (2b/3a antagonist, etc.), at which point the study drug would be resumed. The Division recommended that following the enrollment and randomization of study participants, administration of study drug be withheld until it is determined if additional medical treatment is necessary. This would avoid the administration of a single dose of study drug followed by an immediate "hold" of that study drug when it is decided that the patient requires additional medical treatment.

The FDA was concerned that an imbalance between the number of procedures and/or additional medical treatments administered in the study drug versus the placebo groups would be seen, and that this imbalance would affect the results of the study. The FDA did not believe, however, that disallowing concurrent medical or surgical therapy during the study could be justified, but requested that Sanofi describe in detail how they will handle these situations and include this in the protocol.

Discussion Point #10: Loading dose

The FDA asked for the rationale behind the use of the 300 mg loading dose. Sanofi explained that 10% platelet inhibition is achieved following a single 75 mg dose, whereas 35% platelet inhibition is attained following a single 300 mg dose. It takes 3 to 7 days to reach a plateau of 60% platelet inhibition with the 75 mg daily regimen without a loading dose. Addition of a 300 mg loading dose, should allow for this plateau to be more rapidly attained.

Discussion Point #11: Submission of Protocol amendments

The FDA reminded Sanofi that any amendments to the protocol must be submitted to the IND prior to initiation of the change.

Signature, Minutes Preparer. /S/ Colleen LoCicero

Signature, Meeting Chair: /S/ Robert Temple, M.D.

cc: orig IND
HFD-110
HFD-110/CLoCicero
HFD-110/SBenton

Drafted: 7/6/98 Finaled: 7/24/98

RD:

| | |
|---|---|
| Temple | 7/17/98 |
| Behrman | 7/15/98 |
| Fenichel | 7/10/98 |
| Fredd | 7/9/98 |
| Ganley | 7/9/98 |
| Hammond | 7/8/98 |
| Kapatou | 7/13/98 |

Nuri 7/9/98
Morgenstern 7/24/98