

20-839—S-017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-839/S-017

Trade Name: Plavix Tablets

Generic Name(s): (clopidogrel bisulfate)

Sponsor: Sanofi-Synthelabo, Inc.

Agent:

Approval Date: December 5, 2001

Indication: Provides for CBE manufacture/controls



NDA 20-839/S-017

12-5-01

Sanofi-Synthelabo Inc.
Attention: Yau-Kit Lam
Assistant Director CMC
90 Park Avenue
New York, NY 10016

Dear Mr. Lam:

Please refer to your supplemental new drug application dated June 1, 2001, received June 5, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) Tablets, 75 mg.

We acknowledge receipt of your submission dated July 25, 2001.


This "Changes Being Effected in 30 days" supplemental new drug application provides for manufacturing clopidogrel bisulfate, — drug substance in — and —

We have completed the review of this supplemental application, and it is approved.

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, call Colleen LoCicero, RPh, Regulatory Health Project Manager, at (301) 594-5332.

Sincerely,


{See appended electronic signature page}

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I for the
Division of Cardio-Renal Drug Products, (HFD-110)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Kasturi Srinivasachar
12/5/01 08:11:08 AM

REVIEW OF CHEMISTRY, MANUFACTURING AND CONTROLS
Division of Cardio Renal Drug Products (HFD-110)

1. Chemistry Review # 1
2. **NDA # 20-839 SCM-017 (CBE 30, site change effective 6/30/01)**
3.

Name & Address of Applicant Sanofi-Synthelabo Inc 90 Park Avenue New York, New York 10016 (212) 551-4261	Representative Mr. Yau-Kit Lam Assistant Director CMC Drug Regulatory Affairs (212) 551-4219
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4. Supplement S-017
5. Proprietary Name: Plavix Tablets
6. Nonproprietary Name: Clopidogrel bisulfate
7. Code Name: SR 25990C
8. Chemical Type / Submission Priority: N/A
9. Supplement provides for manufacturing clopidogrel bisulfate. \mathcal{L}
J
10. Previous Documents: None
11. Submissions Reviewed:
 - (a) CBE-30 Supplement dated June 1, 2001, received June 5, 2001
 - (b) Amendment dated July 25, 2001, a response to FDA's information request conveyed by Florian Zielinski to Mr. Lam by telephone on June 26, 2001.
 - (c) DMF () (LOA dated July 12, 2001) for Clopidogrel Bisulfate — drug substance manufactured by \mathcal{L}
J
12. Pharmacological Category / Indication: Reduction of atherosclerotic events in patients with atherosclerosis documented by recent stroke, recent myocardial infarction or established peripheral arterial disease
13. Rx / OTC: Rx
14. Dosage Form: Tablet (film coated) TCM
15. Strength / Potency: Equivalent to 75 mg base
16. Route of Administration: oral
17. Spots: NO

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- (f) Specifications and comparative analytical data for three batches of [redacted] drug substance (Lots OS90002, OS90003 and OS90004) manufactured in Sisteron are provided in Attachment 2. Also, specifications and comparative analytical data for three batches of [redacted] drug substance (Lots 749875, 749876 and 749877) manufactured by [redacted] October 2000 are provided in Attachment 2. *Evaluation: All drug substance specifications are met. There are no significant differences between the analytical data from the two manufacturing sites. However, the level of impurities is [redacted]* 1
manufactured by [redacted]
- (g) Three batches of [redacted] drug substance (Lots 749875, 749876 and 749877) manufactured by [redacted] were entered into the [redacted] stability test protocol. The drug substance is stored in a [redacted] bag with desiccant in a [redacted] Testing followed storage for [redacted] at 25C/60% RH and 40C/75% RH. *Evaluation: All specifications are met.*
- (h) Long term stability test commitment: [redacted] commercial scale lot ([redacted] kg) of [redacted] drug substance (Lot 735191) manufactured by [redacted] in June 2000 was entered into the [redacted] stability test protocol. The drug substance is stored in [redacted] bag with desiccant [redacted] Test data are reported after storage for [redacted] at 25C/60% RH. *Evaluation: All specifications are met.*
- (i) Release data for a lot of Plavix Tablets manufactured on October 19, 2000 from drug substance made by [redacted] confirms that all specifications were met.
- (j) The first commercial batch of Plavix Tablets manufactured by Sanofi-Synthelabo (Ambarès, France) from [redacted] drug substance will be entered into the long-term stability program.
- (k) The container label for drug substance "Clopidogrel Sulfate" manufactured by [redacted] was not provided in the original supplement. It is in the DMF [redacted] dated April 20, 2001, Appendix 4. The label includes manufacturing date, expiration date, NDC 17381-097-40 and CAS 120202-66-6. Net weight is [redacted] kg.

22 Conclusions and Recommendation: I recommend approval of the supplement.

23 Reviewer: Florian Zielinski

24 Date Completed: November 29, 2001

25 Distribution

Original NDA 20-839 S-017
HFD-110 Division File
HFD-110 Project Manager, C. Locicero
HFD-110 Florian Zielinski
Initialed by K Srinivasachar

File Name: NDA 20839 S-017 new facility.doc

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/s/

Florian Zielinski
12/4/01 12:46:40 PM
CHEMIST

Kasturi Srinivasachar
12/5/01 08:01:13 AM
CHEMIST