020839___ S-010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-839/S-010

Trade Name: Plavix Tablets

Generic Name(s): (clopidogrel bisulfate)

Sponsor: Sanofi-Synthelabo, Inc.
Agent:

Approval Date: November 9, 2000

Indication: Provides for alternative manufacturing facility

NDA 20-839/SCM-010

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

Dear Mr. Purpura:

Please refer to your supplemental new drug application dated May 8, 2000, received May 10, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

This supplemental new drug application provides for conducting [ ] manufacturing clopidogrel bisulfate [ ] in an alternative manufacturing facility located at [ ]

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) 594-5334.

Sincerely,

/S/

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

/s/

Kasturi Srinivasachar
11/9/00 04:47:27 PM

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

1. Chemistry Review # 1

2. NDA # 20-839 S-010 (CBE 30, alternative mfg. site)

3. Name & Address of Applicant
Sanofi-Synthelabo Inc
90 Park Avenue
New York, New York 10016
(212) 551-4261

Representative
John Purpura
Associate Director CMC
Drug Regulatory Affairs
(212) 551-4261

4. Supplement S-010

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 conducting — manufacturing clopidogrel bisulfate — in an alternative manufacturing facility located at —

10. Previous Documents: None

11. Submissions Reviewed: Supplement dated May 8, 2000

12 Pharmacological Category: Prevention of vascular ischemia

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

18 Chemical Name: Methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5 (4H)-acetate sulfate (1:1)

CAS # 120202-66-6 $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ MWt base 321.83 MWt salt 419.9

19 Related / Supporting Documents: Type II DMF — dated Mav 4. 2000 describing the synthesis of the drug substance from — specifically the — in the synthesis of clopidogrel bisulfate —. This DMF was not reviewed because it does not contain any significant changes from the synthetic route described in the approved NDA.

20 Status of EES Consult: CGMP Inspection completed September 7, 2000. Drug substance (CSN) manufacturing is conducted within acceptable CGMP Compliance at —
—. (Reference: EES Report dated October 24, 2000)

21 Comments:

(a) This CBE Supplement is submitted according to agreements reached between the applicant and Drs. Short & Srinivasachar on December 17, 1999.

(b) The — in the synthesis of the drug substance is done in — according to the process in the approved NDA. There are no significant changes associated with the addition of the alternative-manufacturing site.

(c) Analytical data for — lots of clopidogrel bisulfate — lots were manufactured in the alternative mfg site (— and . .ots were manufactured in the NDA mfg site (Sisteron, France). (Reference: Attachment 2) All drug substance specifications are met. The —batches are not significantly different.

(d) — batch (9909002) of clopidogrel bisulfate — manufactured in — is entered into the 40°C/75% RH stability testing protocol (Attachment 3). Results obtained after — months of storage indicate acceptable stability. No significant differences are observed between initial and .nonth data.

(e) —batch of Plavix (Batch 0354, drug product) prepared from a batch of clopidogrel bisulfate — manufactured in — : met all release specifications. (Reference: Attachment 4)

(f) The firm commits to enter the first commercial batch of Plavix manufactured from clopidogrel bisulfate — manufactured in — into the stability testing protocol (25°C/60% RH, Attachment 5).

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

23 Reviewer: Florian Zielinski

24 Date Completed: November 7, 2000

25 Distribution:

Original NDA 20-839/S-010
HFD-110 Division File
HFD-110 Project Manager, C. Locicero
HFD-110 Review Chemist, Florian Zielinski

Initialed by K Srinivasachar on November 7, 2000

/s/

Florian Zielinski
11/8/00 02:22:46 PM
CHEMIST

Katsuri Srinivasacha
11/8/00 03:11:23 PM
CHEMIST