

O 20839-S-011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-839/S-011

Trade Name: Plavix Tablets

Generic Name(s): (clopidogrel bisulfate)

Sponsor: Sanofi-Synthelabo, Inc.

Agent:

Approval Date: October 24, 2000

Indication: Provides for manufacturing controls

OCT 24 2000

NDA 20-839/S-011

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

Dear Mr. Purpura:

Please refer to your supplemental new drug application (NDA) 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.

We also acknowledge receipt of your submission dated July 7, 2000.

The supplemental application provides for manufacturing clopidogrel bisulfate at an alternate manufacturing site, Sanofi Chimie, Aramon, France.

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, please contact Ms. Colleen LoCicero, Project Manager at 301-594-5334.

Sincerely yours,



10-24-00

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

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cc:

Original NDA 20-839/S-011

HFD-110/DIVISION FILE

HFD-110/FZielinski

HFD-110/CLoCicero

HFD-95/DISTRICT OFFICE

HFD-810/JSimmons

Init by: KSrinivasachar

Drafted by: TA/10/24/00

APPROVAL

OCT 23 2000

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

1. Chemistry Review # 1
2. **NDA # 20-839 S-011 (CBE 30, alternative mfg. site)**
3. Name & Address of Applicant Representative
Sanofi-Synthelabo Inc John Purpura
90 Park Avenue Associate Director CMC
New York, New York 10016 Drug Regulatory Affairs
(212) 551-4261 (212) 551-4261
4. Supplement S-011
5. Proprietary Name: Plavix Tablets
6. Nonproprietary Name: Clopidogrel bisulfate
7. Code Name: SR 25990C
8. Chemical Type / Submission Priority: N/A
9. The supplement provides for manufacturing clopidogrel
bisulfate in an alternative manufacturing facility located at Sanofi Chimie,
Aramon, France.
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 — that contains a description of clopidogrel bisulfate — by Sanofi Chimie. The original submission is dated March 6, 1997 and pertains to manufacturing drug substance in Sisteron, France. Jim Short reviewed it on Sept 15, 1997.
- (a) Amendment dated Dec 3, 1999 describes —
— This submission was reviewed by Florian Zielinski in order to approve NDA 20-839 / S-005. The DMF review is dated Mar 14, 2000; The supplement was approved Mar 15, 2000.
- (b) Amendment (Annual Report) dated May 4, 2000 states that the synthesis of the drug substance from — specifically —
clopidogrel bisulfate — is identical in Sanofi facilities in Sisteron (currently approved site) and Aramon (proposed site for this supplement, S-011). Manufacturing in both facilities is in conformity with the synthetic route described in the approved NDA.
- (c) Telephone conversation on July 6, 2000: There are no significant differences between the DMF and the NDA per telephone conversation John Purpura.
- 20 Status of Consults and Other Reviews: CGMP Compliance: Drug substance (CSN) manufacturing is conducted within acceptable CGMP Compliance at Sanofi Chimie, Aramon, France according to the attached EES Report.
- 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 — the drug substance is done at Sanofi Chimie, Aramon, France 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 — : 3 lots were manufactured in the alternative mfg site (Sanofi Chimie, Aramon, France) and 3 lots were manufactured in the NDA mfg site (Sisteron, France). (Reference: Attachment 2) All drug substance specifications are met. The 6 batches are not significantly different.
- (d) One batch (9R0003) of clopidogrel bisulfate — manufactured at Sanofi Chimie, Aramon, France is entered into the 40°C/75% RH stability testing protocol (Attachment 3). Results obtained after 3 months of storage indicate acceptable stability. No significant differences are observed between initial and 3 month data.
- (e) One batch of Plavix (Batch 0355, drug product) prepared from a batch of clopidogrel bisulfate — manufactured at Sanofi Chimie, Aramon, France met all release specifications. (Reference: Attachment 4)
- (f) The firm commits to enter the — batch of Plavix manufactured from clopidogrel bisulfate — manufactured at Sanofi Chimie, Aramon, France 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: July 6, 2000

25 Distribution:

Original NDA 20-839/S-011
HFD-110 Division File
HFD-110 Project Manager, C. Locicero
HFD-110 Review Chemist, Florian Zielinski
Initialed by K Srinivasachar

FS
July 6, 2000

FS
10-23-00