020839_S-013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-839/S-013

Trade Name: Plavix Tablets

Generic Name(s): (clopidogrel bisulfate)

Sponsor: Sanofi-Synthelabo, Inc.
Agent:

Approval Date: March 7, 2001

Indication: Provides for CBE manufacturing controls

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-839/S-013

3-7-01

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 September 18, 2000, received September 19, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) Tablets, 75 mg.

This "Changes Being Effected in 30 days" supplemental new drug application provides for the manufacture of clopidogrel bisulfate — drug substance — at an alternative site at Sanofi Chimie, Sisteron, 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, 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

/s/

Kasturi Srinivasachar
3/7/01 06:20:20 PM

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

1. Chemistry Review # 1

2. NDA # 20-839 S-013 (CBE 30, site change)

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-013

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 — **drug substance)** at an alternative site at Sanofie Chimie, Sisteron, France.

10. Previous Documents: None

11. Submissions Reviewed: Supplement dated September 18, 2000
DMF —) Amendment dated July 2000, submitted Sept. 18, 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 $C_{16}H_{16}ClNO_2S - H_2SO_4$ MWt base 321.83 MWt salt 419.9

19 Related / Supporting Documents:
DMF ____ dated March 31, 2000 for — drug substance, — mfg.
Reviewed by FWZ: July 19, 2000
Current Status: Adequate (July 19, 2000)
An amendment dated July 2000 and submitted on September 18, 2000 does not contain significant new information other than the manufacturing site change.

20 Status of Consults and Other Reviews:
CGMP Compliance: Overall acceptable on Sept 28, 2000

21 Comments:

(a) The Letter of Authorization dated September 2000 permitting reference to DMF — is found in Attachment 1

(b) The drug substance — is manufactured — at the alternative facility (Sanofi Chemie, Sisteron, France) according to methods and procedures currently approved (S-009) for the Sanofi Chemie, Aramon, France facility. Details are provided in the original DMF — that was submitted on March 31, 2000. (Reference: NDA 20-839 SCM-013, Cover Letter). This DMF was modified and resubmitted in entirety on September 18, 2000, to correct typographical errors and to update information pertaining to the primary reference & impurity standards and the — monograph. Specifically, the typo on p 87 is corrected, the lot number of the new — reference standard is (p 39), the lot number of the new qualified — impurity reference standard is — (p 64) and the new — monograph for "Purified water in Bulk" is added (p 127). *Evaluation: Acceptable manufacturing site change. The September 18, 2000 modifications are informational rather than substantive. As a result, the current process may be approved for use at the new manufacturing site, Sisteron.*

(c) Three batches of drug substance (Batch Numbers 8R00002, 8R00003 and 8R00004) were manufactured at Aramon in May 1998. Analytical data for these 3 lots are provided for comparison to 3 batches of drug substance (Batch Numbers 0S90002, 0S90003 and 0S90004 manufactured at Sisteron in February 2000. (Reference: Supplement 013, Attachment 2) All drug substance specifications are met. *Evaluation: The 6 batches are not significantly different except that the impurity — is approximately — in the Sisteron DS and NMT — in the Aramon DS. The specification limit is NMT 1.0%. This difference is not likely to be significant in that this impurity is — where as the drug substance is —*

(d) One batch (0S90002) is entered into the 40C/75% RH stability testing protocol. Results are reported in Attachment 3. No significant differences are observed after storage for —

(e) One Certificate of Analyses for the drug product (Batch 013) prepared from a batch of — drug substance manufactured in Sisteron is provided in Attachment 4 of the supplement dated Sept 18, 2000. All drug product specifications are met.

(f) The first batch of Plavix (drug product manufactured at Ambares) prepared from a batch of drug substance manufactured at Sisteron will be tested for long term stability (Attachment 5). Results will be reported in Annual Reports.

(g) Original NDA approved on November 17, 1997

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

23 Reviewer: Florian Zielinski

24 Date Completed: March 7, 2001

25 Distribution
Original NDA 20-839/S-013
HFD-110/Division File
HFD-110/Project Manager, Locicero
HFD-110/F Zielinski
Initialed by: K Srinivasachar
File Name: NDA 20839 S-013 new facility

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20839/013
Priority: 1P
Org Code: 110
Stamp: 19-SEP-2000 Regulatory Due: 19-MAR-2001
Action Goal:
District Goal: 12-FEB-2001
Applicant: SANOFI SYNTHELABO
90 PARK AVE
NEW YORK, NY 100161389
Brand Name: PLAVIX (CLOPIDOGREL BISULFATE) 75MG TABS
Established Name:
Generic Name: CLOPIDOGREL BISULFATE
Dosage Form: TAB (TABLET)
Strength: 75 MG

FDA Contacts:
C. LOCICERO (HFD-110) 301-594-5300 , Project Manager
F. ZIELINSKI (HFD-110) 301-594-5348 , Review Chemist
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation:

ACCEPTABLE on 28-SEP-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 9612650
SANOFI CHIMIE
04201
SISTERON, , FR
DMF No:
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-SEP-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: DRUG SUBSTANCE MANUFACTURER

/s/

Florian Zielinski
3/7/01 04:16:41 PM
CHEMIST

Kasturi Srinivasachar
3/7/01 05:43:02 PM
CHEMIST