020839_ S-014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-839/S-014

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-014

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 October 12, 2000, received October 13, 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 and control of Plavix (clopidogrel bisulfate — Tablets at an alternative site at Bristol-Myers Squibb facilities in Humacao, Puerto Rico.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter. Please submit Final Printed Labeling (Package Insert, container and carton labels) incorporating the "Manufactured for . . ." declaration in your next annual report.

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,

/S/

{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 06:42:16 PM

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

1. Chemistry Review # 1

2. **NDA # 20-839 S-014 (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-014

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 the manufacture and control of Plavix (clopidogrel bisulfate ——— Tablets at an alternative site at Bristol-Myers Squibb Manufacturing Co in Humacao, Puerto Rico.

10. Previous Documents: None

11. Submissions Reviewed: CBE Supplement dated October 12, 2000, effective November 12, 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: None

20 Status of Consults and Other Reviews:
CGMP Compliance: Overall acceptable on Oct 17, 2000

21. Comments:

(a) This supplement describes a Moderate Change (CBE reference page 10 of "Changes to an Approved NDA or ANDA" Nov 1999). Documentation required to support this SUPAC-IR Level 3 site change (page 13) includes updated batch records, release specifications, stability data (3 batches) and dissolution profiles.

(b) Sanofi Winthrop Industrie, Ambares, France is currently approved to manufacture 75-mg tablets from — drug substance manufactured in Aramon, France according to procedures in NDA 20-839 S-009 (Approved July 25, 2000).

(c) Bristol-Myers Squibb, Humacao, Puerto Rico (BMS) is currently approved to manufacture tablets from — drug substance (S-004 approved 1/27/2000)

(d) This supplement requests approval for BMS manufacturing of tablets from — drug substance. *Evaluation: There is no reason to expect that manufacturing problems will be associated with the substitution of — in the tablet production operations.*

(e) Three sets of executed manufacturing batch records for — are reproduced on pages 207-312, 313-421 and 422-5233 of the supplement dated 10/12/00.

(f) Certificates of Analyses for three pilot batches of Plavix Tablets (Lots 030004NCC, 030005NCC and 030006NCC) prepared from 3 different batches of — drug substance are provided on pages 584 to 586 of the supplement dated October 12, 2000. *Evaluation: All drug product specifications are met.*

(g) These three pilot batches of — Tablets were tested for stability. Packaging into — bottles (30 count with desiccant) and — blisters was done in Humacao. Testing followed storage for 3 months at 25C/60% RH and 40C/75% RH. Results are reported in pages 596 to 617. No significant differences between — Tablets manufactured in Humacao and a reference batch of — Tablets manufactured in Ambares, France were observed. *Evaluation: All specifications are met. These stability data support the assignment of the current expiration period, namely — for bottles and — for blisters.*

(h) The first three commercial batches of — Tablets manufactured in Humacao will be entered into the stability program. Results will be reported in Annual Reports.

(i) Dissolution profiles for 2 batches of Plavix — Tablets (Lots 030004NCC and 030006NCC) compare favorably with the reference batch manufactured by Sanofi in Ambares, France (Batch Number SW1A0012). The f2 factors are 75 and 78 respectively.

(j) A telephone conversation with John Purpura on March 7, 2001 confirmed that container and carton labels will state that Plavix Tablets manufactured by BMS (Humacao) were "Manufactured for BMS - Sanofi Pharmaceuticals Partnership, NYC, NY 10016 by BMS Co., Princeton, NJ 08543." In addition, this declaration will be placed at the very end of the Package Insert.

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-014
HFD-110/Division File
HFD-110/Project Manager, Locicero
HFD-110/F Zielinski
Initialed by: K Srinivasachar

File Name: NDA 20839 S-014 new facility

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20839/014
Priority: 1P
Org Code: 110
Stamp: 13-OCT-2000 Regulatory Due: 13-APR-2001
Action Goal:
District Goal: 09-MAR-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 17-OCT-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 2623458
SQUIBB MANUFACTURING INC
STATE RD #3 KM775
HUMACAO, PR 00791
DMF No:
AADA No:

Profile: TCM
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-OCT-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: FINISHED DOSAGE MANUFACTURER

/s/

Florian Zielinski
3/7/01 03:50:25 PM
CHEMIST

Kasturi Srinivasachar
3/7/01 05:40:12 PM
CHEMIST