020839 S-015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-839/S-015

Trade Name: Plavix Tablets

Generic Name(s): (clopidogrel bisulfate)

Sponsor: Sanofi-Synthelabo, Inc.
Agent:

Approval Date: June 18, 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-015

6-18-01

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 December 15, 2000, received December 18, 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 [redacted]

We have completed the review of this supplemental application, and it is approved. Please note, for future, reference that [redacted] process for clopidogrel bisulfate. According to the Guidance for Industry, *Changes to an Approved NDA or ANDA*, any process change made after the [redacted] in drug substance manufacture should be submitted in a prior approval supplement.

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
6/18/01 05:15:55 PM

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

1. Chemistry Review # 1

2. NDA # 20-839 S-015 (CBE 30, process 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-015

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 [redacted]

[redacted] The amount of [redacted] is reduced from [redacted] This represents a [redacted] reduction in the quantity of [redacted] of the synthesis.

10. Previous Documents: None

11. Submissions Reviewed:
(a) CBE Supplement dated December 15, 2000 that refers to data in DMF [redacted]
(b) DMF [redacted] resubmitted November 30, 2000
(c) Type II DMF [redacted]

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:

(a) Type II DMF [ ] resubmitted in its entirety on 11/30/00. (pages 118-134, 182-196. 221-227. 242-245. 301-304 and 316-318)

(b) Type II DMF [ ] drug substance): Sanofi–Synthelabo may obtain drug substance [ ] according to description of the entire synthesis of — drug substance in their DMF —

Evaluation of DMF Status: Acceptable. According to Jim Short's DMF Review (Sept 15, 1997), — may manufacture all the . — the drug substance, (clopidogrel bisulfate — for Plavix Tablets described in NDA 20839. The — the processes for making them are the same for — of the drug substance. -- The last Annual Update of DMF — is dated July 27, 1998. There are no significant CMC changes that require a formal review in the update.

20 Status of Consults and Other Reviews: Verification of CGMP Compliance is not required for this process change. [ ] is a FDA approved manufacturer of [ ] drug substance at present. Additional verification of CGMP Compliance is not required now.

21. Comments:

(a) DMF — that describes the synthesis of clopidogrel bisulfate — is terminated.

(b) Previous versions of DMF — submitted Mar. 31, 2000 and Sept 18, 2000 are terminated.

(c) DMF — (resubmission dated November 2000) contains the updated description of the entire synthesis of the drug substance. [ ]

(d) The comparison of impurity profiles of [ ] in the DMF — (resubmission dated November 2000) page 225.

(e) The comparison of analytical data for drug substance clopidogrel bisulfate — made from the [ ] is in the DMF — (resubmission dated November 2000) pages 301 to 304.

(f) All specifications are met. No specifications are changed

(g) NDA 20-839 was approved November 17, 1997

22 Conclusions and Recommendation:

(a) The letter to the applicant should state that [ ]

(b) Based on CMC Review (#2) dated June 13, 2001 of the Nov 2000 amendment to DMF — **I recommend approval of the supplement.**

23 Reviewer: Florian Zielinski

24 Date Completed: June 18, 2001

25 Distribution

Original NDA 20-839/S-015
HFD-110/Division File
HFD-110/Project Manager, Locicero
HFD-110/F Zielinski
Initialed by K Srinivasachar

File Name: NDA 20839 S-015 new process.doc

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/s/

Florian Zielinski
6/18/01 11:19:27 AM
CHEMIST

Kasturi Srinivasachar
6/18/01 05:08:58 PM
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