CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-839/S-016

Trade Name: Plavix Tablets

Generic Name(s): (clopidogrel bisulfate)

Sponsor: Sanofi-Synthelabo, Inc.

Agent:

Approval Date: July 19, 2001

Indication: Provides for CBE alternative packaging facility
NDA 20-839/S-016

Sanofi-Synthelabo, Inc.
Attention: Haley Zimmerman
90 Park Avenue
New York, NY 10016

Dear Mr. Zimmerman:

Please refer to your supplemental new drug application dated January 22, 2001, received January 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) Tablets, 75 mg.

We acknowledge receipt of your submission dated January 25, 2001.

This "Changes Being Effected in 30 days" supplemental new drug application provides for an alternative packaging facility, Sanofi-Synthelabo, Inc., St. Louis, Missouri to package the finished product in blisters.

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,

[Signature]

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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kasturi Srinivasachar
7/19/01 10:36:22 AM
REVIEW OF CHEMISTRY, MANUFACTURING AND CONTROLS
Division of Cardio Renal Drug Products (HFD-110)

1. Chemistry Review # 1

2. NDA # 20-839 S-016 (CBE-30)

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-016

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 an alternative packaging facility, Sanofi-Synthelabo Inc., 6244 Lemay Ferry Road, St. Louis, MO 63129, to package the finished drug product in blisters.

10. Previous Documents: None

11. Submission Reviewed:
    Supplement dated Jan 22, 2001, received Jan 23, 2001
    Amendment dated Jan 25, 2001, received Jan 26, 2001

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_{3}S - H_{2}SO_{4}   MWt base 321.83   MWt salt 419.9
19 Related / Supporting Documents: None

20 Status of Consults and Other Reviews:
   CGMP Compliance Status: Overall acceptable on March 13, 2001 (See attached EES)

21 Comments:
   (a) A stability study of bulk tablets in the shipping / storage container used to transport
tabets from France to St Louis, MO showed acceptable appearance, dissolution,
assay and impurities after storage for 4 months at 25°C/60 % RH, 30°C/60% RH and
40°C/75% RH. These results confirm that the container closure system is acceptable.
   (b) Sanofi-Synthelabo will add the first production lot of tablets packaged in blisters at
the alternative site (St Louis, MO) and at least one lot annually thereafter to the long-
term stability program using the approved Post-Approval Protocol. (Page 21).
Results will be submitted in Annual Reports. (Stability testing is conducted by
Bristol-Myers Squibb, New Brunswick, NJ)
   (c) Packaging at the alternative site (St Louis, MO) will be done with the same
equipment type, materials, labeling and packaging procedures used in the currently
approved site (Bristol-Myers Squibb facility in Mayaguez, Puerto Rico).
   (d) A categorical exclusion was submitted under 21 CFR § 25.31. The applicant states
that extraordinary circumstances do not exist. There is no information that suggests
that additional environmental information is needed.

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

23 Reviewer: Florian W Zielinski

24 Date Completed: July 16, 2000

25 Distribution:

Original NDA 20-839 S-016
HFD-110 Division File
HFD-110 Project Manager, Birdsong
HFD-110 Review Chemist, F Zielinski

Initialed by: K Srinivasaschar

File name: NDA 20839 S-016, new packager.doc
14-MAR-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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<td>23-JUL-2001</td>
</tr>
<tr>
<td>Applicant:</td>
<td>SANOFI SYNTHELABO</td>
</tr>
<tr>
<td></td>
<td>90 PARK AVE</td>
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<td></td>
<td>NEW YORK, NY 10016/389</td>
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<tr>
<td>FDA Contacts:</td>
<td></td>
</tr>
<tr>
<td>C. LOCICERO</td>
<td>(HFD-110)</td>
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<tr>
<td>F. ZIELINSKI</td>
<td>(HFD-110)</td>
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<tr>
<td>K. SRINIVASACHAR</td>
<td>(HFD-110)</td>
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<td>301-594-5300 , Project Manager</td>
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<tr>
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<td>301-594-5348 , Review Chemist</td>
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<td>301-594-5376 , Team Leader</td>
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Overall Recommendation: ACCEPTABLE on 13-MAR-2001 by J. D. AMBROGIO (HFD-324) 301-827-0062

| Establishment: | 1931009 |
|                | SANOFI SYNTHELABO INC |
|                | 6244 LEMAY FERRY RD |
|                | SAINT LOUIS, MO 63129 |
| DMF No:        |               |
| AADA No:       |               |

Profile: TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 13-MAR-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

APPEARS THIS WAY ON ORIGINAL
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
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Florian Zielinski
7/16/01 12:03:48 PM
CHEMIST

Kasturi Srinivasachar
7/16/01 06:50:49 PM
CHEMIST