0207575005
Sanofi Pharmaceuticals, Inc.
Attention: Gregory Torre, Ph.D., J.D.
90 Park Avenue
New York, NY 10016

Dear Dr. Torre:

Please refer to your March 17, 1998 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avapro (irbesartan) Tablets, 75 mg, 150 mg and 300 mg.

We acknowledge receipt of your submission dated August 6, 1998.

The user fee goal date is September 18, 1998.

The supplemental application provides for an additional manufacturing site for the irbesartan drug substance, at Humacao, Puerto Rico.

We have completed the review of this supplemental application and it is approved with the understanding that you will submit stability data on drug product manufactured using irbesartan synthesized at Humacao, Puerto Rico, as soon as they are available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

K. Srinivasan 9/3/98
Kasturi Srinivasan, Ph.D.
Chemistry Team Leader, DNDC I
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CC:
Bristol-Myers Squibb Company
Attention: Douglas B. Hay, Ph.D.
P.O. Box 4000
Princeton, NJ 08543-4000
cc: NDA 20-759/S-005
    HFD-110/ DIV FILE
    HFD-110/ RMittal 09/03/98
    HFD-110/ Project Manager/ K Bongiovanni
    HFD-92
    DISTRICT OFFICE
    HFD-810/ CHoiberg
    cg 09/03/98

    Approval Date: September 30, 1997
DIVISION OF CARDIO-RENA L DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

<table>
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<tr>
<th>CHEMIST'S REVIEW</th>
<th>1. ORGANIZATION</th>
<th>2. NDA Number</th>
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<td>20-757</td>
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3. Name and Address of Applicant (City & State)
Bristol Myers Squibb Company
P. O. Box 4000
Princeton, NJ 08543-4000

4. Supplement(s)
Number(s) Date(s)
S-005(SNC) 10/25/99

5. Drug Name
6. Nonproprietary Name
Avapro
Irbesartan

7. Supplement Provides for:
[
[ stability data for drug product manufactured at

J with drug substance from Puerto Rico.

9. Pharmacological Category
Angiotensin II Receptor Antagonist/Hypertension

10. How Dispensed
[ x ] RX  [ ] OTC

11. Related IND(s)/NDA(s)/DMF(s)
20-758

12. Dosage Form(s)
--- Tablets

13. Potency(ies)
75 mg, 150mg, and 300 mg.

14. Chemical Name and Structure
2-Butyl-3-[(2'--(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

15. Records/Reports
Current
[ x ] Yes  [ ] No
Reviewed
[ x ] Yes  [ ] No

16. Comments:
See review notes.

17. Conclusions and Recommendations:
Satisfactory and no reply is necessary.

18. REVIEWER
Name: Ramsharan D. Mittal
Signature: [Signature]
Date Completed: 01/06/00

19. Distribution:
[ ] Original Jacket  [ ] Reviewer  [ ] Division File  [ ] CSO

[Signature]
2-23-00
Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-757/SCM-005

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
SCM 17-MAR-98 18-MAR-98 19-MAR-98
SCM(BC) 06-AUG-98 07-AUG-98 07-AUG-98

NAME & ADDRESS OF APPLICANT
Bristol Myers Squibb Company
P. O. Box 4000
Princeton, NJ 08543-4000

SUPPLEMENT PROVIDES FOR:
The approval of Humacao, Puerto Rico facility as an additional manufacturing site for the irbesartan drug substance.

DRUG PRODUCT NAME

Established Name: Irbesartan
Proprietary: AVAPRO
Nonproprietary/USAN: Irbesartan
Code Name/#: SR 47,436, BMS-186295, BMS-186295-01
Chem.Type/Ther.Class: 1/S

AND Suitability Petition/DES/Patent Status:
The U.S. Patent 5,270,317 held by Elf Sanofi was issued for irbesartan and is due to expire on March 2011.

PHARMACOL. CATEGORY/INDICATION: Angiotensin II Receptor Antagonist/Hypertension
DOSAGE FORM: TABLETS
STRENGTH: 75 mg, 150 mg and 300 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: Rx

CHEMICAL NAME 2-Butyl-3-[(2'-{1H-tetrazol-5-yl}biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

CAS # 138402-11-6

MOLECULAR FORMULA C_{25}H_{22}N_{6}O

MOLECULAR WEIGHT 428.5

STRUCTURAL FORMULA
SUPPORTING DOCUMENTS:

DMF# [ ]

RELATED DOCUMENTS (if applicable): NDA 20-758 Irbesartan/Hydrochlorothiazide

CONSULTS: None at present.

REMARKS/COMMENTS:

A request for inspection was submitted on April 08, 1998. As of April 9, 1998 EER status is acceptable and a copy of the EER report is attached at the end of this review.

The applicant has committed to submit [ ] product stability data report after about a month or so.

CONCLUSIONS & RECOMMENDATIONS:

Satisfactory and approval is recommended.

CC:
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

R/D Init by: KSRinivasachary

Ramsharan D. Mittal Ph.D., Review Chemist

filename: C:\NDA\20757\20757SCM.005

8-25-98
Application: NDA 20757/005
Applicant: SANOFI PHARMS
90 PARKE AVE
NEW YORK, NY 10016

Priority: 1S
Brand Name: AVAPRO (IRBESARTAN) TABS
75/150/300 MG
Established Name:
Generic Name: IRBESARTAN TABS 75/150/300MG
Dosage Form: TAB (TABLET)
Strength: 75, 150, 300MG

FDA Contacts:
K. BONGIOVANNI (HFD-110)
R. MITTAL (HFD-110)
J. SHORT (HFD-110)

301-594-5300, Project Manager
301-594-5353, Review Chemist
301-594-5300, Team Leader

Overall Recommendation:
ACCEPTABLE on 09-APR-1998 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: CSN OAI Status: NONE Responsibilities: DRUG SUBSTANCE MANUFACTURER
Last Milestone: QC RECOMMENDATION
Milestone Date: 09-APR-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Appears This Way
On Original