CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 19-898/S025

Trade Name: Pravachol Tablets

Generic Name: pravastatin sodium

Sponsor: Bristol Myers-Squibb

Approval Date: April 9, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-898/S025

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	
Labeling	
Medical Review(s)	
Chemistry Review(s)	X
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-898/S025

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-025

APR 9 1999

Bristol-Myers Squibb
Attention: William J. Regan
Director, CMC, Regulatory Affairs
P.O. Box 5400
Princeton, NJ 08543

Dear Mr. Regan:

Please refer to your supplemental new drug application dated December 10, 1998, received December 11, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pravachol (pravastatin sodium) Tablets.

This supplemental new drug application provides for a change in the manufacture of 10 mg, 20 mg, and 40 mg tablets at the Humacao, Puerto Rico facility, from [redacted] to [redacted], and new [redacted] and [redacted] count bottle sizes.

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.

The final printed labeling (FPL) must be identical to the last approved supplement, Supplement-021, approved August 17, 1998, with the exception of the "How Supplied" section of the package insert which must be identical to the submitted draft labeling (package insert faxed April 8, 1999). It is understood that each new bottlesize will only be added to the FPL when you are ready to begin marketing it.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-898/S-025." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely,

4/9/99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 19-898
HFD-510/Div. Files
HFD-510/M. Simoneau
HFD-510/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: Mas/April 9, 1999
Initialed by:SKelly4.9.99/SMoore4.9.99/EGalliers4.9.99/HAhn4.9.99
final:Mas 4.9.99
filename: 19898.25

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-898/S025

CHEMISTRY REVIEW(S)

APR 9 1999

CHEMIST'S REVIEW

1. ORGANIZATION CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**2. NDA #** 19-898 Original NDA approved: 31-OCT-1991
3. NAME AND ADDRESS OF APPLICANT Bristol-Myers Squibb P.O. Box 4000 Princeton, NJ 08543 (Phone): 609-252-4000	**4. SUPPLEMENT** SCS-025 10-DEC-1998 (Rec. 11-DEC-1998)
	5. Name of the Drug PRAVACHOL™
	6. Nonproprietary Name Pravastatin sodium
7. SUPPLEMENT PROVIDES for a change in the manufacture of 10mg, 20mg, and 40 mg tablets at the Humacao, Puerto Rico facility from [redacted] to [redacted] and new [redacted] and [redacted] count bottle sizes.	**8. AMENDMENT** --

9. PHARMACOLOGICAL CATEGORY Lipid-lowering agent	**10. HOW DISPENSED** Oral	**11. RELATED** -N. A. -
12. DOSAGE FORM Tablet	**13. POTENCY** 10mg, 20mg and 40mg	

14. CHEMICAL NAME AND STRUCTURE

[1S-[1α(βS*,φS*)2α,6α,8β(R*),8α]]-1,2,6,7,8α-hexahydro-β,φ,6-trihydroxy-2-methyl-1-oxobutoxyl)-1-nephthaleneheptanoic acid, monosodium salt

15. COMMENTS See next page.

16. CONCLUSIONS AND RECOMMENDATIONS Satisfactory CMC information has been provided to support the change as indicated in item 7 above. From the Chemistry point of view, this supplement can be approved.

17. REVIEWER NAME (AND SIGNATURE) **DATE**

COMPLETED 08-APR-1999
Sharon Kelly, PhD
R/D INITIATED BY

Sharon Kelly April 9, 1999

filename: 19898s025 NDA

DISTRIBUTION: Original: sNDA 19-898 SCS 025 cc: HFD-510 Division File CSO Reviewer

AP

Stephen L. Moore
4/9/99

26 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 19-698
5025

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 19898/025**
Priority: **1S** Org Code: **510**
Stamp: **11-DEC-1998** Regulatory Due: **11-APR-1999**
Action Goal: District Goal: **07-MAR-1999**
Applicant: **BRISTOL MYERS SQUIBB**
RT 206 PROVINCE LINE RD
PRINCETON, NJ 085434000
Brand Name: **PRAVACHOL TABLETS**
Established Name:
Generic Name: **PRAVASTATIN SODIUM**
Dosage Form: **TAB (TABLET)**
Strength: **10, 20, 40 MG**

FDA Contacts:			
M. SIMONEAU	**(HFD-510)**	**301-827-6418**	**, Project Manager**
W. BERLIN	**(HFD-510)**	**301-827-6370**	**, Review Chemist**
S. MOORE	**(HFD-510)**	**301-827-6430**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 23-DEC-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: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **23-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-898/S025

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ORIGINAL

JAN 2 7 1999

Clinical Pharmacology and Biopharmaceutics Review

NDA:	**19-898**
Generic	**Pravastatin**
(Brand®)	**Pravachol®**
Sponsor	**Bristo-Myers Squibb**
Submission Date:	**12-10-98**
Type of Submission:	**Supplement (S-025)**
Reviewer:	**Xiaoxiong (Jim) Wei**

Synopsis

On December 10, 1998, Bristol-Myers Squibb (BMS) submitted to the Agency the supplement to their approved NDA 19-898 for Pravachol® tablets seeking approval to manufacture Pravachol® tablets, 10 mg, 20 mg, and 40 mg by [redacted] instead of the current [redacted] method.

A PK study was conducted to establish the bioequivalence of a 40 mg [redacted] Pravachol® [redacted] tablet formulation to the 40 mg reference marketed tablet formulation using a stable isotope labeling method (a [redacted]. A total of 24 healthy male subjects were recruited to this open label, single dose, randomized and balanced 2-period crossover study. An analysis of variance was applied to the ratios of [redacted] AUC (INF) and Cmax. Bioequivalence between the two formulations was concluded since the 90% confidence interval for the ratio was entirely contained between 0.80 and 1.25. The results of this study were extrapolated to the two lower strengths: 10 and 20 mg tablets based on the proportional composition of their formula. A telephone conversation taking place on January 25, 1999 with Mr. William Regan, Director of CMC, World Wide Regulatory Affairs of BMS confirmed that the quantitative composition of the formula for these three strengths used in [redacted] are the same as the currently marketed formula and the batch sizes used for dissolution studies are [redacted] of production sizes.

I. Formulation

Three strengths of the [redacted] tablets were proposed. The composition of formulations for individual strengths was indicated in Table 1.

Table 1: Quantitative composition of the 10-mg, 20-mg, and 40-mg strengths expressed as milligrams per tablet.

INGREDIENT	AMOUNT/TABLET		
	10 mg Tablet	20 mg Tablet	40 mg Tablet
Pravastatin Sodium			
Lactose Monohydrate, NF			
Magnesium Oxide, USP			
Povidone, USP			
Microcrystalline Cellulose, NF			
Croscarmellose Sodium, NF			
Ferric Oxide, NF (red)			
Ferric Oxide, NF (yellow)			
Green Lake Blend [redacted]			
Magnesium Stearate, NF			
TABLET WEIGHT			

II. Bioequivalence

One bioequivalence study was performed to establish the bioequivalence of pravastatin in a [redacted] tablet formulation to the marketed tablet formulation. Three different dosage strengths (10, 20, and 40 mg) of the [redacted] tablets will be manufactured from the same formula and these strengths are currently in the US market. The highest strength of the tablet (40-mg) was used in this study. The objective of the study is to establish the bioequivalence of a 40-mg [redacted] tablet formulation to the 40-mg reference marketed tablet formulation.

In order to reduce the intrasubject variability, a stable isotope labeling method was utilized. Each subject received a [redacted] orally when the tablet was administered. 24 healthy male subjects were recruited to this open label, single dose, randomized and balanced 2-period crossover study. The washout period was at least 7 days. Following an overnight fast, subjects received a total of 60 mg oral dose of pravastatin consisting of [redacted] or as the marketed tablet. Blood samples were collected up to 48 hours.

An analysis of variance appropriate for a 2-period, 2-treatment crossover design was applied to the ratios of [redacted] AUC (INF) and Cmax. The [redacted] ratios were log transformed prior to conducting the analysis. Bioequivalence between the two formulations was concluded since the 90% confidence interval for the ratio was entirely contained between 0.80 and 1.25.

Table 2: Summary of PK parameters and the statistical comparisons

[redacted] ratio of Variable (N=24)	Geometric Means		Ratio of Geometric Means (Compressed/Marketed)	
	[redacted] Tablet	Marketed Tablet	Point Estimate	90% Confidence Interval
Cmax	1.68	1.78	0.942	(0.808, 1.098)
AUC (INF)	1.70	1.70	1.002	(0.886, 1.132)

III. Assay Method and Validation

The serum concentrations of pravastatin [redacted] and [redacted] were determined using a validated LC/MS/MS method with a lower limit of detection of [redacted] Peak area ratio was used for quantification of the analytes. The standard curve ranged from [redacted] If the predicted concentrations would be greater than the highest standard (> ULQ, upper limit quantitation), these ULQ samples were diluted with blank serum and reanalyzed.

Table 3: Pravastatin Analytical QC

Nominal Concentratio (ng/ml)	2.0000	30.0000	50.0010	80.0000	100.0000	500.0000
Mean Observed Concentration	1.9826	29.9569	49.6147	79.1015	99.2200	479.5104
Accuracy (%)	-0.8716	-0.1438	-0.7726	-1.1231	-0.7800	-4.0979
Between Run Precision (%RSD)	1.2725	3.1781	2.7175	2.5524	N/A	N/A
Within Run Precision (%RSD)	5.7261	2.5323	2.3508	1.7916	N/A	N/A

Table 4: [redacted] Pravastatin Analytical QC

Nominal Concentratio (ng/ml)	2.0000	30.0000	80.0000	100.0000
Mean Observed Concentration	1.9680	29.8244	78.4462	100.0646
Accuracy (%)	-1.6021	-0.5854	-1.9422	0.0646

Between Run Precision (%RSD)	0.0000	3.3274	3.4724	N/A
Within Run Precision (%RSD)	5.6057	3.2071	1.7102	N/A

Reviewer's comment:
The assay validation is acceptable.

IV. Dissolution

A tablet dissolution profile for batch of each potency of Pravachol® tablets manufactured at Squib Manufacturing, Inc., in Humacao, Puerto Rico (test batch) by was compared with the dissolution profile for corresponding batches of tablets manufactured at Bristol Laboratories in Mayaguz, Puerto Rico (reference batch).

reference and test batches were tested for dissolution profiles in water (approved medium) using USP apparatus 2 (paddles) at 50 rpm. Aliquots were removed at 5, 10, 20, and 30 minutes intervals. Essential comparable dissolution profiles showed that the test batches meet the NDA specification that not less than (Q) of the labeled amount of pravastatin is dissolved in 30 minutes. The dissolution results for the batches compare well giving SUPAC similarity factors (f_2) of 56, 66, and 53 for the 10-mg, 20-mg, and 40 mg, respectively, which are within the recommended range of 50-100. All test samples were at least 96% (average of tablets) dissolved within 20 minutes (see attached).

V. Comments (not to be sent to sponsor)

1. The quantitative composition of these three strengths of tablets is proportional. Therefore, they can be considered to be the same formula.

2. Overall BE study design and results are acceptable. Since the quantitative composition of three strengths, 10 mg, 20 mg, and 40 mg tablets is proportional, this reviewer agrees with the sponsor that the results of this study can be extrapolated to the two lower strengths: 10 and 20 mg tablets.

3. Dissolution results are acceptable since the f_2 values of 56, 66, and 53 for the 10-mg, 20 mg, and 40 mg are within the recommended range of 50-100.

Recommendations
The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed a supplement to NDA 19-898 for Pravachol® submitted on 12-10-98. The overall Human Pharmacokinetic Section is acceptable to OCPB The recommendation should be sent to the sponsor as appropriate.

Xiaoxiong (Jim) Wei, Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 1/20/99
FT

CC: NDA 19-898 (orig., 1 copy), HFD-510(Parks, Simoneau), HFD-850(Lesko, Huang), HFD-870(M. Chen, Ahn, Wei), Central Document Room (Barbara Murphy)

Code : AP

7 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 19-898 5025

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-898/S025

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-025

Bristol Myers Squibb
P.O. Box 4000
Princeton, NJ 08543-4000

DEC 16 1998

Attention: William J. Regan, Director,
CMC, Regulatory Affairs

Dear Mr. Regan:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Pravachol ® (pravastatin sodium) Tablets
NDA Number:	19-898
Supplement Number:	S-025
Date of Supplement:	December 10, 1998
Date of Receipt:	December 11, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 9, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 19-898/S-025
HFD-510/Div. Files
HFD-510/CSO/M. Simoneau

filename: C:\DATA\WPFILES\19898ACK.

SUPPLEMENT ACKNOWLEDGEMENT

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 5400 Princeton, NJ 08543-5400
609 818-4732 Fax: 609 818-5832

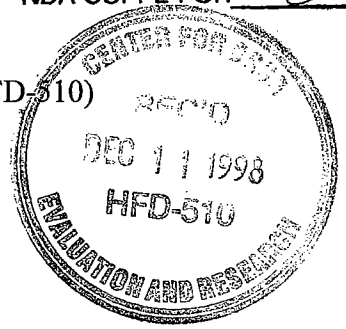
REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

William J. Regan
Director, CMC
North American Regulatory Affairs

December 10, 1998

NDA NO. 19-898 REF NO. 025
NDA SUPPL FOR SCS

Supplement to NDA 19-898
PRAVACHOL® (pravastatin sodium) Tablets



Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Center of Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Sobel:

This supplement to our approved NDA 19-898, PRAVACHOL (pravastatin sodium) Tablets seeks approval to manufacture PRAVACHOL Tablets, 10mg, 20mg, and 40mg, by [redacted] rather than by the current [redacted] method. This [redacted] manufacturing process shall be conducted at our Humacao, Puerto Rico, facility that currently manufactures PRAVACHOL Tablets, 20mg, by the [redacted] process. (Humacao as a manufacturing site for PRACACHOL Tablets, 20mg, was the subject of the "Changes Being Effected" supplement, S023, submitted 8-13-98.) The packaging and control sites remain unchanged.

This supplement includes the report of a bioequivalence study. A detailed summary of this supplement may be found in the Introduction and Summary Section. In addition, a Table of Contents describing the components of this submission follows this letter.

Based on 21 CFR Part 25.31(a), we request a waiver of the requirement for an environmental assessment.

Bristol-Myers Squibb Company certifies that field copies of this supplemental application have been provided to the North Brunswick office (120 North Center Drive, North Brunswick, NJ 08902) and to the San Juan, P. R. Office (466 Fernandez Juncos Avenue, Puerta de Tierra, San Juan, Puerto Rico 00901) of the Food and Drug Administration. We further certify that the field copies are true copies of this supplemental application.

Should you have any questions concerning this supplement, please contact me at (609) 818-4732.

Sincerely,

Howard M. Kessler

for William J. Regan
Director
CMC - Marketed Products
Worldwide Regulatory Affairs