CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-898/S032

ADMINISTRATIVE DOCUMENTS

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000

Worldwide Regulatory Affairs

NDA 19-898/S-032
PRAVACHOL® (pravastatin sodium) Tablets

January 21, 2000

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

Attention: Document Control Room (14B-19)

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898. Additional reference is made to Supplemental Application S-032 to NDA 19-898 submitted on April 13, 1999. This supplemental application provided for labeling changes to the CLINICAL PHARMACOLOGY and INDICATIONS section of the label to reflect data obtained in the pravastatin LIPID trial.

At this time we are providing the revised draft labeling (in side-by-side format) which reflects changes discussed with Dr. Mary Parks regarding the format of data presented on the Pravachol® secondary prevention trials.

If you have any questions concerning this submission, please contact me at (609) 252-5610.

Sincerely,

Fred Henry
Director
FDA Liaison
Global Regulatory Science Department

Desk Copies: Ms. Margaret Simoneau (HFD-510, PKLN 14B-04)
Dr. Mary Parks (HFD-510, PKLN 14B-04)

PATENT INFORMATION

The Pravachol® (pravastatin) products described in Bristol-Myers Squibb Company's SNDA No. 19-898/S____ for which approval has been applied for April 13, 1999, are covered by the following patents:

(1) U.S. Patent No. 4,346,227 (assigned to Sankyo Co. Ltd.) expires October 20, 2005, and its claims cover pravastatin as a new chemical entity or composition;

(2) U.S. Patent No. 5,030,447 (assigned to E.R. Squibb & Sons, Inc.) expires July 9, 2008, and its claims cover a formulation containing pravastatin;

(3) U.S. Patent No. 5,180,589 (assigned to E.R. Squibb & Sons, Inc.) expires July 9, 2008, and its claims cover a formulation containing pravastatin;

Patents (1), (2) and (3) are now listed in the Orange Book.

The pravastatin composition patent is owned by Sankyo Co. Ltd. E.R. Squibb & Sons, Inc., a wholly owned subsidiary of Bristol-Myers Squibb Company, is a licensee under this patent, has a place of business at Province Line Road and Route 206, P.O. Box 4000, Princeton, NJ 08543 and is authorized to receive notice of patent certification under §505(b)(3) and (j)(2)(B) of the Act and §§314.52 and 314.95.

The two pravastatin formulation patents are owned by E.R. Squibb & Sons, Inc., a wholly owned subsidiary of Bristol-Myers Squibb Company.

In accordance with 21 CFR §§314.53(c) and 314.53(d)(2), certification of the above-listed patents, which cover Pravachol® described in this SNDA is made on the attached sheet.

CERTIFICATION OF PATENT INFORMATION

As the undersigned, I hereby make the following declaration under 21 CFR §§314.53(c) and 314.53(d)(2) concerning the following composition and formulation patents that cover the Pravachol® products currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

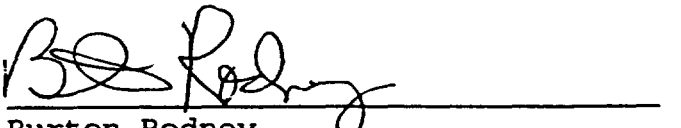
The undersigned declares that

U.S. Patent No. 4,346,227 (assigned to Sankyo Co. Ltd.) expiring October 20, 2005, U.S. Patent No. 5,030,447 (assigned to E.R. Squibb & Sons, Inc.) expiring July 9, 2008, and U.S. Patent No. 5,180,589 (assigned to E.R. Squibb & Sons, Inc.) expiring July 9, 2008, are patents that have been previously submitted to the FDA and identified as covering the product Pravachol® (pravastatin) covered by NDA No. 19-898. In accordance with 21 C.F.R. 314.53(d)(2) the undersigned certifies that these patents cover the product that is the subject of SNDA 19-898/S____. The use of the product Pravachol® composition and formulations for the following indications is the subject of this SNDA for which approval has been applied for on April 13, 1999:

> Reduction of total hospitalizations, reduction of risk of total mortality, reduction of the risk of death due to coronary heart disease, and reduction of the risk of stroke and stroke/transient ischemic attack (TIA).

As the undersigned, I hereby make the following declaration under 21 CFR §§ 314.53 (d)(2)(D)(iii):

> In the opinion and to the best knowledge of Bristol-Myers Squibb Company, there are no patents that claim the specific uses of pravastatin for the indications sought in the subject SNDA.



Burton Rodney
Senior Associate Counsel - Patents
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

Dated: April 5, 1999

EXCLUSIVITY SUMMARY FOR NDA # 19-898 SUPPL # 32

Trade Name Pravachol Generic Name Pravastatin

Applicant Name Bristol-Myers Squibb HFD # 510

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /✓/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

/S/

Signature
Title: Project Manager

2/3/00
Date

/S/

Signature of Office/
Division Director

2/10/00
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

/BLA # 19-898 Supplement # S-032 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

/ 510 Trade and generic names/dosage form: Pravachol (PRAVASTATIN) Action: (AP) AE NA

Applicant Bristol-Myers Squibb Therapeutic Class Lipid Altering Drugs

Indication(s) previously approved Primary prevention of Coronary events + Secondary Prevention of CV events

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application secondary prevention of coronary events, reduction in total mortality

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓ Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) ___ Infants (1month-2yrs) ✓ Children (2-12yrs) ✓ Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

✓ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

✓ c. The applicant has committed to doing such studies as will be required.

- ✓ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ___ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Team Leader (e.g., medical review, medical officer, team leader)

/S/ 2-8-00

Signature of Preparer and Title Date

Orig NDA/BLA # 19-898
HFD-510 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PRAVACHOL® (Pravastatin Sodium) Tablets

DEBARMENT CERTIFICATION
UNDER THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Bristol-Myers Squibb Company certifies that it did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this supplemental application.

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC USE INFORMATION

Pursuant to 21 CFR 314.55 (b) (1) (a) we are requesting a deferral of the requirement for providing pediatric use information until the studies in the pediatric population are completed. Our Proposed Pediatric Study Request was submitted to [redacted] Our studies in this population are currently ongoing.

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR WAIVER OF ENVIRONMENTAL ASSESSMENT

The subject of the proposed action will not have a significant effect on the environment and hence a waiver is requested for an environmental assessment per 21 CFR 25.31(b) and CDER "Guidance for Industry" dated July 1998. The drug product will continue to be used to treat cardiovascular disease. This action is expected to increase the use, however, the Expected Introduction Concentration (EIC) remains well [redacted] At the expected levels of exposure, the drug product is not anticipated to be toxic to organisms in the environment.

The EIC calculation is provided on the following page.

APPEARS THIS WAY
ON ORIGINAL

CONFIDENTIAL BUSINESS INFORMATION

Environmental Introduction Concentration

The [redacted] production volume in the [redacted] is estimated based on the projected sales volumes expressed as KgW equivalent of pravastatin drug substance for all uses and dosage forms of the drug product in the United States.

Kilograms KgW Pravastatin, US Market	
Year	KgW
[redacted]	[redacted]

Based on the volume of [redacted] the Expected Introduction Concentration for pravastatin is [redacted] as calculated below. The EIC for pravastatin represents the Maximum Expected Environmental Concentration (MEEC).

$$EIC = A \times B \times C \times D \times E$$

Where:

A = [redacted]
B = [redacted]
C = [redacted]
D = [redacted]
E = [redacted]

The MEEC of [redacted] meets [redacted] as defined in *Guidance for Industry Environmental Assessment in Human Drug and Biologics Application*, dated July 1998.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-032

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

JUN 8 1999

Attention: Mr. Warrren C. Randolph, Director
U.S. Regulatory Liaison

Dear Mr. Warren C. Randolph:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	PRAVACHOL(pravastatin sodium) Tablet
NDA Number:	19-898
Supplement Number:	S-032
Date of Supplement:	April 13, 1999
Date of Receipt:	April 13, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 12, 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

/S/

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

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000

Worldwide Regulatory Affairs

NDA 19-898/S-032
PRAVACHOL® (pravastatin sodium) Tablets

January 21, 2000

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

Attention: Document Control Room (14B-19)

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898. Additional reference is made to Supplemental Application S-032 to NDA 19-898 submitted on April 13, 1999. This supplemental application provided for labeling changes to the CLINICAL PHARMACOLOGY and INDICATIONS section of the label to reflect data obtained in the pravastatin LIPID trial.

At this time we are providing the revised draft labeling (in side-by-side format) which reflects changes discussed with Dr. Mary Parks regarding the format of data presented on the Pravachol® secondary prevention trials.

If you have any questions concerning this submission, please contact me at (609) 252-5610.

Sincerely,

Fred Henry
Director
FDA Liaison
Global Regulatory Science Department

Desk Copies: Ms. Margaret Simoneau (HFD-510, PKLN 14B-04)
Dr. Mary Parks (HFD-510, PKLN 14B-04)

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 4000 Princeton, NJ 08543-4000 609 921-4000

NC

DUPLICATE

NDA 19-898
PRAVACHOL® (pravastatin sodium) Tablets

December 17, 1999

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

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898, and to our supplemental application dated April 13, 1999 (S-032). This supplement provided for revisions to the Pravachol® package insert, based upon results from the LIPID trial (27,201-095).

Additional reference is made to a teleconference between BMS representatives and Dr. Joy Mele, of the FDA, in which Dr. Mele requested additional information as follows:

- Programs applied to electronic files of hospitalization data which was previously submitted and the resultant datasets.

- Programs and resultant datasets of patient discontinuation records.

A detailed description of the contents of these datasets and program files is provided in the attachment to this letter, along with a CD-ROM which contains this information.

Please let me know if you have any questions regarding this information at (609) 252-5610.

Sincerely,

Fred Henry
Director
FDA Liaison and Global Regulatory Strategy
Global Regulatory Science Department

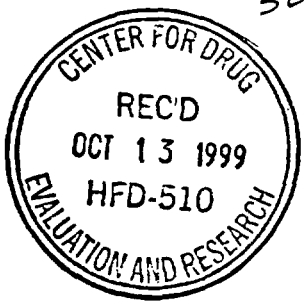
Attachment
Desk Copies: M. Simoneau (HFD-510, PKLN 14B04)
J. Mele (HFD-715, PKLN14B45) with CD-ROM disk

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 4000 Princeton, NJ 08543-4000
609 252 5225 Fax 609 252 6000

DUPLICATE

NDA SUPP AMEND
SE1-032 BV

Warren C. Randolph
Director
U.S. Regulatory Affairs



NDA 19-898/S-032
PRAVACHOL (pravastatin sodium) Tablets

October 12, 1999

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

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898, and to our supplemental application dated April 13, 1999 (S-032). This supplement provided for revisions to the Pravachol® package insert, based upon results from the LIPID trial.

Additional reference is made to a teleconference between BMS representatives and Dr. Mary Parks, in which Dr. Parks requested additional information, as follows:

- Treatment assignments and lipid-lowering medications for "Drop-ins" (those subjects requiring additional lipid-lowering therapy; and
- Use of hormone replacement therapy (HRT), insulin and oral hypoglycemics at baseline.

At this time we are providing the requested information, together with the following explanatory notes:

- Use of HRT, insulin and oral hypoglycemics at baseline.

– The description of percent of subjects receiving specified therapies (e.g., oral hypoglycemic agents) is based upon inspection of concomitant therapies administered at baseline, prior to randomization. It is also based upon the World Health Organization classification scheme for medications (i.e., the ATC code). Thus subjects receiving medications at baseline with the ATC code "A10B" were considered to have received oral hypoglycemic agents for the purpose of this analysis.

– Hormone replacement therapy requires further clarification. As is usual for a study of the size and duration of LIPID, the generic term for concomitant therapies was recorded, but the indication(s) for each concomitant therapy were not recorded. The menopausal status of women was not recorded on the CRF. Accordingly, we identified all female subjects who received estrogenic therapy at baseline, regardless of menopausal status. Estrogenic medications that are typically used for contraception were excluded from the analysis.

- Treatment group and lipid-lowering medications – Drop-ins.

– Line listings are provided for subjects who received lipid-lowering therapies (drop-ins). Subjects in the line listing are identified by registration number, patient identification number, date of randomization, treatment group assignment (sorted by placebo, pravastatin), "final date", date of drop-in, and generic term for drop-in medication. Two sets of line listings are provided. The first identifies subjects who dropped in prior to the "final date". Final date is defined as the earlier of date of last scheduled visit or date of death. This corresponds to the data in Table 5.1B of the LIPID Final Study Report. The second line listing identifies subjects who dropped in after the final date. These data are provided separately because some subjects dropped in (were started on pravastatin) after the final date due to the fact they became eligible for an open-label extension of the LIPID study (i.e., the COHORT study)."

Please contact me at (609) 252-5228 with any questions.

Sincerely,

for Howard M. Kessler

Warren C. Randolph
Director
US Regulatory Liaison
Worldwide Regulatory Science

WCR/ls/dk
Desk Copy: Mary Parks, M.D. (HFD-510, Room 14B04)

NDA SUPP AMEND
SE1-032-BM

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 Fax: 609 252-6000

ORIGINAL

Warren C. Randolph
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs

NDA 19-898/S-032
PRAVACHOL (pravastatin sodium) Tablets

July 29, 1999

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

Attention: Document Control Room (14B-19)

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898 and to pending Supplement S-032, submitted April 13, 1999, which supports changes in the Pravachol® labeling based on the results of the Long-Term Intervention With Pravastatin In Ischemic Disease (LIPID) study, Protocol [redacted]95.

In the April 13, 1999 submission we provided patent information on page 092 of volume 54.1. Upon approval of this supplement we wish to claim three years of market exclusivity under 21 CFR§314.108(b)(5). The LIPID study is a new clinical investigation that is essential to the approval of this supplemental application. We certify that, to the best of our knowledge, published studies do not exist which would provide a sufficient basis for the approval of the proposed labeling changes. We are providing a list of the available published reports of clinical investigations (attached). The list was obtained through a search of the following literature databases [redacted]

As the sponsor of the LIPID study, Bristol-Myers Squibb certifies that it provided more than [redacted] of the cost of conducting the study.

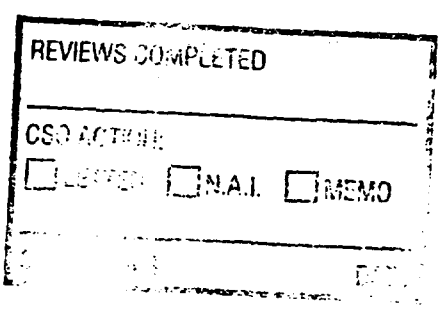
If you have any questions, please feel free to contact me at (609) 252-5228.

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
US Regulatory Liaison
Worldwide Regulatory Affairs

WCR/HMK/dk
Attachments



Bristol-Myers Squibb
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NDA NO. 19898 REF. NO. 032
NDA SUPPL FOR SE1

Warren C. Randolph
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Worldwide Regulatory Affairs

ORIGINAL

NDA 19-898
PRAVACHOL (pravastatin sodium) Tablets

April 13, 1999

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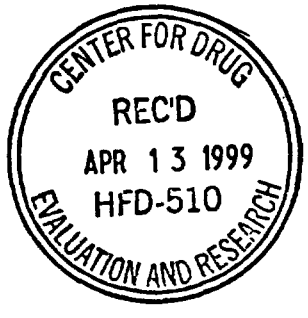

Attention: Document Control Room (14B-19)

Dear Dr. Sobel:

Reference is made to our approved new drug application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898. Reference is also made to our submission of May 27, 1998 which requested a waiver from the requirement to include case report tabulations (CRTs) in this sNDA since we would be providing the appropriate SAS datasets. This waiver was granted in the FDA letter of June 23, 1998. However, this issue is now moot because we are following the January 1999 Guidances for Industry: Providing Regulatory Submissions in Electronic Format – General Considerations and Providing Regulatory Submissions in Electronic Format – NDAs, which require that CRTs be submitted as SAS datasets.

Pursuant to 21 CFR §314.70(b) we are now submitting a supplemental New Drug Application with the results of the Long-Term Intervention With Pravastatin In Ischemic Disease (LIPID) study, Protocol [redacted]95. LIPID was a secondary prevention trial in 9,014 men and women who had an acute myocardial infarction or who had been hospitalized for unstable angina pectoris between three months and three years prior to screening. Their baseline total plasma cholesterol was between 4.0 and 7.0 mmol/L (155 - 271 mg/dL). This range of total cholesterol includes the levels found in the majority of CHD patients. The subjects were followed for a median of 5.9 years.

A prespecified analysis which examined the relationships between levels of lipid fractions and CHD events in the LIPID trial is included in this supplement, as is a similar analysis of data from the CARE trial. These are referred to as the Events Reduction Analyses (ERA).

Proposed, draft labeling included in this submission incorporates the following changes, based upon data from the LIPID trial and the ERA analyses:

- Text describing results of the LIPID trial has been added under the section heading CLINICAL PHARMACOLOGY.

- The subsection previously titled "Atherosclerosis and Myocardial Infarction" in CLINICAL PHARMACOLOGY has been retitled "Secondary Prevention of Cardiovascular Events". Text has been added to this subsection to provide a detailed description of the LIPID trial and to describe ERA for both the LIPID and CARE trials.

In addition to the labeling changes based upon the LIPID trial results and the CARE ERA, other modifications to the pravastatin package insert are proposed in the draft labeling submitted herein. These primarily involve reorganization of information in CLINICAL PHARMACOLOGY and consolidation of indications listed under Secondary Prevention of Cardiovascular Events in INDICATIONS AND USAGE. Please note that addition of the description of the CARE study results under the section heading CLINICAL PHARMACOLOGY is identical to the previously-approved text under the Secondary Prevention of Cardiovascular Events subsection. The reorganizations of the CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE sections are shown in the side-by-side presentation of the proposed draft labeling.

We are also proposing to change the initial paragraph under INDICATIONS AND USAGE to state that [redacted]." instead of the current "[redacted]Text concerning the use of lipid-altering agents with diet in the same paragraph has been relocated to the subsection Hypercholesterolemia and Mixed Dyslipidemia in the proposed draft labeling.

The LIPID trial has demonstrated that Pravachol significantly reduces the risk for cardiac events in patients with a history of unstable angina, the first time that a lipid-lowering agent has demonstrated such efficacy in this subpopulation. The LIPID trial also demonstrated that Pravachol significantly reduces total mortality in patients with coronary heart disease and cholesterol levels that are typical for this population. Additionally, this trial has shown that Pravachol treatment of patients with histories of myocardial infarction or unstable angina can reduce hospitalization. The significance of these results from the LIPID trial is such that we believe this application should receive a priority review classification.

The following information is incorporated into this letter to conform to the aforementioned guidances for electronic submissions. The table addresses the status of each part of this submission as electronic and/or paper.

The Archival Copy of this submission consists of both paper and electronic components which are indicated in the following table:

Item	Description	Paper archive copy volume number	Electronic archive copy folder
1	- Table of Contents - Form FDA 356h - Cover letter with Reviewers Guide attached	54.1	N19898\suppltoc.pdf N19898\356h.pdf N19898\cover.pdf
2	Labeling	54.1	na
3	Summary	54.1 – 54.3	na
4	Chemistry – request for waiver of environmental assessment only	54.1	na
5	Nonclinical Pharmacology and Toxicology	na	na
6	Human Pharmacokinetic and Bioavailability	na	na
7	Microbiology	na	na
8	Clinical Data	54.1 – 54.17	na
9	Safety Update Report	na	na
10	Statistical Data	54.1 – 54.17	na
11	Case Report Tabulations (CRTs) and documentation -CRTs table of contents -Dataset table of contents -Annotated blank CRF -Formats file containing decodes -Raw SAS datasets and documentation -Analysis SAS datasets and documentation -Supplemental SAS datasets and documentation	na na na na na na na na	N19898\CRT N19898\CRT\crttoc.pdf N19898\CRT\datatoc.pdf N19898\CRT[redacted]95\blankcrf.pdf N19898\CRT[redacted]95\formats.xpt N19898\CRT[redacted]95\raw\ SAS Transport files (.xpt) and define.pdf file (i.e., data definition table) N19898\CRT[redacted]95\analysis\ SAS Transport files (.xpt) and define.pdf file (i.e., data definition table) N19898\CRT[redacted]95\supple\ SAS Transport files (.xpt) and define.pdf file (i.e., data definition table)
12	Case Report Forms (CRFs) -CRF table of contents -CRFs for patients who died or discontinued due to AEs	na na na	N19898\CRF N19898\CRF\crftoc.pdf N19898\CRF[redacted]95\site number\patient file
13	Patent Information	54.1	na
14	Patent Certification	54.1	na
15	Establishment Description	na	na
16	Debarment certification	54.1	na
17	Field Copy Certification	na	na
18	User Fee Cover Sheet	54.1	N19898\other\userfee.pdf
19	Other (Financial Disclosure)	54.1	na

The electronic SAS datasets as functional CRTs (NDA Item 11), case report form images for patients who died or discontinued due to AEs (NDA Item 12), and respective documentation comply with the CDER guidances dated January 27, 1999 and referenced above. This includes the ability to navigate from the overall table of contents (N19898\suppltoc.pdf) to all parts of the electronic submission by bookmarks and hyperlinks.

This electronic submission is provided on one [redacted] should be considered the Archival copy. This [redacted] also contains files in portable document format (PDF) of the cover letter, overall table of contents, and user fee information.

[redacted]

The files have been checked for viruses on April 2, 1999 with [redacted] and are virus free.

The electronic submission has been provided on a digital linear tape [redacted] to the Central Document Room.

Please refer to the Overall Tables of Contents and Reviewer's Guide, which are attachments to this letter, for additional information. If you have any questions, please feel free to contact me at (609) 252-5228.

Sincerely,

Warren C. Randolph

APPEARS THIS WAY
ON ORIGINAL

Warren C. Randolph
Director
US Regulatory Liaison
Worldwide Regulatory Affairs

WCR/HMK/lp
Attachments:
Appendix 1, Reviewer's Guide
Appendix 2, Overview of all Electronic Components
Appendix 3, Notes to Information Technology Staff at FDA