CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019898, S034

Trade Name: PRAVACHOL TABETS

Generic Name: PRAVASTATIN SODIUM

Sponsor: BRISTOL-MYERS SQUIBB

Approval Date: 10/14/99

INDICATION(s): LIPID-ALTERING AGENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 019898, S034

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 019898, S034

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APPROVED

NDA 19-898/S-034

OCT 14 1999

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director US Regulatory Liaison Worldwide Regulatory Affairs
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

Please refer to your supplemental new drug application dated May 24, 1999, received May 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pravachol (pravastatin sodium) Tablets.

We acknowledge receipt of your submission dated September 14, 1999.

This supplemental new drug application provides for the addition of the reduction in apolipoprotein B (apo B) to the "Hypercholesterolemia and Mixed Dyslipidemia" subsection of the INDICATIONS AND USAGE section of the Pravachol package insert.

We have completed the review of this supplemental application, as amended, 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 submitted draft labeling (package insert submitted May 24, 1999).

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-034." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the

requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until March 31, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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,

/S/ 10/14/09

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

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898, S034

MEDICAL REVIEW(S)

NDA 19-898/S-034
Pravachol (pravastatin sodium) tablets
Bristol-Myers Squibb
Date of submission: July 21, 1999
Date of review: September 29, 1999

Proposed change in labeling to add reduction in apolipoprotein B to indications

No new clinical studies were submitted in this application. The sponsor has referenced clinical trial data from the original NDA. Pravastatin significantly lowers apo B levels at all doses studied relative to placebo in patients with Types IIa and IIb hyperlipoproteinemia (primary hypercholesterolemia and mixed dyslipidemia). Apo B levels are highly correlated with LDL-C levels in patients with primary hypercholesterolemia and with the sum of LDL-C + VLDL-C in patients with mixed dyslipidemia and thus reflect the burden of potentially atherogenic particles in plasma. The effect on apo B levels is common across the statin class. Other statins, notably Lipitor and Zocor, have labeling that includes reduction in apo B in *Indications* as an expected effect of the drugs. The change in the pravastatin label is therefore consistent with other members of the class and is acceptable.

David G. Orloff, M.D.
Medical Team Leader
DMEDP/CDER/FDA

/S/
9-29-99

Recommendation code: AP

Cc:
NDA 19-898
HFD-510
HFD-510: simoneau

APPEARS THIS WAY
ON ORIGINAL

Memo to Division Files

NDA #: 19-898/SE1-034
Sponsor: Bristol-Myers-Squibb
Drug name: pravastatin (pravachol)
Indication: to include in labeling a statement describing the reduction of apolipoprotein B in both normal volunteers and patients with hypercholesterolemia
Date received: May 25, 1999
Date reviewed: July 21, 1999
Medical Officer: Mary H. Parks, MD (HFD-510)
Studies submitted with application: No clinical studies were submitted with this supplement. Data supporting this labeling change are provided in the studies submitted with the original NDA.

Comments: Clinical studies submitted to the original NDA for pravastatin have demonstrated lowering of apolipoprotein B levels in normal volunteers and patients with hypercholesterolemia. Based on the fact that Apo B levels are highly correlated with LDL-C, a positive risk factor for cardiovascular disease, it is acceptable to incorporate these findings into the pravastatin label as proposed in this submission.

/S/ 7-21-99
Mary H. Parks, MD
Medical Reviewer (HFD-510)

/S/ 7-21-99

cc: DOrloff, MD (medical team leader)
MSimoneau, RPh (project manager)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898, S034

CHEMISTRY REVIEW(S)

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** SE1-034 24-MAY-1999 (Rec. 25-MAY-1999)
	5. Name of the Drug PRAVACHOL™
	6. Nonproprietary Name Pravastatin sodium
7. SUPPLEMENT PROVIDES for a labeling change to add reduction in apo B to the indications in the package insert.	**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 This supplement does not provide additional CMC information.

16. CONCLUSIONS AND RECOMMENDATIONS This supplement meets the requirements for a categorical exclusion from submitting an environmental assessment, 21 CFR §25.31(b). From the Chemistry point of view, this supplement can be approved. Issue an approvable letter.

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

COMPLETED 20-SEPT-1999

Sharon Kelly, PhD /S/ Sept 29, 1999

R/D INITIATED BY

filename: 19898#034 NDA

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

AP

/S/
9/20/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898, S034

PHARMACOLOGY REVIEW(S)

510/Lemneck

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS:

AUG 1 6 1999

Reviewer Name: Ronald W. Steigerwalt, Ph.D. Pharmacology Team Leader
Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP)
HFD#510
Review Completion Date: August 6, 1999
Review number: 4 (for this reviewer)

IND/NDA NUMBER: NDA 19-898
Serial number/date/type of submission: S-034/ May 5, 1999
Information to sponsor: Yes () No (X)
Sponsor (or agent): Bristol-Meyers Squibb Pharmaceutical Research Institute; P.O. Box 5400 Princeton, NJ 08534-5400

DRUG

Trade Name: PRAVACHOL®
Chemical Name: 1-Naphthalene-hepatnoic acid, 1,2,6,7,8,8a-hexahydro-(β)],6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-,monosodium salt, [1S-[1(α)(β)S*,[δ]S*)2α,6(α),8(β)(R*),8a(α)]]-

Relevant INDs/NDAs/DMFs: NDA 19-898 approved in 1991

Drug Class: HMG-CoA Reductase inhibitor "statin"

Indication: Cholesterol lowering drug: Primary prevention of coronary events, secondary prevention of cardiovascular events; reduction of risk of recurrent myocardial infarction.

Clinical formulation: 10, 20, 40 mg tablets with inactive ingredients of croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. Each tablet size also contains approved dyes.

Route of administration: Oral

Proposed clinical protocol or Use: Supplement S–034 Includes a new indication as follows: Decrease in apo B.

SUMMARY:
PRAVACHOL® is an HMG-CoA Reductase inhibitor that was approved in 1991 at the doses indicated in this supplement. This supplement contained only clinical or clinical pharmacology modifications. There were no preclinical studies submitted with thus supplement. No nonclinical data were necessary to support the proposed changes. No further review from pharmacology is necessary. There is an additional, separate supplement which addresses preclinical labeling issues and labeling will be considered under the appropriate supplement.

RECOMMENDATIONS:

From a pharmacology standpoint, the supplement 034 may be approved.

/S/

APPEARS THIS WAY
ON ORIGINAL

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

8/6/99

cc: IND Arch
HFD510
HFD510/Steigerwalt/Simoneau/
Review Code: AP
Filename: 19898.034.doc

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ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898, S034

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

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 the accompanying SNDA 19-898/S-034. The use of the Pravachol® composition and formulations for the following indication is the subject of this SNDA.

Modification of Apolipoprotein B levels as follows:

Lowering Apolipoprotein B levels in patients with primary hypercholesterolemia and mixed dyslipidemia

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 use of pravastatin for the indication sought in the subject SNDA.

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

Dated: Sept. 9, 1999

PATENT INFORMATION

The Pravachol® (pravastatin) products described in Bristol-Myers Squibb Company's SNDA No. 19-898/S-034 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.

EXCLUSIVITY SUMMARY FOR NDA # 19-898 SUPPL # 34

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?

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# 19-898 Pravachol N-000

NDA# _____ _____

NDA# _____ _____

2. Combination product. N/A

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?

N/A 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 /___/

Skip to 3(c)

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:

19-898 — The study to support the indication was submitted in the original NDA

Protocol -07 conducted by BMS in the U.S.

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:

SEE ADDENDUM

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? N/A

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 /_V_/

If yes, explain: _____

See addendum

APPEARS THIS WAY
ON ORIGINAL

/S/
Signature
Title: Project Manager

October 6, 1999
Date

/S/
Signature of Office/
Division Director

10/14/99
Date

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

APPEARS THIS WAY
ON ORIGINAL

Addendum to Exclusivity Checklist for NDA 19-898/SE1-034 Pravachol (pravastatin sodium) Tablets

It is not clear how to respond to some of the checklist questions, because clinical data were required for approval of the supplement but those data were reviewed in prior submissions (so no "new studies" were submitted). However, the specific information concerning the two endpoints (added in this supplement) was reviewed previously, and those data are necessary for approval of this supplement.

The data needed to support the change in the INDICATIONS AND USAGE section were submitted and reviewed in the original NDA. Measurement of the effect of the drug on apolipoprotein B (ApoB) was included with measurement of LDL-, HDL-, and total cholesterol in hypercholesterolemia trials. ApoB measurements were not considered standard, and they were not required; however, the applicant did do them. The information needed to support this supplement was submitted in the original NDA. The data were accumulated under Protocol 27,201-07, and the study was conducted by the applicant, BMS, in the United States.

At the time the original NDA was submitted, Division policy was to not allow statements regarding the lowering of ApoB in the INDICATIONS AND USAGE section of lipid altering drug labeling. That policy changed recently, and this information is now permitted in the labeling.

(With respect to User Fees, the supplement was said to have clinical data "by reference" to previously reviewed and analyzed submissions, thus incurring no User Fee.)

c:\data\word\19898x34.doc

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-034 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

505 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 Prim Prev of Coronary events / Secondary Prev of CV events

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

Proposed indication in this application _____

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 Medical Team Leader (e.g., medical review, medical officer, team leader)

/S/

Signature of Preparer and Title

11/22/99

Date

Orig NDA/BLA # _____

HF_____/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.

Pravastatin
NDA 19-898/S-034

Warren C. Randolph September 9, 1999

M. SIMONE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-034

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

JUN 8 1999

Attention: Warren C. Randolph,
Director, U.S. Regulatory Liaison

Dear Mr. Randolph:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Pravachol® (pravastatin sodium) Tablets
NDA Number:	19-898
Supplement Number:	S-034
Date of Supplement:	May 24, 1999
Date of Receipt:	May 25, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on July 24, 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
609 252-5228 Fax: 609 252-6000

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

NDA 19-898/S-034
PRAVACHOL (pravastatin sodium) Tablets

September 14, 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 S-034 submitted May 24, 1999. This supplement provided draft labeling which proposed the addition of reduction in apolipoprotein B (apo B) to the INDICATIONS AND USAGE section of the Pravachol® package insert.

Additional reference is made to my September 9, 1999 telephone conversation with Ms. Margaret Simoneau, in which she indicated that since S-034 has been classified as an efficacy supplement, Bristol-Myers Squibb should provide documentation to fulfill the requirements for environmental assessment, patent information and debarment certification. These documents were transmitted to Ms. Simoneau by facsimile on September 9th and we are now providing the hard copies.

Please contact me at (609) 252-5228 if you have any questions.

Sincerely,

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

WCR/LS/jh
Attachments

Waiver of Requirement for an Environmental Assessment NDA 19-898/S-034

The action proposed in this supplemental application will not significantly affect the quality of the human environment, and meets the requirements for a categorical exclusion from submitting an environmental assessment, 21 CFR 25.31(b). This action may increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

Be assured that Bristol-Myers Squibb operates its facilities in compliance with applicable environmental requirements.