CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 019898/S020

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19898/S-020

MAR 11 1998

Bristol-Myers Squibb Company
Attention: Warren C. Randolph
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

Please refer to your supplemental new drug application dated August 29, 1997, received September 2, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pravachol (pravastatin sodium) tablets.

We acknowledge receipt of your submissions dated October 27, November 26, 1997, and March 10, 1998 (fax). The User Fee goal date for this application is September 2, 1998.

The supplemental application provides for the reduction of triglycerides as a new indication. The heading of the subsection (within INDICATIONS AND USAGE) is changed from "Hypercholesterolemia" to "Hypercholesterolemia and Mixed Dyslipidemia", the target populations are described as patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb), and the table entitled "Classification of the Hyperlipoproteinemias" is eliminated.

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 submitted draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on November 26, 1997.

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 "FINAL PRINTED LABELING for approved supplemental NDA 19898/S-020." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the

promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be 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 20852-9787

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

Sincerely yours,

/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

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898/S020

MEDICAL REVIEW(S)

NDA # 19-898/S-020
Pravachol (pravastatin sodium) Bristol-Myers Squibb
Proposed changes to labeling without new data
Date of submission: August 29, 1997
Date of review: October 14, 1997

Medical officer's review

Brief summary of proposed changes
This supplemental application proposes changes to approved labeling to include the reduction of triglycerides in the indications for the use of pravastatin. The heading of the subsection (within INDICATIONS AND USAGE) would also be changed from Hypercholesterolemia to Hypercholesterolemia and Mixed Dyslipidemia and the target populations would be described as patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb). Finally, the sponsor proposes eliminating the table entitled "Classification of the Hyperlipoproteinemias" in keeping with the approved labeling for atorvastatin.

Background
While effecting their principal lipid altering effects on LDL-C, HMG-CoA reductase inhibitors (statins) clearly lower plasma triglycerides as well. This effect has been demonstrated by all members of the class and was noted in the original pivotal efficacy trials for these drugs. As a rule, the effects on TG are much more variable than those on LDL-C, and thus the mean changes in TG have not always been dose-dependent. However, mean TG reductions that are statistically significantly different from placebo have been demonstrated across the class, if not for the entire approved dosage range of a given drug. Finally, it appears that per degree of LDL-C lowering, the TG lowering efficacies of the statins are similar.

The mechanism of LDL-C lowering by statins has long been felt to result predominantly from the perturbation of hepatic cholesterol synthesis, leading to a reduction in one or more intracellular cholesterol pools. This sensed "need" for hepatic cholesterol leads to the increased expression of LDL-receptors, with increased clearance of plasma LDL-C and eventual attainment of a lower steady-state LDL-C concentration in the plasma.

The efficacy of high-dose statins in patients with homozygous, receptor-negative, familial hypercholesterolemia has led to the conclusion that direct inhibition of apo B-containing lipoprotein particle assembly and secretion may also play a role in the general mechanism of action of these drugs. Such a decrease in VLDL synthesis may in part explain the TG-lowering effects of these agents.

Extreme variability within and across individuals in post-prandial lipid metabolism, both in the synthesis and clearance of TG-rich lipoproteins, may explain the variability in the real and apparent response to statin therapy. The effects of genetics, diet, exercise, alcohol, drugs, adiposity, and other factors on lipoprotein metabolism, via impact on HDL level and function,

lipoprotein lipase activity, and on remnant clearance, among others, all contribute to the complexity of TG metabolism.

While epidemiologic and experimental data continue to accumulate in support of the atherogenicity of certain TG-rich lipoproteins (containing apo B-100), it has been difficult to separate, in multivariate analyses, elevated TG levels as an independent risk factor for atherosclerosis, at least in part because of the frequent association with low HDL-C levels, themselves strongly associated with increased incidence of CHD.

With regard to the impact of clinical interventions to lower plasma TG on CHD risk, the data are at best inconsistent. In a few, but by no means all, subgroup analyses from large trials, the most notable being from the Helsinki Heart Study using gemfibrozil, clinical benefit manifest as a reduction in coronary morbidity and mortality was demonstrated in patients with high TG and low HDL. Most of these analyses have been *post hoc*, and as stated above, not all have shown apparent benefit. In sum, the independent effects of clinical interventions to lower TG and to raise HDL have not been established.

The proposed labeling changes follow the approval of labeling for atorvastatin, currently the statin approved at doses effecting the greatest reductions in total and LDL-C. The marked LDL-C lowering effects of this agent are accompanied by impressive TG lowering, especially at the higher doses. However, as stated above, the TG lowering potency per LDL-C lowering potency of atorvastatin appears to be shared by the other members of the class.

A recent analysis of data from a large study comparing simvastatin to fibrate therapy in patients with primary hypercholesterolemia and mixed dyslipidemia clearly demonstrated that the degree of TG lowering by simvastatin was greater in patients with higher baseline TG levels. That is, patients with Type IIb showed greater TG responses than those with Type IIa. This too may explain the poor dose-response with regard to TG in many small trials of statin efficacy. Differences in the distribution of patients with regard to lipoprotein phenotype across small treatment groups may have significant effects on the measured TG effects of statin therapy.

In summary, statins, including pravastatin, do effect reductions in TG in patients with primary hypercholesterolemia and mixed dyslipidemia. While the clinical consequences of TG lowering are not known, in some instances, it may well be salutary. Regardless, it is clearly an expected effect of statin therapy and merits inclusion in labeling.

The sponsor also proposes eliminating the table of the Fredrickson classification. Instead, the proposal is to include the definitions of Types IIa and b, and Type III, in a reference at the end of the label.

Recommendations

The proposed changes in labeling are acceptable. The additional changes below are requested and should be conveyed to the sponsor.

1) The following disclaimer must be added to the Clinical Pharmacology section of the label and should be included in promotional materials:

Though frequently found in association with low HDL, elevated plasma triglyceride (TG) has not been established as an independent risk factor for coronary heart disease. The independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

2) The above should be inserted in Clinical Pharmacology, third paragraph, as the new fourth sentence, following "...and inversely with the level of HDL-C."

3) Finally, the existing fourth sentence, beginning "In multicenter clinical trials, those pharmacologic and non-pharmacologic..." should be deleted, as this information does not apply to the specific effects of Pravachol that are included in the label in this and other sections.

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

/S/
10-14-87

cc:
NDA Arch 19-898
HFD-510
HFD-510 Simoneau

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898/S020

CHEMISTRY REVIEW(S)

JAN 20 1998

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEDP II, HFD-510	19-898

3. NAME AND ADDRESS OF APPLICANT	4. SUPPLEMENT NUMBER, DATE
Bristol-Myers Squibb Pharmaceutical Research Institute P.O. Box 4000 Princeton, NJ 08543-4000	SNC-020 8-29-97

5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Pravachol Tablets	pravastatin sodium	10-27-97

8. SUPPLEMENT PROVIDES FOR

Changes to the Pravachol package insert to include reduction of triglycerides in the "Indications and Usage" section.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
antihypercholestermic	RX	

12. DOSAGE FORM	13. POTENCY
tablets, oral	10, 20, 40 mg

14. CHEMICAL NAME AND STRUCTURE

See Chemistry Review #1

15. COMMENTS

To be consistent with other drugs in this class, the sponsor has proposed to include "reduction of triglycerides" in the "Indications" section of the package insert. This information is currently listed in the "Clinical Pharmacology" section. Other, more editorial changes intended to clarify the PI and to standardize it with other drugs in this class are also included. The changes are acceptable based on chemistry issues. Because this supplement is an efficacy supplement, the sponsor has provided a request for a categorical exclusion from the requirement to prepare an Environmental Assessment under 21CFR 25.31(b) (see amendment dated 10-27-97). The sponsor noted that this action may increase the use of the product, but that the estimated concentration of the substance entering the environment will be This request for a waiver from the requirement to prepare an EA is acceptable.

16. CONCLUSION AND RECOMMENDATION

The labeling changes proposed by the sponsor reflect merely re-organization and editorial revision of the PI. The sponsor has requested a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(b), and this request is acceptable. This application is approvable based on chemistry issues.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
WILLIAM K. BERLIN	/S/	1-20-98

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

AP /S/
1/20/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898/S020

ADMINISTRATIVE DOCUMENTS

Certification of Patent Information

As the undersigned, I hereby make the following declaration under 21 CFR §§ 314.50(h)(ii):

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

APPEARS THIS WAY
ON ORIGINAL

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

Dated: March 9, 1998

APPEARS THIS WAY
ON ORIGINAL

PRAVACHOL® (pravastatin sodium) Tablets

NDA 19-898/S-020

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 new drug application.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 19898 SUPPL # 20

Trade Name Pravachol **Generic Name** Pravastatin
Applicant Name Bristol-Myers Squibb **HFD-** 510

Approval Date _____

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 questions 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 /✓/ CLIN=REF

   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:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

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d) Did the applicant request exclusivity?

YES /___/ NO /✓/

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

_____

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?

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).

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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 /___/

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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ON ORIGINAL

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 /___/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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 /___/
Investigation #3	YES /___/	NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

APPEARS THIS WAY
ON ORIGINAL

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"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

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/

_____ 3/9/98

Signature Date

Title: PM

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ON ORIGINAL

/S/

_____ 3/11/98

Signature of Division Director Date

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

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.

NDA/BLA # 19-848 / S-020 Supplement # S-020 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF S/C Trade and generic names/dosage form: Pravachol (pravastatin) Action: AP AE NA

Applicant Bristol-Myers Squibb Therapeutic Class Lipid Lowering Agents

Indication(s) previously approved _____

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

Proposed indication in this application to include the reduction of triglycerides in the indications

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) ___Adolescents(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 _____ (e.g., medical review, medical officer, team leader)

/S/ 3-5-98

Signature of Preparer and Title 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

NDA 19-898/S-020

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 new drug application.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

CORRESPONDENCE

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 /20
Pravachol® (pravastatin sodium) Tablets

August 29, 1997

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.

Pursuant to 21CFR§314.70 (b) we are submitting a Supplemental New Drug Application for changes to the Pravachol® package insert. These proposed revisions do not add any new information to the labeling, but change the presentation of existing triglyceride data to be consistent with that in the labeling for a more recently approved drug in the same class.

Currently, the Pravachol® package insert only addresses triglycerides in the CLINICAL PHARMACOLOGY section. The proposed labeling adds the reduction of triglycerides to the INDICATIONS AND USAGE section; the proposed change for the subsection heading under which it is included would be from Hypercholesterolemia to Hypercholesterolemia and Mixed Dyslipidemia, to more precisely characterize the patient population. The population under the subsection would be further described as patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb). Consistent with more recently approved statin labeling, we are also proposing elimination of the table entitled "Classification of Hyperlipoproteinemias".

Editorial changes concerning triglycerides and the description of patient populations are also proposed in the CLINICAL PHARMACOLOGY section. All proposed changes are shown in the right-hand column of the side-by-side draft labeling which follows this letter.

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

Sincerely,

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

APPEARS THIS WAY
ON ORIGINAL

WCR/dk

Desk Copy: Dr. David Orloff
Ms. Margaret Simoneau

APPEARS THIS WAY
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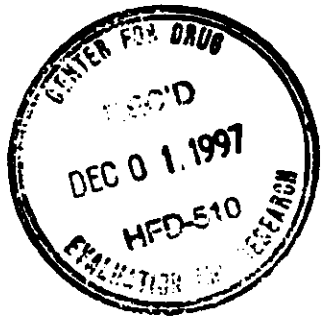
NDA AMENDMENT ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O Box 4000 Princeton, NJ 08543-4000
609 252-4656 Fax: 609 252-6000

John F. Bedard
Vice President
Worldwide Regulatory Affairs



NDA 19-898/S-020
Pravachol® (pravastatin sodium) Tablets

November 26, 1997

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. Additional reference is made to our submission of August 29,1997 which provided changes to the Pravachol® package insert concerning the presentation of the triglyceride data. Reference is also made to the following items:

1. The facsimile transmission of October 16, 1997 from Dr. D. Orloff (copy attached), which requested that the Clinical Pharmacology section of the insert be revised by adding a disclaimer regarding the effects of HDL and triglycerides and by deleting the fourth sentence of the third paragraph.

2. The teleconference of October 27, 1997 among Dr. Orloff and Drs. Belder and Staten and Mr. Randolph, during which S-020 was discussed. Dr. Orloff agreed that the could be omitted from the insert and stated that the inclusion of the disclaimer was non-negotiable.

We are now supplying four copies of the draft package insert revised as requested by Dr. Orloff. The text of the added disclaimer is presented in italics. The fourth sentence of the third paragraph of the Clinical Pharmacology section has been deleted.

No other changes have been made from the draft submitted on August 29. If there are any questions concerning this submission, please contact Mr. Warren Randolph at (609) 252-5228.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

John F. Bedard
Vice President
Worldwide Regulatory Affairs

WCR/HMK/lb
Attachments
Desk Copy: Ms. M. Simoneau (HFD-510, PKLN 14B-04)

APPEARS THIS WAY
ON ORIGINAL

Noted/Acceptable
2-1-98
/S/

SUPPL NEW CORR ORIGINAL

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-020
PRAVACHOL® (pravastatin sodium) Tablets

October 27, 1997

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. Additional reference is made to our Supplemental New Drug Application (S-020), submitted August 29, 1997 which revised the Pravachol® package insert to be consistent with labeling for a more recently approved drug in the same class. No new information was submitted, but the presentation of existing triglyceride data was modified as outlined in the August 29 submission.

At this time we are providing a request for a waiver for the Environmental Assessment for supplement S-020.

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

/S/
11-25-97

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
Worldwide Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 11/22/97
CSO INITIALS DATE

WCR/MOB/lp
Attachments
Desk Copy: Ms. Margaret Simoneau, HFD-510 (PKLN 14B-04)

/S/ 12/1/97

/S/ 12/1/97

REQUEST FOR WAIVER OF ENVIRONMENTAL ASSESSMENT

The subject of the proposed action 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.

APPEARS THIS WAY
ON ORIGINAL

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-020
Pravachol® (pravastatin sodium)

March 10, 1998

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. Additional reference is made to Supplemental New Drug Application, S-020, (submitted August 29, 1997) which provided for revisions to the Pravachol® package insert. The revisions changed the presentation of existing triglyceride data to be consistent with another approved drug in the same class. Finally, reference is made to a telephone conversation on March 9, 1998 between Ms. Margaret Simoneau and myself in which Ms. Simoneau requested patent and debarment certifications for S-020.

At this time, we are providing the information requested by Ms. Simoneau.

If you have any questions concerning this submission, please contact me at (609) 252-5228.

Sincerely,

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

WCR/GH/lp
Attachments
Desk Copy: **Ms. M. Simoneau (HFD-510, PKLN 14B-04)**