CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019898/S017

Trade Name: PRAVACHOL TABLETS

Generic Name: PRAVASTATIN SODIUM

Sponsor: BRISTOL-MYERS SQUIBB COMPANY

Approval Date: 04/15/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 019898/S017

APPROVAL LETTER

APR 15 1997

NDA 19-898/S-017

Bristol-Myers Squibb Company
Attention: Mr. Warren Randolph
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Mr. Randolph:

Please refer to your supplemental new drug application dated November 4, 1996, 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 March 12 and March 26, 1997.

The User Fee goal date for this application is November 4,1997.

The supplemental application provides for a change in the WARNINGS section of the labeling to recommend that liver function tests be performed prior to and at 12 weeks after initiation of therapy or elevation in dose.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the draft labeling submitted on March 12, 1997 (with pages 3 and 6 amended on March 25, 1997). Accordingly, the supplemental application is approved effective on the date of this letter.

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

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 NDA 19-898. 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, further revision of that labeling may be required.

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 Ms. Margaret Simoneau, at (301) 443-3410.

Sincerely yours,

/S/ 4/15/97

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

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 19-898
HFD-510
HFD-510/DOrloff/WBerlin/SMoore
HFD-511/MSimoneau
DISTRICT OFFICE
HF-2/Medwatch (w labeling)
HFD-92/DDM-DIAB (w labeling)
HFD-40/DDMAC (w labeling)
HFD-613/OGD (w labeling)

cc:EGalliers 4/8/DOrloff 4/9/WBerlin 4/9/EBarbehenn 4/10/SMoore 4/10/RSteigerwalt 4/9/97

Final: JWeber 4/10/97

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898/S017

MEDICAL REVIEW(S)

ORIGINAL

FEB 11 1997

NDA# 19-898/S-017
PRAVACHOL (pravastatin sodium) tablets
Bristol-Myers Squibb
Date of submission: November 4, 1996

Team leaders comments

This efficacy supplement provides data and analyses in support of changes in the approved package insert for PRAVACHOL. Specifically, the sponsor requests changes in the WARNINGS section of the label with regard to recommendations for liver function monitoring of patients on PRAVACHOL. Based on the data from the WOSCOPS trial, it appears that normal LFTs at 12 weeks after initiation of therapy with 40 mg pravastatin predict a very small chance of a subsequent clinically important abnormality. Indeed, the rate of subsequent consecutive elevations in ALT or AST to >3X ULN was not different between placebo and active drug groups. By contrast, among the small number of patients with elevated ALT or AST at 12 weeks, there was a higher incidence of subsequent consecutive abnormal LFTs, though no patients had consecutive elevations to greater than 3X ULN.

The sponsor performed one other analysis on 2-11-97 at my request. In order to exclude the possibility that the low rate of subsequent abnormalities in the 12-week-normal group was due to accelerated dropout in that cohort, they analyzed the dropout rates by treatment and by normal versus abnormal LFTs at week 12. There were no significant differences noted.

In sum, having normal LFTs at week 12 after initiation of therapy predicts a very low chance of subsequent clinically important LFT abnormalities.

I concur with the medical officer's recommendation that this supplement be approved as proposed by the sponsor.

APPEARS THIS WAY
ON ORIGINAL

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

/S/

2-11-97

cc:
NDA 19-898 Arch
HFD-510

APPEARS THIS WAY
ON ORIGINAL

NDA NO. 19-898/S-017
DRUG: Pravachol® (pravastatin)
SPONSOR: Bristol-Meyers Squibb
DATE OF SUBMISSION: November 4, 1996

REVIEW OF EFFICACY SUPPLEMENT

This labeling Supplement, which is an addendum to Supplement #015 (approved 7/2/96)[1], provides for a change in the Pravachol® (pravastatin) package insert regarding monitoring of liver function tests. Specifically, based on safety data from The West of Scotland Coronary Prevention Study ("WOSCOPS"), this submission proposes changes in the **WARNINGS** section to recommend that liver function tests be performed only at 12 weeks after initiation of pravastatin treatment (or following an elevation in dose), unless elevated transaminase levels are found at the week 12 timepoint.[2] Also included in the proposed labelling is a brief description of the incidence of clinically important transaminase elevations in the pravastatin versus placebo cohorts observed during the course of the study.

WOSCOPS was a randomized, double-blind, placebo-controlled, multicenter trial in which pravastatin 40 mg was administered over a 4.8 year median treatment period to men with LDL-C levels ≥155 mg/dL and no evidence of a prior myocardial infarction. A total of 3216 patients were randomized to pravastatin and 3203 to placebo. During the first year of study medication, clinical laboratory parameters were obtained every three (3) months and thereafter every six months for the duration of the trial. Subjects with laboratory abnormalities judged clinically significant by the investigator were retested within one (1) month. If retest results remained outside acceptable ranges, a decision on withdrawal was then made. Patients withdrawn from treatment could be re-challenged if after a period of not less than four (4) weeks, the abnormal value had returned to normal.

There was no statistically significant difference between treatment groups with respect to the incidence of serious and nonserious treatment-emergent adverse events in the hepatic/biliary system (Table 2.1, pg. 11, vol. 45.1). Overall, the incidence of these events--which included abnormal liver function, cirrhosis, fatty liver, gallbladder disorder, gallbladder surgery, hepatitis, hepatomegaly, jaundice, liver biopsy, liver pain, and malignant neoplasm (hepatic/biliary)--was quite small. The duration of study drug treatment encompassed

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[1] See Joint Medical/Statistical review of initial submission dated 4/26/96.

[2] Current labelling recommends monitoring of liver function tests before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically (e.g., semiannually) thereafter.

the dosing period up to and including 30 days following the last dose of study drug.

There were four (4) subjects in each treatment group who were discontinued from study medication due to adverse events in the hepatic/biliary system (Table 2.3, pg. 13, vol. 45.1). In the four (4) pravastatin treated patients, assessment of relationship to study drug was complicated in the first case by concomitant medications (atenolol, allopurinol, ranitidine, and metoclopramide) and a history of alcohol abuse; in the second case by a history of Gilbert's disease; in the third by gallstones; and in the fourth by concomitant antibiotic treatment.

During the period of blinded treatment (and including 30 days following the last dose of study drug) one (1) patient in the pravastatin group and two (2) in the placebo group died due to adverse events related to this body system. The pravastatin-treated patient was ultimately found to have biopsy evidence of poorly differentiated adenocarcinoma, which was thought to be metastatic from the gastrointestinal tract.

For AST and ALT, the criteria for clinically significant (marked) abnormalities were values three (3) times the upper limit of normal, or four (4) times the pretreatment value if the baseline value was moderately above the upper normal limit. No overall statistical difference between treatment groups in the incidence of marked abnormalities was found for these parameters (Table 2.4, pg. 23, vol. 45.1):

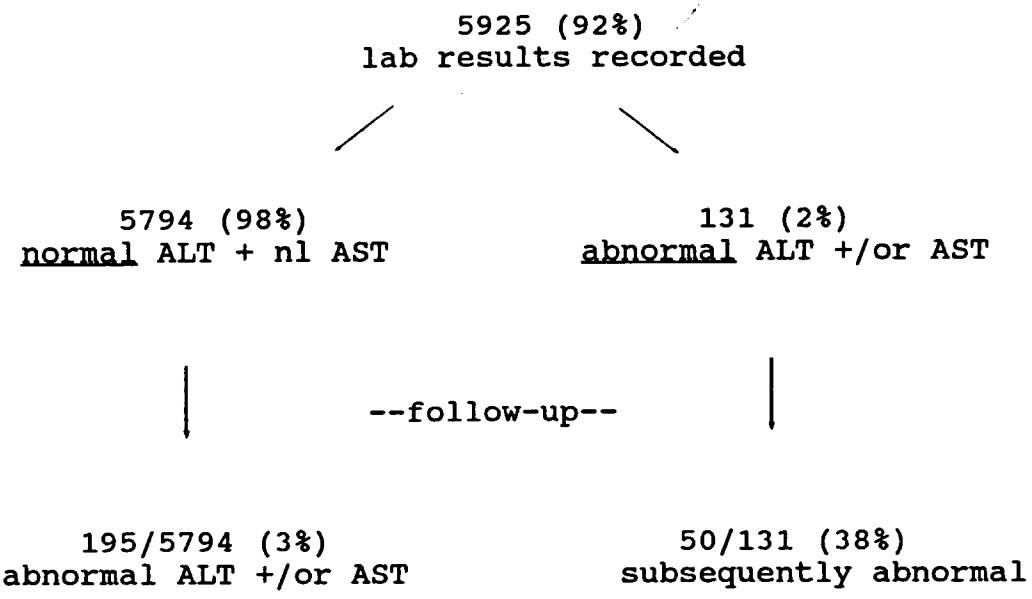
PARAMETER	N[1]	PRAVASTATIN	N[1]	PLACEBO	P-VALUE[2]
ALT	3046	23 (0.8)	3060	20 (0.7)	0.650
AST	3046	14 (0.5)	3060	11 (0.4)	0.556

[1]Number of subjects with baseline and any follow-up ALT or AST data.
[2]Fisher's Exact Test.

With respect to the proposed labeling changes, safety data from Visit 1 (12 weeks post-randomization) is of particular importance. The intention-to-treat population comprised 6419 subjects, i.e., individuals who received at least one dose of study drug. A total of 5925 patients, i.e., 2956 pravastatin patients (92%) and 2969 placebo patients (93%) had laboratory profiles measured at the Visit 1 timepoint. Findings are summarized below. Of the 131 patients with an abnormal ALT and/or AST (81 pravastatin; 50 placebo), 50 had persistent abnormalities (to >ULN) on two or more consecutive visits [34 (42%) pravastatin; 16 (32%) placebo]. The proportion of subjects with elevations in transaminases to two times ULN was similar between the treatment groups [3 (4.5%) pravastatin and 2 (4.4%) placebo for ALT; 1 (3.7%) pravastatin and 0 placebo for AST].

There were no transaminase elevations to three times ULN in either group.

ALT/AST FINDINGS: WEEK 12
(I.T.T. Population = 6419 patients)



Of the 5794 patients whose ALT and AST were normal at the Week 12 timepoint, 195 developed an ALT and/or AST abnormality (to >ULN) on two or more consecutive visits [110 (3.8%) pravastatin; 85 (2.9%) placebo]. The percentage in each treatment cohort who developed consecutive elevations to two times ULN was identical. There were no elevations to three times ULN in either treatment cohort. Of the above 195 subjects, six (6) died (1 pravastatin; 5 placebo) and seven (7) discontinued blinded medication due to adverse events (3 pravastatin; 4 placebo). None of the six (6) deaths were attributable to events in the hepatic/biliary system. Adverse events leading to discontinuation among subjects with a normal ALT and AST at the Visit 1 timepoint (12 weeks post-randomization) who developed any elevation in ALT and/or AST on two or more consecutive study visits are reproduced in the table below (from Table 2.5.1B, pg. 18, vol 45.1).

COMMENTS: Use of the intention-to-treat population is frequently the most appropriate (and conservative) approach in assessing efficacy; however, for safety parameters this is a potentially biased approach if there is a significant difference between treatment groups in drug exposure--either as a function of time on study and/or compliance with study drug. In WOSCOPS, the cumulative discontinuation rate over the course of the trial was in fact quite large: of the 6595 subjects randomized, 2164

PRIMARY TERM	PRAVASTATIN (N = 110)	PLACEBO (N = 85)
Abnormal Liver Function	1	1
Hepatic/Biliary Malignancy	0	1
Jaundice	1	0
Substance Abuse	0	1
Rhythm Disturbance, Subjective	0	1
Urticaria	1	0

(32.8%) discontinued study medication. However, judging by the number of available transaminase measurements, the number of patients on study at the Week 1 timepoint (12 weeks post-randomization), was still quite high (92%). In addition, the overall discontinuation rates due to adverse events were the same for both treatment groups over the course of the trial. Differential exposure to drug due to poor compliance is also a potential source of bias, but again, the discontinuation rates did not differ between treatment groups on this basis.[3]

Drug dose is ordinarily an important covariate is assessing safety parameters. With the exception of idiosyncratic reactions, adverse clinical and/or laboratory events, whether mechanism based or not, frequently show a dose-response relationship. WOSCOPS participants, however, were randomized to the highest currently marketed dose, 40 milligrams, as a fixed daily regimen.

In the apparent absence of any confounding factors, the data presented suggest the following: 1) drug-related adverse events in the hepatobiliary system are rare; 2) routine transaminase measurements in asymptomatic patients are not likely to identify those patients at risk for such events; and 3) at 12 weeks of therapy, an elevated ALT or AST value is qualitatively predictive of subsequent consecutive transaminase elevations. I would therefore recommend that the sponsor's proposed labeling revision be approved as submitted.

/S/

Steven Aurecchia, M.D.
1/13/97

cc: NDA Arch. 19-898
HFD-510
hfd-510/DOrloff/JMele

/S/
1-13-97

[3]See Joint Medical/Statistical review of initial submission, pg. 23.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898/S017

CORRESPONDENCE

NDA SUPPL AMENDMENT ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-4000 Fax: 609 252-5360

NDA 19-898/S-017
PRAVACHOL® (pravastatin sodium) Tablets

March 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 Supplemental New Drug Application (S-017), submitted November 4, 1996, which provided for a change in the requirement for liver function testing in the WARNINGS section of the PRAVACHOL® labeling.

Please refer also to:

- Telephone conversations with Dr. Orloff held with John Bedard and myself on March 10 and 11, 1997.
- A fax transmittal received from Dr. Orloff on March 10 that provided changes the Agency was requesting to the draft labeling which was submitted November 4, 1996.
- Our submission of revised, draft labeling that incorporated the requested changes.
- A telephone conversation between Ms. Margaret Simoneau and myself on March 25, 1997, in which she informed me of two errors which had appeared in the labeling text that had been submitted on March 12.

Ms. Simoneau pointed out that the figure showing survival distsributions from our primary prevention trial had appeared under the Atherosclerosis and Myocardial Infarction subsection of the CLINICAL PHARMACOLOGY section, rather than under Prevention of Coronary Heart Disease where it belongs. Also, in the Endocrine Function subsection of PRECAUTIONS, the citation for the rise in plasma testosterone appeared as •50% rather than as ≥50%.

We are providing herein replacement pages (page 3 of 9 and page 6 of 9) for the draft labeling submitted on March 12, in which the noted errors have been corrected. The pages bear the previous March 11 date, but also have a notation, "revised 3/25/97".

We hope that with these corrections all requirements have been met and that approval of the revised labeling will be possible in the very near future.

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

Sincerely,

Joan M. Keaney for

Warren C. Randolph

REVIEWS COMPLETED
Approval Letter Initialed
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS /S/ 4/1 DATE

Attachments

Desk Copies: Dr. D. Orloff, HFD-510 (PKLN 14B-04)
Ms. M. Simoneau, HFD-510 (PKLN 14B-03)

/S/
3-31-97

Noted
4/7/97
/S/

Noted
/S/ 4/4/97

ORIGINAL

NDA SUPPLEMENT

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-017
PRAVACHOL® (pravastatin sodium) Tablets

March 12, 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 Supplemental New Drug Application (S-017), submitted November 4, 1996, which provided for a change in the requirement for liver function testing in the WARNINGS section of the PRAVACHOL® labeling. The requested change was based on data from the West of Scotland Coronary Prevention Study (WOSCOPS), which showed that if transaminase levels are normal at week 12 of dosing, there is no safety advantage in continuing testing beyond this point.

Finally, reference is made to telephone conversations which Dr. Orloff held with John Bedard and myself on March 10 and 11, 1997 and to a fax transmittal received from Dr. Orloff on March 10 (copy attached). The fax provided changes that the Agency was requesting to the draft labeling which was submitted November 4, 1996. Dr. Orloff communicated one additional change by telephone on March 11. This change referred to the last sentence of the proposed text in the fax, to include those patients with normal liver function at week 12 who later discontinued medication due to elevations in transaminase levels. One pravastatin patient and one placebo patient were discontinued due to elevated transaminase levels. However, in the case of the placebo, this was the same patient who had AST levels greater than three times normal on two consecutive measurements, so the placebo number remains unchanged by the addition of discontinuations.

The specific changes which were made in response to the requests provided in the March 10 fax are as follow:

1) The overall incidence of AST and/or ALT elevations in the WOSCOPS study population, 1.05% in pravastatin-treated patients and 0.75% in the placebo group, has been included.

2. The overall number and incidence of patients discontinued due to transaminase elevations is provided for each treatment group, pravastatin=1 (0.03%) and placebo=2 (0.06%).

3) The text describing the lack of ALT elevations to greater than three times normal on two consecutive occasions in patients with normal liver function at 12 weeks has been deleted.

We are now submitting revised, draft labeling which we believe addresses all of the requested changes. If there are any questions regarding this submission, please contact me at (609) 252-5228.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

Warren C. Randolph

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

Attachments
WCR/dd/lp
Desk Copy: Dr. D. Orloff, HFD-510 (PKLN 14B-04)
Ms. M. Simoneau, HFD-510 (PKLN 14B-03)

Noted. The revisions are consistent with those discussed in Tcon.
/S/
3/18-97

Noted
/S/ 3/19/97

NDA SUPPL FOR [redacted]

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

NON SUPPLEMENT

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

Labeling: _____

NDA No: _____ **Rc'd.** _____

Reviewed by: _____

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

NDA 19-898
PRAVACHOL® (pravastatin sodium) Tablets

November 4, 1996

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 approved Supplemental New Drug Application (S-015) for primary prevention of coronary events. This supplement was based upon the results of the West of Scotland Coronary Prevention Study (WOSCOPS), which included over 6,000 men who were followed for a median of 4.8 years.

Liver function tests were measured sequentially over the course of WOSCOPS at intervals of three months for the first year and every six months thereafter. These sequential measurements over a median of almost five years in a large population provided an opportunity to evaluate the effectiveness of liver enzyme monitoring as currently recommended in the Pravachol package insert.

This submission contains a report entitled "An Assessment of Liver Function Monitoring in the West of Scotland Coronary Prevention Study (WOSCOPS)", which discusses the results of liver function testing in this study. The results indicate that if transaminase levels are normal at week 12, there is no safety advantage in continuing the testing beyond that point. Accordingly, we are proposing changes to the WARNINGS section of the labeling to recommend that liver function tests be performed only at 12 weeks after initiation of treatment or elevation in dose, unless elevated transaminase are found at week 12.

The contents of this submission are described in the Table of Contents. We have also included a Reviewer's Guide, which is intended to facilitate your review of this application. If you have any questions concerning the submission, please contact me at 609-252-5228.

REVIEWS COMPLETED
approval Cable
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS /S/ 3/6/97 DATE

Sincerely,

Warren C. Randolph

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

WCR/dd

Desk Copies: (Volume 1 only) Drs. Sobel and Orloff and Ms. Julie Rhee

3/4/97
/S/

1/13/97
see attached memo
/S/

/S/ 3/6/97

N.D.A.
/S/ 3/6/97