DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-050

Bristol-Myers Squibb Pharmaceutical Research Institute
Attention: Jerry Gennaro, Ph.D.
Director, Regulatory Science
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gennaro:

Please refer to your supplemental new drug application dated October 12, 2001, received October 15, 2001, 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 April 25 and June 11, 2002. Your submission of April 25, 2002 constituted a complete response to our April 11, 2002 action letter.

This supplement proposes revisions to the **ADVERSE REACTIONS, OVERDOSAGE**, and **STORAGE** sections of the Package Insert. The specific changes are as follows:

The **ADVERSE REACTIONS**; Adverse Clinical Events; Short-Term Controlled Trials, Long-Term Controlled Morbidity and Mortality Trials and Postmarketing Experience subsections were added.

To the **ADVERSE REACTIONS,** Adverse Clinical Events, Short-Term Controlled Trials, subsection, the first paragraph has been changed to read:

> All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in placebo-controlled trials of up to four months duration are identified in **Table 6**; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

Table 6 has been changed to read, "**Adverse Events in > 2 Percent of Patients Treated with Pravastatin 10-40 mg in Short-Term Placebo-Controlled Trials**."

The **ADVERSE REACTIONS,** Adverse Clinical Events, Long-Term Controlled Morbidity and Mortality Trials subsection has been added to read:

> Adverse event data were pooled from seven double-blind, placebo-controlled trials (West of Scotland Coronary Prevention study [WOS]; Cholesterol and Recurrent Events study [CARE]; Long-term Intervention with Pravastatin in Ischemic Disease study [LIPID]; Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study [PLAC I]; Pravastatin, Lipids and Atherosclerosis

in the Carotids study [PLAC II]; Regression Growth Evaluation Statin Study [REGRESS]; and Kuopio Atherosclerosis Prevention Study [KAPS]) involving a total of 10,764 patients treated with pravastatin 40 mg and 10,719 patients treated with placebo. The safety and tolerability profile in the pravastatin group was comparable to that of the placebo group. Patients were exposed to pravastatin for a mean of 4.0 to 5.1 years in WOS, CARE, and LIPID and 1.9 to 2.9 years in PLAC I, PLAC II, KAPS, and REGRESS. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these seven trials represent 47,613 patient-years of exposure to pravastatin. Events believed to be of probable, possible, or uncertain relationship to study drug, occurring in at least 1% of patients treated with pravastatin in these studies are identified in **Table 7**.

Table 7 Adverse Events in ≥ 1 Percent of Patients Treated with Pravastatin 40 mg in Long-Term Placebo-Controlled Trials

Body System/Event	**Pravastatin (N = 10,764) % of patients**	**Placebo (N = 10,719) % of patients**
Cardiovascular		
Angina Pectoris	3.1	3.4
Dermatologic		
Rash	2.1	2.2
Gastrointestinal		
Dyspepsia/Heartburn	3.5	3.7
Abdominal Pain	2.4	2.5
Nausea/Vomiting	1.6	1.6
Flatulence	1.2	1.1
Constipation	1.2	1.3
General		
Fatigue	3.4	3.3
Chest Pain	2.6	2.6
Musculoskeletal		
Musculoskeletal Pain (includes arthralgia)	6.0	5.8
Muscle Cramp	2.0	1.8
Myalgia	1.4	1.4
Nervous System		
Dizziness	2.2	2.1
Headache	1.9	1.8
Sleep Disturbance	1.0	0.9
Depression	1.0	1.0
Anxiety/Nervousness	1.0	1.2
Renal/Genitourinary		
Urinary Abnormality (includes dysuria, frequency, nocturia)	1.0	0.8
Respiratory		
Dyspnea	1.6	1.6
Upper Respiratory Infection	1.3	1.3
Cough	1.0	1.0
Special Senses		
Vision Disturbance (includes blurred vision, diplopia)	1.6	1.3

Events of probable, possible, or uncertain relationship to study drug that occurred in < 1.0% of pravastatin-treated patients in the long-term trials included the following; frequencies were similar in placebo-treated patients:

Dermatologic: pruritus, dermatitis, dryness skin, scalp hair abnormality (including alopecia), urticaria.
Endocrine/Metabolic: sexual dysfunction, libido change.
Gastrointestinal: decreased appetite.
General: fever, flushing.
Immunologic: allergy, edema head/neck.
Musculoskeletal: muscle weakness.
Nervous System: paresthesia, vertigo, insomnia, memory impairment, tremor, neuropathy (including peripheral neuropathy).
Special Senses: lens opacity, taste disturbance.

The **ADVERSE REACTIONS,** Adverse Clinical Events, Postmarketing Experience subsection has been added to read:

In addition to the events reported above, as with other drugs in this class, the following events have been reported rarely during postmarketing experience with PRAVACHOL, regardless of causality assessment:
Musculoskeletal: myopathy, rhabdomyolysis.
Nervous System: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), peripheral nerve palsy.
Hypersensitivity: anaphylaxis, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, asthenia, photosensitivity, chills, malaise, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis, hepatoma.
Dermatologic: A variety of skin changes (e.g., nodules, discoloration, dryness of mucous membranes, changes to hair/nails).
Reproductive: gynecomastia.
Laboratory Abnormalities: elevated alkaline phosphatase and bilirubin; thyroid function abnormalities.

The **OVERDOSAGE** section was changed to read:

To date, there has been limited experience with overdosage of pravastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required. (See **WARNINGS**.)

The **STORAGE** section was changed to read:

Store at 25° C (77° F); excursions permitted to 15°-30° C (59° - 86° F) [see USP Controlled Room Temperature]. Keep tightly closed (protect from moisture). Protect from light.

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 June 11, 2002).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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 18-898/S-050." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" 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, call Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff

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