CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-387

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Bristol-Myers Squibb
Attention: Porter P. Layne, Ph.D.
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

Please refer to your correspondence, dated February 14, 2001, containing your rationale for a co-package pravastatin/aspirin product for use in the management of coronary artery disease. Additionally, this correspondence describes certain aspects of the format and content of the New Drug Application for this product that you plan to submit in April 2001.

We have completed our review of your correspondence and have the following comments and recommendations.

1. The labeling for the components of the co-package product (pravastatin and aspirin) will differ from the labeling approved for each component's individual application and monograph, respectively. The co-package product labeling will be the intersection of the labeling of the two separate products. Therefore, as aspirin is not labeled for the primary prevention of coronary events, the primary prevention claim for pravastatin will not be included in the labeling for the co-package products.

2. The application should cover the full dose range for both products. The current proposal does not provide for this. For example, although pravastatin is currently marketed as 10, 20, and 40 mg tablets, only the 40 mg dose is proposed for co-packaging. Co-packaging should not alter the practice of medicine and providing limited combinations of these products might do so.

3. At a minimum, you will need to perform a pharmacokinetic interaction study and pharmacodynamic interaction study, although we have not established yet the criteria for the pharmacodynamic study. We request that you develop a proposal of possible pharmacodynamic studies that use surrogate endpoints for cholesterol lowering and platelet function and submit the proposal to the Division for review and comment.

4. Full Chemistry, Manufacturing, and Controls (CMC) data for aspirin will be needed for the co-package NDA. It will not be acceptable to rely on the aspirin Over-The-Counter (OTC) monograph for the CMC information for aspirin. For the pravastatin CMC information, it

will be acceptable to reference the CMC information from the pravastatin individual NDA. In addition, stability data for the co-package products will be needed.

5. You will need to perform a meta-analysis of the data on subjects on both pravastatin and aspirin from studies in the proposed indication, secondary prevention of coronary events. You will need to provide the point estimates and confidence intervals for this analysis in the NDA.

6. At this time, it is premature to discuss your proposal for a biowaiver of an *in vivo* bioequivalence study for the Bufferin® 81 mg tablets.

7. Provided you are still interested in pursuing a pravastatin/aspirin co-package product, we recommend that you meet with the Division of Cardio-Renal Drug Products to further discuss your proposal. In preparation for and prior to this meeting, please provide the Division with the pharmacodynamic interaction study proposal described above. This meeting would provide an opportunity to discuss your biowaiver proposal and the issues identified in your February 14, 2001 proposal that we have not addressed in this correspondence.

If you have any questions, please call:

Ms. Colleen LoCicero
Regulatory Health Project Manager
(301) 594-5332.

Sincerely yours,

/S/

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Raymond Lipicky
4/11/01 05:01:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-387

Bristol-Myers Squibb Company
Attention: Porter P. Layne, Ph.D.
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

We have received your new drug application (NDA) resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Pravachol/Aspirin (pravastatin sodium/aspirin) Co-Packaged Products

Review Priority Classification: Standard (S)

Date of Application: May 8, 2001

Date of Receipt: May 9, 2001

Our Reference Number: NDA 21-387

We note that this application was withdrawn on April 9, 2002.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 8, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 9, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call:

Colleen LoCicero, RPh
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

/S/

{See appended electronic signature page}

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Natalia Morgenstern
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-387

Bristol-Myers Squibb Company
Attention: Porter P. Layne, Ph.D.
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

We have received your new drug application (NDA) resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Pravachol/Aspirin (pravastatin sodium/aspirin) Co-Packaged Products

Review Priority Classification: Standard (S)

Date of Application: May 8, 2002

Date of Receipt: May 9, 2002

Our Reference Number: NDA 21-387

We note that this application was withdrawn on April 9, 2002.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 8, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 9, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

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Rockville, Maryland 20852-1420

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Colleen LoCicero, RPh
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

/S/

{See appended electronic signature page}

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Natalia Morgenstern
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-387

Bristol-Myers Squibb Company
Attention: Porter P. Layne, Ph.D.
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Pravachol/Aspirin (pravastatin sodium/aspirin) Co-Packaged Products, 40/81 mg, 40/325 mg Tablets
Review Priority Classification:	Standard (S)
Date of Application:	June 22, 2001
Date of Receipt:	June 22, 2001
Our Reference Number:	NDA 21-387

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 21, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 22, 2002 and the secondary user fee goal date will be June 22, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

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Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
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Rockville, Maryland 20857

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Rockville, Maryland 20852-1420

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Colleen LoCicero, RPh
Regulatory Health Project Manager
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Sincerely,

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Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Natalia Morgenstern
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