

Minutes of a meeting

Date of meeting:

April 5, 2001

Application:

Product:

pravastatin/aspirin co-package

Sponsor:

Bristol-Myers Squibb

Purpose:

pre-NDA

Meeting Chair:

John Simmons, Ph.D.

Meeting Recorder:

Colleen LoCicero

Participants:

FDA

John Simmons, Ph.D.

Director, Division of New Drug Chemistry I
(HFD-810)

Kasturi Srinivasachar, Ph.D.

Team Leader, Chemistry, HFD-810

Angelica Dorantes, Ph.D.

Clinical Pharmacologist and
Biopharmaceutist, Division of
Pharmaceutical Evaluation I (HFD-860)
Regulatory Health Project Manager,
Division of Cardio-Renal Drug Products
(HFD-110)

Colleen LoCicero

Bristol-Myers Squibb

Melody A. Brown

Director, Chemistry, Manufacturing and
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Executive Director, PRI Moreton & Nazaire
Director, Global Regulatory Affairs,
Worldwide Consumer Medicines

Mary Peters

Allen Skupp

Background

The sponsor requested this meeting to discuss their plans for the Chemistry, Manufacturing and Controls (CMC) section of their anticipated NDA submission for a Pravachol/Bufferin (pravastatin/aspirin) co-package product.

The meeting

The sponsor started the discussion by providing their rationale for providing a pravastatin/aspirin co-package product, and the anticipated design of the product packaging. BMS has learned that 82% of post-myocardial infarction (MI) patients are prescribed both pravastatin and aspirin. In surveying practitioners about a potential pravastatin/aspirin co-package product, more than 50% indicated they would use (prescribe) such a product. The practitioners believed such a product would enhance patient compliance, as patients would be less likely to forget to take one or the other of the medications as they would be side by side in a single package. Along these same

lines, the practitioners believed the co-package product would facilitate the managed care of their post-MI patients. Currently, the practitioners are never sure that these patients are taking the aspirin component of their regimen, as there is no mechanism for tracking the aspirin since it does not require a prescription. As the co-package will require a prescription, it will be possible to track the compliance with both components of the regimen.

BMS plans to market an 81 mg Bufferin/40 mg Pravachol and a 325 mg Bufferin/40 mg Pravachol co-package product. Each product will be packaged as a 28-day supply. There will be four cards per box with 14 tablets per card, seven Pravachol tablets on one side and seven Bufferin tablets on the other. Each card will provide a week's worth of medication.

Discussion Point #1: Aspirin data

BMS does not plan to include in the NDA any aspirin CMC data, as they intend to rely on the aspirin tentative final monograph, as described under 21 CFR 330.11. The Agency did not find this plan acceptable. According to Dr. Ganley, Director of the Over-The-Counter (OTC) Drug Products Division, this regulation (21 CFR 330.11, monograph deviation) is an OTC regulation and does not apply to products that will be marketed as prescription only. As the co-package products will require a prescription, this regulation does not apply. The Agency noted that full CMC information for OTC iron tablets was provided in the marketing applications for oral contraceptives containing these OTC iron tablets. The reason for requiring full CMC data in the NDA is to facilitate the management of possible post approval changes. It would be extremely difficult to manage post approval changes if this information is not provided in the original marketing application. Since BMS has all this information in their possession, the Agency did not believe providing the information in the NDA would be an undue burden on them.

A discussion ensued as to exactly what aspirin data would be needed in the original application and what data might be submitted later, during the review. As BMS currently markets 325 mg Bufferin tablets, they proposed to provide full CMC data for the 325 mg tablets in the original submission, and as much CMC data as they have on the 81 mg tablets (which they do not currently market) at the time of submission. BMS would commit to submit the remainder of the 81 mg data (i.e., batch records, release data, stability data, etc.) via amendments to the NDA as they obtain the data.

While this proposal might be acceptable, the Agency needs to discuss and consider the proposal further and will get back to BMS with a definite answer.

Discussion Point #2: Stability data

The 325 mg Bufferin tablets are currently marketed in — bottles and foil pouches. Pravachol is currently marketed in — bottles, foil pouches, and conventional blister packs. The — bottles and conventional blisters are less protective than the cold-form foil blisters proposed for the marketing of the co-package products. The protection provided by the foil pouches is equivalent to that provided by the cold-form foil blisters. Each Pravachol and Bufferin tablet will be provided in a separate cavity with no contact between the two tablets. The packaging site proposed for the production of the cold-form foil blisters has not been used previously by BMS to package Bufferin or Pravachol.

Because the cold-form foil blisters provide equivalent or better protection than the packaging for the currently marketed Bufferin and Pravachol products, BMS proposes not to include any stability data for the co-package product packaging (the cold-form foil blisters) in the NDA. BMS has three-year stability data at room temperature and ICH accelerated conditions for the Pravachol tablets in foil pouches. BMS has three-year stability data at room temperature for the 325 mg Bufferin tablets in foil pouches and three-year data in — bottles at room temperature and ICH accelerated conditions. BMS believes the stability data for the currently marketed 325 mg Bufferin tablets support the stability of the 81 mg tablet.

While full stability data for the Bufferin and Pravachol tablets in the actual (cold-form foil blisters) packaging may not be needed, some stability data to confirm that the stability of the co-package products is equivalent to that of the individual components will be needed. Exactly what is needed and at what point in the NDA process (i.e., in the original submission, during the review, etc.) these data are needed needs further consideration. Full stability data for the 325 mg Bufferin tablet (in the currently marketed packaging) should be provided in the NDA. Complete manufacturing information on the cold-form foil blisters should be included in the NDA along with the rationale for not providing full stability data for the tablets in the actual packaging. While the Agency agreed that the 325 mg Bufferin stability data support the stability of the 81 mg tablet, some stability data for the 81 mg tablet in the actual package will be needed.

The Agency will consider further the needed stability data for both the 325 mg and 81 mg Bufferin co-package products and at what point these data will need to be submitted to the Agency and provide BMS with a more definite response.

Discussion Point #3: Expiration date

To support a three-year expiration date for the co-package products, BMS will likely need to provide supporting real time data for the actual package for both doses.

CSO Overview of NDA 21-387

Pravigard PAC (pravastatin/aspirin co-package) 20/81, 20/325, 40/81, 40/325, 80/81 & 80/325 mg
September 13, 2002; Updated December 13, 2002, Updated March 6, 2003, Updated June 13, 2003

Sponsor: Bristol-Myers Squibb

Related IND:

Chemical Type & Therapeutic Potential: 4S

Background:

In summary, following the sponsor's initial co-package proposal (submission dated February 14, 2001), it was decided by Drs. Lipicky (DCRDP) and Orloff (Division of Metabolic and Endocrine Drug Products, DMEDP) that this application would be reviewed by DCRDP.

At the April 5, 2001 CMC pre-NDA meeting, the Division informed the sponsor that it would not be acceptable to rely on the aspirin OTC monograph for the CMC information in the co-package application and that full CMC information for aspirin would be expected.

A Pre-NDA meeting was held on May 8, 2001.

This application was presented before the Cardiovascular and Renal Drugs Advisory Committee on January 18, 2002. Although the Committee agreed overall that the combination meets the efficacy standard for approval, they raised two safety concerns with the application. The first concern was that the range of pravastatin doses for the co-packaged products is not adequate. The second concern was that combining pravastatin and aspirin would present a bleeding risk, as patients might not realize they are taking a product that contains aspirin and fail to discontinue the product prior to dental, surgical or other invasive procedures.

Because of time constraints, the application was withdrawn on April 9, 2002. It was resubmitted on May 9, 2002. The application was presented again before the Cardiovascular and Renal Drugs Advisory Committee on July 18, 2002 and the Committee recommended approval.

Medical Reviews

In his review dated April 2, 2002, Dr. Karkowsky made no recommendations as to approvability. He did include labeling recommendations should the July 18, 2002 Advisory Committee recommend approval.

Biopharmaceutics

In her review dated December 21, 2001, Dr. Dorantes granted the bio-waiver request for the lower strength of the buffered aspirin, agreed the dissolution specifications are adequate and that the proposed labeling is appropriate and adequate.

Pharmacology

Although the application did not contain a pharm/tox section, Dr. Resnick reviewed the labeling. His review dated January 18, 2002 contains his comments and recommendations.

Chemistry

In his review dated January 27, 2002, Dr. Zielinski recommended that the application not be approved because the overall establishment evaluation was WITHHOLD. After his review, the establishment evaluation has been revised to ACCEPTABLE. At the time the NDA was resubmitted, the chemistry review was reassigned to Dr. Mittal. The establishment had to be inspected again and the overall recommendation is, again, WITHHOLD. In his review dated March 6, 2003 stated that, from a CMC standpoint, the application is not approvable because of the Overall Recommendation of WITHHOLD by the Office of Compliance.

In his review dated June 6, 2003, Dr. Mittal recommended that the application be approved. The Compliance recommendation was changed to Acceptable after the Sponsor withdrew the site on June 3, 2003.

Environmental Assessment:

Adverse environmental effects are not expected. See FONSI dated November 14, 2001.

Trade Name Review: In their trade name review dated July 12, 2002, DMETS found the proprietary name, Pravigard PAC, acceptable. The trade name was re-reviewed and found acceptable on December 10, 2002. The trade name was re-reviewed again and found acceptable on March 31, 2003.

EER:

Overall compliance recommendation: Acceptable on June 4, 2003.

Methods Validation:

Not needed because no new methods are used.

Advisory Committee Meeting

Advisory Committee Meetings were held on January 18, 2002 and July 18, 2002. In the July 18, 2002 the Advisory Committee recommended that the application be approved.

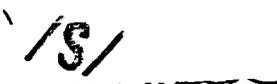
PM Summary

An approvable letter issued on March 7, 2003. BMS submitted final printed labeling on February 27, 2003, and again on May 30, 2003 with the change requested in the approvable letter and changes to the patient package insert that were requested in a FAX dated May 13, 2003, and it is acceptable.

In a July 20, 2001 e-mail, Dr. Rosemary Roberts concluded that the NDA does not trigger the Pediatric Rule, therefore, reference to the rule does not need to be included in the approval action letter when it issues.

Recently, it was determined that this application should have been listed as a 505(b)(2) application because of the aspirin component. The checklist and action letter have been change to reflect this.

To my knowledge, there are no issues that might prevent action on this NDA.


Zelda McDonald, Chief, Project Management Staff

98 pages redacted from this section of
the approval package consisted of draft labeling



MEMO

To: Douglas Throckmorton, MD
Director, Division of Cardio-Renal Drug Products
HFD-110

From: Scott Dallas, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Zelda McDonald
Project Manager, Division of Cardio-Renal Drug Products
HFD-110

Date: March 28, 2003

Re: ODS Consult 02-0114-2;
Pravigard PAC (Buffered Aspirin Tablets and Pravastatin Sodium Tablets);
NDA 21-387

This memorandum is in response to a March 10, 2003 request from your Division for a re-review of the proprietary name, Pravigard PAC and the final printed labeling.

The Division of Medication Errors and Technical Support (DMETS) has not identified any additional proprietary or established names that have the potential for confusion with Pravigard PAC since we conducted our reviews dated August 9, 2002 (ODS consult 02-0114) and December 5, 2002 (ODS consult 02-0114-1), that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

DMETS has reviewed the final printed container labels, carton labeling, patient information and package insert labeling located in the electronic document room with a letter date of February 27, 2003. The labels and

labeling were reviewed to determine if the labels and labeling were revised to address the safety issues *identified during our initial consult, and if there are any new safety issues. We have identified some of the* same safety issues that were noted during our first consult. DMETS has also identified additional safety issues that could cause possible medication errors. DMETS offers the following comments (previous and new recommendations) on areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (Blister Cards)

1. The gray and mustard color print on the 325 mg/20 mg and 81 mg/20 mg blister cards do not provide sufficient contrast, thus making the labels difficult to read. DMETS recommends increasing the prominence of the text on the labels with a different or darker color or some other means.
2. Each individual blister contains only one tablet. Therefore, DMETS recommends the word "Tablets" should be replaced with the word "Tablet".
3. Increase the size and/or prominence of the phrase "Take together".

B. CARTON LABELING

1. The carton uses the phrases "aspirin tablets" and "buffered aspirin tablets". This is inconsistent with the established name that appears on the blister card. DMETS recommends revising the carton label to be consistent with the blister card (i.e., buffered aspirin tablets).
2. The established name is presented as "(Buffered Aspirin and Pravastatin Sodium)". This implies the product is a combination tablet. DMETS suggests the proprietary name, established name, and dosage strength be presented as:

Pravigard PAC

Buffered Aspirin Tablets xxxmg

Pravachol (Pravastatin Sodium Tablets) xxmg

3. The approved proprietary name is "Pravigard PAC". The word "PAC" is presented at a 90 degree angle to the word "PRAVIGARD" and with a smaller font size, resulting in much less prominence. If the product is not known as PRAVIGARD PAC, but as PRAVIGARD it may imply the product is a combination tablet that contains two active ingredients. Physicians may not realize that a patient is required to take two tablets with different active ingredients, but assume each tablet contains both active ingredients. See comment B.2.
4. DMETS recommends the net quantity statement be relocated so it does not appear in conjunction with the established name.
5. The dosage strength for both the buffered aspirin tablets and pravastatin sodium tablets is presented within a boxed rectangular shape. Individuals may interpret the visual image of the boxed rectangular shape to represent a tablet. This interpretation would also imply each tablet contains both active ingredients. We suggest the deletion of any visual image that may suggest that each tablet contains both active ingredients.

6. Revise the "See Package Insert for Full Prescribing Information" statement to read "Usual Dosage: *Take one buffered aspirin tablet and one Pravachol® (pravastatin sodium tablet) daily at the same time*".
7. The statements: "Warning: Children and teenagers should not use aspirin for chicken pox or flu symptoms..." and "Alcohol Warning: If you consume 3 or more..." are statements required on OTC product labeling. Please delete.
8. Insert a warning statement to reduce the risk that patients could take duplicate aspirin and/or other pravastatin products. For example, include a statement, which conveys that "Pravigard PAC" contains the medications Buffered Aspirin and Pravachol. If you are taking Pravachol (pravastatin sodium) or products containing aspirin, consult your physician or pharmacist about continued use of those medications before you start taking Pravigard PAC tablets.

C. PACKAGE INSERT LABELING

1. The proprietary name is not presented in a consistent manner through the text of the package insert. DMETS recommends the proprietary name should only be referred to as Pravigard PAC and not Pravigard.
2. See comment B.2. concerning the proper presentation of the established name.
3. In the section titled "How Supplied", DMETS recommends the description of the two strengths of buffered aspirin tablets be presented in the same format as the description of Pravachol tablets.

D. PATIENT INFORMATION

1. See comments B.2. and B.8.
2. In the section titled "What is PRAVIGARD PAC?" it reads "PRAVIGARD PAC has 2 medicines in it, buffered aspirin and pravastatin sodium (PRAVACHOL®). DMETS recommends inclusion of the word "tablets". This will help clarify to the patient the product contains buffered aspirin tablets and pravastatin sodium tablets.
3. In the section titled "How should I take PRAVIGARD PAC?" it reads, "The usual dose of PRAVIGARD PAC is 1 aspirin tablet with..." DMETS recommends inclusion of the word buffered, so the statement reads "1 buffered aspirin tablet".

The Division of Medication Errors and Technical Support (DMETS) considers this a final name review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

DMETS would also like the opportunity to re-review the labels and labeling, since this consult has identified a number of safety issues that could cause possible medication errors.

If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-3242.

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/s/

Scott Dallas
3/31/03 01:08:49 PM
PHARMACIST

Denise Toyer
3/31/03 02:18:10 PM
PHARMACIST

Carol Holquist
3/31/03 03:05:43 PM
PHARMACIST

MEMO

To: Douglas Throckmorton, MD
Director, Division of Cardio-Renal Drug Products
HFD-110

From: Kevin Dermanoski, RPh
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Denise Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Zelda McDonald
Project Manager, Division of Cardio-Renal Drug Products
HFD-110

Date: December 5, 2002

Re: ODS Consult 02-0114-1; Pravigard PAC
(Pravastatin Sodium Tablets 20 mg, 40 mg, and 90 mg) and
(Buffered Aspirin Tablets 81 mg and 325 mg)
NDA 21-387

This memorandum is in response to a November 18, 2002 request from your Division for a re-review of the proprietary name, Pravigard PAC.

The Division of Medication Errors and Technical Support has not identified any additional proprietary or established names that have the potential for confusion with Pravigard PAC since we conducted our initial review on August 9, 2002 (ODS Consult 02-0114). Therefore, we have no objections to the use of this proprietary name. Carton and package insert labeling and container labels were not submitted for re-review. DMETS refers to the labeling, packaging and safety related issues identified in the August 9, 2002 review.

ODS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam, Project Manager, at 301-827-3242.

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/s/

Denise Toyer
12/10/02 09:54:52 AM
PHARMACIST

Carol Holquist
12/10/02 10:34:57 AM
PHARMACIST

Office of Drug Safety
Division of Medication Errors and Technical Support
(DMETS, HFD-420)
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 9, 2002

NDA# 21-387

NAME OF DRUG: Pravigard PAC
(Pravastatin Sodium Tablets, 20 mg, 40 mg, and 80 mg)
(Buffered Aspirin Tablets, 81 mg and 325 mg)

NDA HOLDER: Bristol-Myers Squibb Company

I. INTRODUCTION:

This review is in response to a request from the Division of Cardio-Renal Drug Products, to review the proprietary name Pravigard PAC, regarding potential name confusion with other proprietary/established drug names. The 30-day patient supply unit-of-use container labels, carton labeling, and package insert labeling were reviewed for possible interventions to minimize medication errors. The Unimatic unit dose (for institutional use) labels and carton labeling however, were not part of the submission, and therefore not reviewed.

PRODUCT INFORMATION

Pravigard PAC is the proposed name for the co-packaging of Pravachol (Pravastatin Sodium Tablets) with buffered aspirin tablets. Pravigard PAC contains individual daily doses of buffered aspirin 81 mg tablets or 325 mg tablets packaged with either Pravachol 20 mg, 40 mg, or 80 mg tablets for oral administration. Pravigard PAC is indicated

Pravigard PAC is designed to be a convenience package to facilitate the daily administration of its individual components. Within a blister pack, an aspirin tablet and a pravastatin sodium tablet are presented side-by-side in a separate cavity in a cold-form foil blister card. Each cold-form foil blister card will contain 5 aspirin tablets and 5 pravastatin sodium tablets, and the carton will contain 6 blister cards. The carton is a unit-of-use package containing a 30-day supply of medication. The outer carton includes a location for the pharmacy to place a label for individual patients.

The unit-dose packs are available in cartons containing either 50 buffered aspirin 81 mg or 325 mg packed with either 50 Pravachol 40 mg or 80 mg tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to "Pravigard PAC" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.⁴ The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies, consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Pravigard PAC. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified several proprietary names of concern with look-alike or sound-alike similarities to Pravigard PAC. These are Periogard, Avagard, Provigil, Pravachol, and Radguard (see Table I on page 4).
2. DDMAC expressed no concerns regarding promotional aspects of Pravigard PAC.

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table I: Potential Sound-Alike and/or Look-Alike Names Identified by DMETS Expert Panel for Pravigard PAC

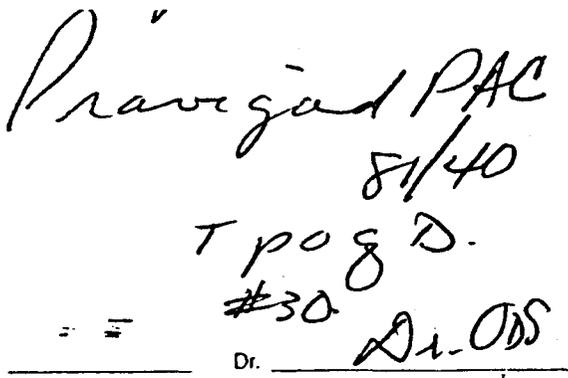
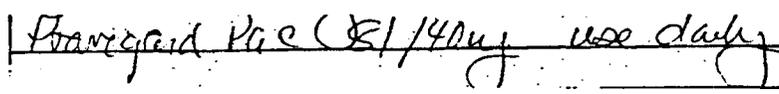
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Pravigard PAC	Buffered Aspirin 81 mg or 325 mg Tablets Pravachol (Pravastatin Sodium) 20 mg, 40 mg, or 80 mg Tablets	One pair of tablets daily. (aspirin & pravastatin) Dose Range: 81 mg/20 mg, 81 mg/40 mg, 81 mg/80 mg, 325 mg/20 mg, 325 mg/40 mg, 325 mg/80 mg	
Periogard	Chlorhexidine Gluconate 0.12% Solution	Twice daily mouth rinsing using 15 mL for 30 seconds, expectorate, not to be swallowed.	SA/LA
Avagard	Alcohol 61% w/w and Chlorhexidine 1% w/w Solution	For health-care personnel hand wash. For surgical scrub.	SA/LA (OTC)
Pravachol	Pravastatin Sodium 10 mg, 20 mg, 40 mg, and 80 mg Tablets	Dose ranges from 10 mg to 80 mg taken once daily.	S/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) ***ANDA not yet approved.			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

DMETS conducted three studies within FDA for the proposed proprietary name Pravigard PAC, to determine the degree of confusion with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 108 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. The study included an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and a prescription for Pravigard PAC (see page 5). These prescriptions were optically scanned and an inpatient order and an outpatient prescription were delivered to a random sample of health professionals via e-mail. In addition, an outpatient order was recorded on voice mail. The voice mail message was then sent to a random sample of health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretation of the orders via e-mail to the medication error staff.

Table III: Pravigard PAC Prescription Samples

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p>  <p><u>Inpatient RX:</u></p> 	<p>The next prescription is for Pravigard PAC, 81 mg/40 mg, take one tablet daily, and dispense thirty.</p>

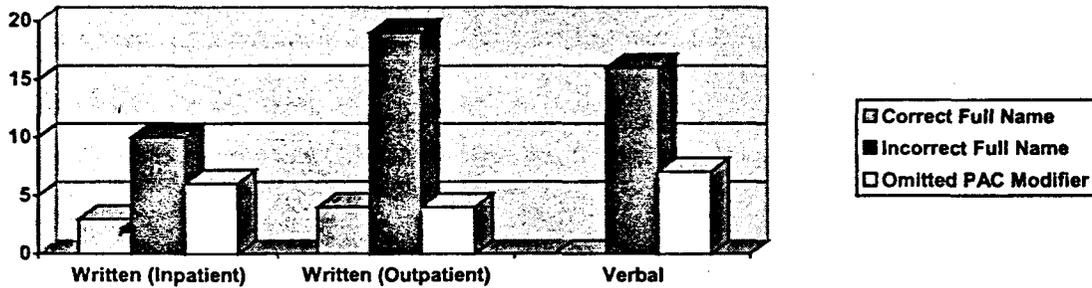
2. Results of the Pravigard PAC studies are summarized below.

Table II: Results of Pravigard PAC Studies

Study	# Of Participants	Total # of Responses	*Correctly Interpreted Full Name	*Incorrectly Interpreted Full Name	**Omitted PAC Modifier
Written Inpatient	33	19 (58%)	3 (16%)	10 (53%)	6 (31%)
Written Outpatient	39	27 (69%)	4 (15%)	19 (70%)	4 (15%)
Verbal	36	23 (64%)	0 (100%)	16 (70%)	7 (30%)
Total	108	69 (64%)	7 (10%)	45 (65%)	17(25%)

* Full Name = "Pravigard PAC."

** Omitted modifier = "PAC" not included in the response.



Three (16%) of the 19 respondents in the written inpatient study interpreted the name correctly. The 10 incorrect interpretations were Pravegard PAC (7), Pranegard PAC (1), Pravegard PAK (1), and Pravigaid PAC (1). Six (31%) of the 19 respondents omitted the "PAC" modifier of the name and responded with solely a Pravigard interpretation. Four (66%) of the 6 respondents who omitted the modifier interpreted Pravigard correctly. The 2 incorrect interpretations were "Pravegard."

Four (15%) of the 27 respondents in the written outpatient study interpreted the name correctly. The 19 incorrect responses were Pravigad PAC (12), Pravigal PAC (2), Pravaquid PAC (1), Pravegard PAC (1), Pravigand PAC (1), Pravigerd PAC (1), and Pravuquid PAC (1). Four (15%) of the respondents omitted the "PAC" modifier of the name and responded only with a Pravigard interpretation. None (100%) of the 4 respondents who omitted the modifier interpreted Pravigard correctly. The incorrect interpretations were Pravigad (3) and Pravigod (1).

None of the 23 respondents in the verbal prescription study interpreted the name correctly. The 16 incorrect responses were Pravigard Pack (3), Pravigard Pak (2), Provaguard Pack (2), Pravigard Pack (2), Pravigard Pak (1), Pravigard Pack (1), Provagard PAC (1), Provagard PAK (1), Provaguard Pack (1), Provaguard Packet (1), and Pravigard Pack (1). Seven (30%) of the respondents omitted the "PAC" modifier of the name and responded with only a Pravigard interpretation. None (100%) of the 7 respondents who omitted the modifier interpreted Pravigard correctly. The incorrect interpretations were Provagard (3), Pravigard (2), and Praviguard (2).

C. SAFETY EVALUATOR RISK ASSESSMENT

Name Assessment

The products identified as having the greatest potential for name confusion with Pravigard PAC are Periogard, Avagard, — and Pravachol.

Periogard is an oral rinse containing 0.12% chlorhexidine gluconate indicated for use between dental visits for the treatment of gingivitis. Periogard and Pravigard may look or sound similar depending upon how they are scripted (see page 7) or pronounced. Particularly if the provider fails to use the "PAC" modifier in prescription orders. Each name contains nine characters, begins with "P" and has the same final syllable "gard." The second syllable of both names is similar ("ri vs. "vi") and may contribute to the look or sound-alike similarities as well. However, Periogard contains 4 syllables (vs. 3 for Pravigard), and the "o" sound helps distinguish the name when pronounced. The products also differ in other ways that reduce the potential for medication errors. Periogard is available in only one strength (0.12%) while Pravigard PAC will be available in 6 different combinations (81 mg/20 mg, 81 mg/40 mg, 81 mg/80mg, 325 mg/20 mg, 325 mg/40 mg, and 325/80 mg). Prescriptions for Pravigard PAC will require a strength when prescribed. The products also differ in dosage form (solution for dental rinse vs. tablet) and dosing frequency (twice daily vs. once daily). Overall, these product differences reduce the potential for medication error due to name confusion between Periogard and Pravigard PAC.

Periogard

Periogard

Pravigard

Pravigard

Avagard solution contains 69% Alcohol w/w and Chlorhexidine 1% w/w for use as a surgical scrub and health care personnel hand wash. Avagard and Pravigard may look-alike depending upon how they are scripted, particularly if the modifier "PAC" is omitted in a prescription (see below). Avagard and Pravigard may also sound alike. Both are three syllable names that end with "gard" and share the letters "av" in their first syllable. The "ava" in Avagard may sound like the "avi" in Pravigard. The sound-alike similarities increase if the "P" in Pravigard is not heard. There are however, product differences that reduce the chance for medication errors. Avagard is available in only one concentration. Pravigard PAC however, is available in six combination strengths and therefore a dosage must be included in the prescription. In addition, Avagard and Pravigard PAC differ in the frequency of administration (as needed vs. once daily), dosage form (solution vs. tablet), product packaging (bottle vs. blister-pack), legend status (OTC vs. prescription) and route of administration (topical vs. oral). Furthermore, Avagard will mainly be used by healthcare personnel in hospital or office settings. Overall, the product differences reduce the potential for medication errors between Avagard and Pravigard PAC due to name confusion.

Avagard

Avagard

Pravigard

Pravigard

Pravigard

Pravigard

Pravachol is an antilipemic drug used to reduce low-density lipoprotein and total cholesterol levels in hypercholesterolemia and to prevent coronary events. Pravachol tablets will be co-packaged with buffered aspirin products in Pravigard PAC. Pravachol and Pravigard may sound-alike depending upon pronunciation particularly if the modifier "PAC" is omitted from the prescription order. Eighteen (26%) of the respondents in the prescription studies failed to include the modifier 'PAC' when interpreting the name. Both Pravigard and Pravachol are 3-syllable names that begin with "Prav" and share second syllables that sound alike ("va" and "vi"). In addition, the last syllable of each name begins with a hard consonant sound ("ch" and "g") that may sound alike. The endings however ("ol" and "rd"), help distinguish the names when pronounced. Factors that increase the potential for error include: both products are taken once daily, oral tablets, and both have partial common elements in their dosage expression (20 mg, 40 mg, and 80 mg is expressed in both products). There are also product differences that reduce the potential for medication errors. Pravigard PAC requires that the strength of two tablets be expressed (81 mg or 325 mg of buffered aspirin and 20 mg, 40 mg, or 80 mg of Pravachol). Pravachol prescriptions however, only require that one strength be noted (20 mg, 40 mg, or 80 mg). In addition, Pravigard PAC will be marketed in a unique packaging configuration. Pravigard PAC will be packaged in a 30-day supply, unit-of-use blister pack whereas Pravachol is packaged in bottles of 100 and unit dose. Although, Pravachol is one of the components of Pravigard PAC and the names sound similar; the differences in the endings, packaging configuration, and the dosage expression decrease the potential for medication errors due to name confusion.

Packaging Safety Issues

In the review of the container labels, carton and insert labeling of Pravigard PAC, DMETS focused on safety issues relating to possible medication errors. We identified areas of possible improvement, which might minimize potential user error.

1. When comparing the 6 different Pravigard PAC cartons side-by-side, it is difficult to distinguish them. This increases the risk of dispensing errors by selection of the wrong strength. The labeling should be revised to distinguish each Pravigard PAC product by using contrasting colors, boxing, or some other means.
2. It is difficult for patients to identify separate daily doses using the proposed container labels (cold-form foil blister cards). This increases the potential for patients to take a wrong combination of tablets. For example, a patient may take either two aspirin or two pravastatin tablets instead of one of each. The container label needs reformatting to reduce this potential for error. This includes inserting a statement "Day 1, Day 2, through Day 5" over each day's dose and inserting a horizontal perforated line that separates each daily dose.
3. The "Dosage and Administration" section of the package insert states "the recommended daily dose of buffered aspirin is either 81 mg or 325 mg coadministered with a daily dose of Pravachol 40 mg." However, there are no guidelines that include criteria to base prescribing the aspirin 81 mg vs. the aspirin 325 mg dose. The package insert should be revised to provide practitioners that information.

4. Patients may receive products for Pravachol or Aspirin prescribed by one practitioner while receiving Pravigard PAC prescriptions from an alternate practitioner. This presents the risk of duplicative and overdosed pravastatin and/or aspirin therapy. The availability of aspirin products without prescription further increases the risk for aspirin toxicity. To reduce this risk, a warning statement should be added to the carton labeling and package insert labeling that conveys: "patients should be made aware that Pravigard PAC contains the same ingredient in Pravachol (pravastatin) tablets and also contains aspirin." A similar warning statement using language for patients should be included in the patient information sheets (questions & answers).

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. CONTAINER LABEL (Cold-form Foil Blister Card)

1. The 5 daily doses are not clearly distinguished on the cold-form foil blister card. Patients may take two tablets daily proceeding down each column instead of horizontally across by row. (For example, patients may take two Pravachol tablets instead of a Pravachol and buffered aspirin tablet.) To reduce this potential for error revise as follows.
 - Separate each daily dose by inserting the heading "Day 1," "Day 2," etc. above each dose
 - Insert a perforated line between each dose
 - Increase the length and/or prominence of the horizontal arrow
 - Increase the size and/or prominence of the phrase "Take together."
2. The dosage form in the established name of each drug product should read "Tablet." Revise accordingly.

B. CARTON LABELING

1. The established name listed as "xx mg buffered aspirin and xx mg pravastatin sodium" implies the product is a combination formulation of the two ingredients in a single tablet. Consistent with other marketed co-packaged dosage form products, the established drug names should appear separately. Revise to read as follows:

Each PAC contains:
Buffered Aspirin tablets (81 mg or 325 mg)
Pravachol (pravastatin) tablets (20 mg, 40 mg, or 80 mg).

2. When comparing the 6 different Pravigard PAC cartons side-by-side, it is difficult to distinguish them. This increases the potential of medication errors by selection of the wrong strength of Pravigard PAC. Revise to distinguish each Pravigard PAC product by using contrasting colors, boxing, or some other means.
3. Revise the statement "Buffered Aspirin and Pravachol should be taken at the same time" to read: "Usual Dosage: Take one buffered aspirin tablet and one Pravachol (pravastatin) tablet provided in the PAC daily at the same time."

4. The statements: "Warning: Children and teenagers should not use aspirin for chicken pox or flu symptoms..." and "Alcohol Warning: If you consume 3 or more...." are statements required on OTC product labeling. Please delete.
5. Insert a warning statement to reduce the risk that patients could take duplicate aspirin and/or other pravastatin products. For example, include a statement, which conveys that "Pravigard PAC" contains the medications Pravachol and Aspirin. If you are taking Pravachol (pravastatin) or products containing aspirin, consult your physician or pharmacist about continued use of those medications before you start taking Pravigard PAC tablets."

C. INSERT LABELING

1. The "How Supplied" section mentions _____ We have not received the labels and labeling for review and comment.
2. To reduce the risk of duplicative and overdosed aspirin or pravastatin therapy, a warning statement should be added to the package insert that conveys: "patients should be made aware that Pravigard PAC contains the same ingredient in Pravachol (pravastatin) tablets and also contains aspirin."
3. Amend the package insert to include the patient information (question & answer sheets).
4. Insert statements that provide practitioners criteria for prescribing a recommended dose of aspirin 81 mg vs. aspirin 325 mg.

D. PATIENT INFORMATION (Question & Answer Sheets)

1. The word _____ in "Q.2" should appear in uppercase to provide a greater prominence. Revise accordingly.
2. Insert a warning statement to reduce the risk that patients could take duplicate aspirin and/or other pravastatin products. For example, include a statement that conveys "Pravigard PAC contains the medications Pravachol and Aspirin. If you are taking Pravachol (pravastatin) or products containing aspirin, consult your physician or pharmacist about continued use of those medications before you start taking Pravigard PAC tablets."

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, Pravigard PAC.
- B. DMETS recommends implementation of the labeling revision outlined in Section III of this review.

This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval date of this NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/s/

Kevin Dermanoski, RPh Date
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/s/

Denise Toyer, PharmD Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Kevin Dermanoski
8/14/02 02:32:03 PM
PHARMACIST

Denise Toyer
8/14/02 02:52:20 PM
PHARMACIST

Jerry Phillips
8/14/02 02:57:34 PM
DIRECTOR

REQUEST FOR CONSULTATION

(Division/Office):
Associate Director, Medication Error Prevention
Office of Post Marketing Drug Risk Assessment, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM: HFD-110

DATE: 5/20/02	IND NO.	NDA NO. 21-387	TYPE OF DOCUMENT: RS (resubmission of NDA)	DATE OF DOCUMENT 5/8/02
NAME OF DRUG: pravastatin/aspirin co-packaged product		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG: 4S	DESIRED COMPLETION DATE: See below

NAME OF FIRM: Bristol-Myers Squibb Company

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
-----------------------------------	--------------------------------------

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Please review the Sponsor's proposed tradename for this co-packaged product (Pravigard PAC).

Although the PDUFA goal date for this application is March 9, 2003, the Agency expects to take an action much sooner, as this is a resubmission of the original NDA. At this time, the Agency plans to act on this NDA within a few weeks/months of the July 18th Advisory Committee meeting for this application. A response to our request for a tradename review of this product would be appreciated by the end of August, beginning of September 2002, or sooner, if possible.

PDUFA DATE: See above..

ATTACHMENTS: Draft Package Insert & PPI (marked up & clean versions), Container and Carton Labels

SIGNATURE OF REQUESTER: Colleen LoCicero	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Colleen LoCicero
5/21/02 10:31:02 AM

REQUEST FOR CONSULTATION

(Division/Office):

Associate Director, Medication Error Prevention
Office of Post Marketing Drug Risk Assessment, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM: HFD-110

DATE 3/12/02	IND NO.	NDA NO. 21-387	TYPE OF DOCUMENT Request for tradename review	DATE OF DOCUMENT 2/14/02
NAME OF DRUG Pravastatin/aspirin co-package		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE See below

NAME OF FIRM: Bristol-Myers Squibb

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: The user fee goal date for this application is 4/22/02. However, provided the Sponsor does not withdraw the application first, the Office Director plans to "not approvable" the application on 4/22 and informed the Sponsor of this on 3/8/02. At the recommendation of Ms. Sammie Beam, the Division is forwarding the tradename review request at this time, despite the uncertainty of the status of the application. The Division will keep OPSS informed of the application's status (i.e., if the application is withdrawn, etc.) in an effort to avoid any unnecessary efforts on the part of OPSS.

The container labels and tradename were submitted on 2/14/02, while the PI was included in the original application, submitted June 2001. None of these documents were submitted electronically and will be forwarded to OPSS in hardcopy. If you have any questions, please contact Colleen LoCicero.

PDUFA DATE: 4/22/02

ATTACHMENTS: none. Hard copies of container labels, proposed tradename, and PI will be forwarded to OPSS.

NATURE OF REQUESTER Colleen LoCicero	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Colleen LoCicero
3/12/02 02:38:57 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 16, 2002

TO: Douglas Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products
HFD-110

VIA: Zelda McDonald, Regulatory Health Project Manager,
Division of Cardio-Renal Drug Products
HFD-110

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for pravastatin/aspirin tablets,
NDA 21-387

The following are minor revisions to sections of the September 30, 2002, DSRCS review of patient labeling for pravastatin/aspirin tablets, NDA 21-387. The revisions reflect discussion that occurred at the October 11, 2002, labeling meeting.

Who Should Not Take Tradename?

1

1

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the approval package consisted of draft labeling

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/s/

Jeanine Best
10/16/02 11:24:31 AM
CSO

Anne Trontell
10/16/02 06:04:23 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 30, 2002

TO: Douglas Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products
HFD-110

VIA: Zelda McDonald, Regulatory Health Project Manager,
Division of Cardio-Renal Drug Products
HFD-110

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for pravastatin/aspirin tablets,
NDA 21-387

The labeling that follows is a revised Patient Package Insert for pravastatin/aspirin tablets, NDA 21-387. It has been reviewed by our office and by DDMAC. We have simplified wording, made it consistent with the PI, removed promotional language and other unnecessary information, and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Outstanding questions or comments for the review division appear in the text and are bolded, italicized, and underlined. A Word version of this PPI was sent to the division in an earlier E-mail. Please let us know if you have any questions.

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the approval package consisted of draft labeling

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/s/

Jeanine Best
9/30/02 11:12:17 AM
CSO

Anne Trontell
10/1/02 05:45:48 PM
MEDICAL OFFICER

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: 609-252-6000
Attention: Mr. Porter Lane
Company Name: BMS
Phone: 609-252-4722
Subject: Labeling Change
Date: 5/13/03
Pages including this sheet: 2
From: Zelda McDonald
Phone: 301-594-5328
Fax: 301-594-5494

Table 6, bottom row - font size needs to be made consistent with the rest of the table.

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the approval package consisted of draft labeling

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FOOD AND DRUG ADMINISTRATION**



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Transmitted to FAX Number: 609-252-6000

Attention: Porter Layne, Ph.D.

Company Name: BMS

Phone: 609-252-4722

Subject: Confirmation of 10/31/02 Telecon

Date: 10/22/02

Pages including this sheet: 2

From: Zelda McDonald
Phone: 301-594-5333
Fax: 301-594-5494

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Confirmation of Telecon

Drug: NDA 21-387
Sponsor: Bristol-Myers Squibb
Our Request
Date Confirmation Faxed: October 22, 2002
Type: Labeling
Classification: C

Telecon Date: October 31, 2002
Telecon Time: 3:00 pm
Location: Conference Room "F," Fifth Floor, Woodmont Office Complex 2
1451 Rockville Pike, Rockville MD

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
Douglas C. Throckmorton, M.D.	Director, Division Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
Zelda McDonald	Regulatory Health Project Manager, HFD-110
David Orloff, M.D.	Director, Division Metabolic & Endocrine Drug Products, HFD-510
Mary Parks, M.D.	Medical Officer, HFD-510
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Angelica Dorantes, Ph.D.	Pharmacokineticist, HFD-860
Andrew Haffer	Senior Regulatory Reviewer, Division Drug Marketing Advertising & Communication, HFD-42
Toni Hepp Piazza	Supervisory Pharmacist, Division Surveillance, Research & Communication, HFD-410

Confirmation of Meeting

Drug: NDA 21-387
Sponsor: Bristol-Myers Squibb
Date Meeting Requested: July 27, 2002
Date Confirmation Faxed: August 12, 2002
Type: Guidance – Follow-up to July Advisory Committee Meeting
Classification: C

Meeting Date: August 21, 2002
Meeting Time: 11:30 am
Location: Conference Room "F," Fifth Floor, Woodmont Office Complex 2
1451 Rockville Pike, Rockville MD

FDA Participants:

Robert Temple, M.D.	Director, Office of New Drug Evaluation I, HFD-101
Douglas C. Throckmorton, M.D.	Director, Cardio-Renal Drug Products Division, HFD-110
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Angelica Dorantes, Ph.D.	Pharmacokineticist, HFD-860
Zelda McDonald	Regulatory Health Project Manager, HFD-110

Note:

When you arrive at the Security Desk at the Woodmont II building, please have Security telephone our main number, 301-594-5300, to announce your arrival. Please be prepared for a security check of all items being carried into the building.



**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



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Rockville, MD 20852

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Transmitted to FAX Number: 609-252-6000

Attention: Porter Layne, Ph.D.

Company Name: BMS

Phone: 609-252-4722

Subject: Confirmation of 8/28/02 Meeting

Date: 8/12/02

Pages including this sheet: 2

From: Zelda McDonald
Phone: 301-594-5333
Fax: 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

dfe

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FOOD AND DRUG ADMINISTRATION



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Transmitted to FAX Number: (609) 818-5831
Attention: Melody Brown
Company Name: Bristol-Myers Squibb
Phone: (609) 818-3243
Subject: pravastatin/aspirin co-package CMC information
Date: 5/25/01
Pages including this sheet: 2
From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Melody,

In follow up to our April 5, 2001 CMC pre-NDA meeting for [redacted] (pravastatin/aspirin co-package), I am faxing a summary, as drafted by Dr. Srinivasachar, of the CMC information requested for the NDA. He has differentiated between that which is requested for the original submission and that which can be submitted later.

This is based on the assumption that the NDA will provide for pravastatin 40 mg co-package products only. If the application provides for additional co-package products (e.g., 20 mg pravastatin/81 mg aspirin and 20 mg pravastatin/325 mg aspirin), the requested CMC information will be revised.

Regards,
Colleen

CMC Information Requested for Pravachol/Bufferin Co-Package NDA

The following information should be provided for Pravachol drug substance and drug product at the time of NDA submission:

Pravachol Drug Substance:

Summary of approved manufacturing sites
Brief description of synthesis or a reference to a DMF, if appropriate
Regulatory Specifications
Summary of stability data or reference to a DMF, if appropriate

Pravachol Drug Product:

Summary of approved manufacturing sites
Components/Composition
Summary of manufacturing method
Regulatory Specifications
Summary of analytical methods
Approved container/closures
Stability data

Please Note: the above information is being requested, in addition to cross reference to the approved NDA for Pravachol, as an aid to the reviewer.

The following information should be provided for Bufferin, 325 mg, at the time of NDA submission:

Complete CMC information on both drug substance and drug product, including stability in the currently marketed container/closures.

For Bufferin, 81 mg:

As much CMC on drug substance/drug product as available at the time of NDA submission.
Complete CMC information in an amendment within 3 months of NDA submission.

Stability Data for Co-Package Product:

Pravachol 40 mg/Bufferin 325 mg: 6 months accelerated data and all available long-term data at time of NDA submission

Pravachol 40 mg/Bufferin 81 mg: 3 months accelerated data either at time of NDA submission or in an amendment within 3 months. All available long term data.

MODE = MEMORY TRANSMISSION

START=AUG-22 15:46

END=AUG-22 15:47

FILE NO. #626

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	*	916092526000	004/004	00:00:44

-FDA, CDER, OND, ODEI, DCRDP -

***** -CARDIO RENAL - ***** 301 594 5494- *****

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Transmitted to FAX Number: 609-252-6000

Attention: Porter Layne, Ph.D.

Company Name: BMS

Phone: 609-252-4722

Subject: Minutes of 8/21/02 Telecon

Date: 8/22/02

Pages including this sheet: 4

From: Zelda McDonald

Phone: 301-594-5333

Fax: 301-594-5494

YOU ARE RESPONSIBLE FOR NOTIFYING US OF ANY SIGNIFICANT DIFFERENCES IN UNDERSTANDING YOU MAY HAVE REGARDING THE MEETING OUTCOMES (AS REFLECTED IN THE MINUTES).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

dfs
6/5/02

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Transmitted to FAX Number: (609) 252-6000

Attention: Porter Layne, Ph.D.

Company Name: Bristol-Myers Squibb

Phone: (609) 252-4722

Subject: teleconference minutes

Date: 6/5/02

Pages including this sheet: 5

From: Colleen LoCicero

Phone: 301-594-5332

Fax: 301-594-5494

Porter,

The minutes of our May 9, 2002 teleconference regarding NDA 21-387 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the teleconference outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

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Transmitted to FAX Number: (609) 252-6000

Attention: Porter Layne, Ph.D.

Company Name: Bristol-Myers Squibb Company

Phone: (609) 252-4722

Subject: meeting minutes

Date: 4-9-02

Pages including this sheet: 6

From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Porter,

The minutes of our March 8, 2002 meeting regarding NDA 21-387 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

dfw X

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Transmitted to FAX Number: (609) 252-6000
Attention: Porter Layne, Ph.D.
Company Name: Bristol-Myers Squibb
Phone: (609) 252-4722
Subject: teleconference minutes
Date: 1-28-02
Pages including this sheet: 3
From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Dear Porter,

The minutes of our January 11, 2002 teleconference regarding NDA 21-387 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the teleconference outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

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Transmitted to FAX Number: (609) 252-6000

Attention: Porter Layne, Ph.D.

Company Name: Bristol-Myers Squibb

Phone: (609) 252-4722

Subject: teleconference minutes

Date: 1-30-02

Pages including this sheet: 4

From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Porter,

The minutes of our January 8, 2002 teleconference regarding NDA 21-387 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the teleconference outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

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Transmitted to FAX Number: (609) 252-6000

Attention: Porter Layne, Ph.D.

Company Name: Bristol-Myers Squibb

Phone: (609) 252-4722

Subject: teleconference minutes

Date: 1-8-02

Pages including this sheet: 3

From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Dear Porter,

The minutes of our December 11, 2001 teleconference regarding NDA 21-387 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the teleconference outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

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Transmitted to FAX Number: (609) 252-6000

Attention: Porter Layne, Ph.D.

Company Name: Bristol-Myers Squibb

Phone: (609) 252-4722

Subject: teleconference minutes

Date: 11-13-01

Pages including this sheet: 4

From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Porter,

The minutes of our October 24, 2001 teleconference regarding NDA 21-387 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the teleconference outcomes (as reflected in the minutes). Please let me know you received this fax.

Dr. Lipicky tells me it is still too early to commit to a specific date for the Advisory Committee discussion. I will keep asking and keep you informed.

Regards,
Colleen

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Transmitted to FAX Number: (609) 252-6000

Attention: Porter Layne, Ph.D.

Company Name: Bristol-Myers Squibb

Phone: (609) 252-4722

Subject: meeting minutes

Date: 6/4/01

Pages including this sheet: 6

From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Porter,

The minutes of our May 8, 2001 meeting regarding [redacted] (a pravastatin/aspirin co-package application) accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Transmitted to FAX Number: (609) 818-5831
Attention: Melody Brown
Company Name: Bristol-Myers Squibb
Phone: (609) 818-3243
Subject: meeting minutes
Date: 5-3-01
Pages including this sheet: 5
From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Melody,

The minutes of our April 5, 2001 meeting regarding a pravastatin/aspirin co-package product accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached lists for 27,201-82/REGRESS and CV123-234 prava-aspirin interaction study

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Fred T. Fiedorek, M.D.		TITLE Vice-President, Metabolics Clinical Development and Life Cycle Management	
FIRM/ORGANIZATION Bristol-Myers Squibb Company			
SIGNATURE 		DATE 18 May 2001	

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

PRAVASTATIN/ASPIRIN CO-PACKAGED PRODUCT

FINANCIAL DISCLOSURE INFORMATION

Much of the financial disclosure information required for this NDA has been previously submitted in various Pravachol[®] NDA 19-898 supplements. These SNDA's have been approved and cover the following studies which are also included in the metanalysis presented in this NDA. Please refer to NDA 19-898 for this information:

<u>Study No./Designation</u>	<u>Supplement No.</u>	<u>Date Submitted</u>	<u>Date Approved</u>
27,201-26/PLAC II 27,201-50/PLAC I	S-029	March 18, 1999	January 18, 2000
27,201-67/CARE	S-026	March 18, 1999	January 18, 2000
27,201-95/LIPID	S-032	April 13, 1999	February 10, 2000

Another study included in the metanalysis is 27,201-82/REGRESS. The results of this study were included in NDA 19-898/S-013 which was submitted May 19, 1995 and approved March 22, 1996. Financial disclosure information was not collected at the time this study was conducted (December, 1989 to December, 1993). Recent attempts were made to contact several investigators and subinvestigators who participated in this study. They were all located in the Netherlands during the study. This resulted in responses from only 9 of the participants, all of which indicated no disclosable financial information. However, Bristol-Myers Squibb Company, based on company policy and available information, is able to certify that it did not enter into any financial arrangements with any of the REGRESS investigators and subinvestigators whereby the value of their compensation could be affected by the outcome of the study. In addition, Bristol-Myers Squibb Company, based on available information, can also certify that none of the listed REGRESS investigators and subinvestigators held a proprietary interest in the product. These two financial disclosure parameters are the only ones required for studies completed prior to February 2, 1999 (since the stock of Bristol-Myers Squibb Company is publicly traded). Based on the above information we are including a form FDA 3454 for the REGRESS study.

Financial disclosure information for the pravastatin and aspirin drug interaction study, CV123-234, is also attached.

27,201-82.PRAV
December 21, 1994 - FINAL REPORT

Supplemental Table 3.2
Investigators, Subinvestigators, and the Study Centers
Protocol 27,201-82

Central Coordinating Center: Interuniversity Cardiology Institute of The Netherlands
Investigator: Frits L. Meijler, MD, PhD
Subinvestigator: _____

Study Center & Initials: AMC - University of Amsterdam - AG
Investigators: A.J. Dunning, MD, PhD
Gerard Hoedemaker, MD
Ron J. P. Peters, MD

Study Center & Initials: VU - Free University of Amsterdam - AV
Investigators: Carel C. de Cock, MD, PhD
Michel A. Galjee, MD
Henry P.J. de Haan, MD
Jan P. Roos, MD, PhD

Study Center & Initials: Medical Center Alkmaar - AR
Investigators: Joost A. Henneman, MD
Jacob H. Ruiter, MD

Study Center & Initials: Delft - Reinier de Graaf Gasthuis - DE
Investigator: Adrianus J.A.M. Withagen, MD

Study Center & Initials: Enschede - Medisch Spectrum Twente - EN
Investigators: Johannes W. Louwerenburg, MD
Gilles P. Molhoek, MD

Study Center & Initials: University of Groningen - GR
Investigators: Kong I. Lie, MD, PhD
Adrianus J. van Boven, MD

Subinvestigator: _____

PRISM:STATUS-APPROVED VEIN: -1.0, CONSULT CONSULT VEIN

IDIS:910046394 VD-V1.0, C-V1.0



27,201-82.PRAV
December 21, 1994 - FINAL REPORT

Supplemental Table 3.2 (continued)
Investigators, Subinvestigators, and the Study Centers
Protocol 27,201-82

Study Center & Initials: University of Leiden - LD
Investigators: Cornelis J. Begeman, MD
Marianne Bootsma, MD
Albert V.G. Brusckke, MD, PhD

Study Center & Initials: University of Maastricht - MA
Investigators: Frank Vermeer, MD, PhD
Hendrick J.J. Wellens, MD, PhD

Study Center & Initials: Nieuwegein - St. Antonius Hospital - NG
Investigators: Clemens G.K.M. Fauser, MD
Eliza G. Mast, MD

Study Center & Initials: University of Nijmegen - NM
Investigators: Ad P. Backx, MD
Jacques D. Barth, MD, PhD
Evert J.P. Lamfers, MD

Study Center & Initials: University of Utrecht - UT
Investigator: Rienk Rienks, MD

IDIS:910046394 VD-V1.0, C-V1.0

PKISM: status=approved veld

910046394

**LIST OF INVESTIGATORS AND SUBINVESTIGATORS FOR STUDY
CV123-234**

Investigator

Samuel Serfaty, M.D.

Subinvestigators

FINISH: status approved vs12
1.01, COMPLETE CONTROL V02

**PRAVASTATIN SODIUM TABLETS 40 MG/ASPIRIN TABLETS 81
MG OR 325 MG CO-PACKAGED PRODUCT**

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

1 NDA NUMBER

This NDA covers the pravastatin tablets 40 mg co-packaged with aspirin tablets 325 mg or 81 mg. The NDA number has not yet been assigned.

2 SPONSOR

Bristol-Myers Squibb Company is the sponsor of this application.

3 INDICATIONS

_____ cardiac events and strokes in patients with clinically evident coronary heart disease.

4 AGE RANGES INCLUDED IN REQUEST

All pediatric group age ranges are included in this request.

5 REASONS FOR WAIVING PEDIATRIC STUDIES

Atherosclerosis is a rare cause of morbidity and mortality in children. In children with homozygous familial hypercholesterolemia, which has a prevalence of about one in a million, the children rarely present with myocardial infarction until late adolescence, despite grossly elevated LDL levels. Myocardial infarction in children, due to coronary artery disease, most commonly occurs as a coronary vasculitis secondary to Kawasaki syndrome (Rowley AH, Shulman ST, Kawasaki syndrome *Pediatr. Clin. North Am* 1999;46:313-329). In neither post-infarctional population it is likely that the pravastatin/aspirin product would be effective in reducing the incidence of secondary events. A study to demonstrate this effect would be highly impractical.

A waiver is also justified by the fact that arteriosclerosis, of which atherosclerosis is part, is included within the list of "Disease-Specific Waivers" in the FDA Draft Guidance for Industry, dated November 27, 2000. FDA developed this list of diseases, which have

extremely limited applicability to pediatric patients, to help identify products that are likely to be granted a waiver.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-387	Efficacy Supplement Type SE- NA	Supplement Number NA
Drug: Pravigard PAC (pravastatin/aspirin) Co-Package		Applicant: Bristol-Myers Squibb
RPM: Zelda McDonald/After AP – Meg Pease-Fye		HFD-110 Phone # 301-594-5328
Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		4
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		3/9/03 (AE), 8/6/03 (AP)
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted (for Pravachol)		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted PATENT CERTIFICATION NOT NEEDED SINCE ASPIRIN HAS AN OTC MONOGRAPH, AND THERE IS NO REFERENCE LISTED DRUG		21 CFR 314.50(i)(1)(j)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
❖ Exclusivity Summary (approvals only)		X
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		3/6/03 (PM) 3/6/03 (ADRA), 6/9/03

General Information	
❖ Actions	
• Proposed action	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only) ALL READY SUBMITTED TO DDMAC	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release (x) Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	ODS 8/14/02; 12/10/02; DSRCS 9/30/02; 10/16/02; DDMAC 10/30/02 & 12/3/02 (under Advertizing tab)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	X
• Reviews	ODS 8/14/02; 12/10/02
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	Medical 5/8/01; CMC 4/5/01
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	X
❖ Advisory Committee Meeting	
• Date of Meeting	1/18/02 & 7/18/02
• 48-hour alert	No – Minutes of both mtgs in pkg.
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	July 3, 2002
❖ Clinical review(s) (indicate date for each review)	4/2/02 & 6/17/02
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	NA
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	NA
❖ Statistical review(s) (indicate date for each review)	None
❖ Biopharmaceutical review(s) (indicate date for each review)	12/21/01
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	None
• Bioequivalence studies	None
CMC Information	
❖ CMC review(s) (indicate date for each review)	2/27/02 & 6/6/03
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	11/14/01
• Review & Environmental Impact Statement (indicate date of each review)	11/14/01
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	NA
❖ Facilities inspection (provide EER report)	Date completed: 6/4/03 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Not Needed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	NA
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: 609-252-6000

Attention: Mr. Porter Lane

Company Name: BMS

Phone: 609-252-4722

Subject: Approval Letter

Date: 6/24/03

Pages including this sheet: 40

From: Zelda McDonald
Phone: 301-594-5328
Fax: 301-594-5494

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**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Transmitted to FAX Number: 609-252-6000

Attention: Mr. Porter Lane

Company Name: BMS

Phone: 609-252-4722

Subject: AE Letter & Labeling

Date: 3/7/03

Pages including this sheet: 41

From: Zelda McDonald
Phone: 301-594-5333
Fax: 301-594-5494

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