

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-387

Administrative Documents

PATENT INFORMATION CERTIFICATION

In accordance with the provisions of 21 CFR §314.53, Bristol-Myers Squibb Company, submits the following patent information:

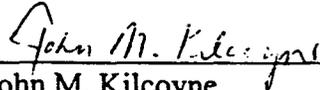
Patent Number: 4,346,227
Date of Patent Expiration: October 20, 2005
Type of Patent: Composition
Name of Patent Owner: Sankyo Company, Limited

Patent Number: 5,030,447
Date of Patent Expiration: July 9, 2008
Type of Patent: Formulation
Name of Patent Owner: E. R. Squibb & Sons, Inc.

Patent Number: 5,180,589
Date of Patent Expiration: July 9, 2008
Type of Patent: Formulation
Name of Patent Owner: E. R. Squibb & Sons, Inc.

Patent Number: 5,622,985
Date of Patent Expiration: April 22, 2014
Type of Patent: Method of Use
Name of Patent Owner: Bristol-Myers Squibb Company

The undersigned declares that the currently listed patents, Patent No. 4,346,227, Patent No. 5,030,447, Patent No. 5,180,589 and Patent No. 5,622,985, cover the formulation, composition, and/or method of use of Pravachol® (pravastatin). This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.



John M. Kilcoyne
Associate Counsel – Patents
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dated: May 21, 2001



FIELD COPY CERTIFICATION

NDA 21-387

Pravastatin Sodium Tablets 40 mg/Aspirin Tablets 81 mg or 325 mg Co-Packaged
Product

Bristol-Myers Squibb Company certifies that the field copy of the CMC section is a true copy of that section as supplied to the FDA in the archival and review copies of this application.

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 21-387 SUPPL #

Trade Name: ^{Pravastatin} Pravastatin PAC Generic Name: pravastatin sodium/buffered aspirin

Applicant Name Bristol-Myers Squibb Company HFD-110

Approval Date June 24, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES / / NO / /
- b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type (SE1, SE2, etc.)?

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-898 Pravachol (pravastatin sodium)

NDA # aspirin monograph

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_NO new clinical studies_/_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

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

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

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!
!

Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature of Preparer
Title:

Date

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Zelda McDonald
6/24/03 02:38:12 PM

Zelda McDonald
6/24/03 02:38:12 PM

Robert Temple
6/24/03 02:44:51 PM

Locicero, Colleen L

From: *Roberts, Rosemary*
Date: Friday, July 20, 2001 1:24 PM
To: Locicero, Colleen L
Cc: Crescenzi, Terrie L; Roberts, Rosemary
Subject: ?re: copackaged product

Colleen,

Terrie and I discussed the question re: the co-packaged NDA for pravastatin and aspirin. This NDA does not trigger the Peds Rule so you do not need to include information about the rule in letters.

Let me know if this does not answer your question. Sorry for the delay in response.

RR

NDA - 016

USE: PEDIATRIC RULE PARAGRAPHS FOR APPROVAL LETTERS—STUDIES NEEDED. NOTE: USE FOR NDAs FOR NEW CHEMICAL ENTITIES, AND SUPPLEMENTS FOR NEW DOSAGE FORMS, ~~AND/OR~~ NEW INDICATION EXCEPT WHERE THE INDICATION IS DESIGNATED ORPHAN. USE FOR EFFICACY SUPPLEMENTS FOR NEW INDICATIONS (SE1), NEW DOSING REGIMEN (SE2), AND NEW ROUTE OF ADMINISTRATION (SE3) PLUS ANY OTHER SUPPLEMENTS THAT THE DIVISION HAS SPECIFICALLY CONCLUDED TRIGGER THE PEDIATRIC RULE. DO NOT USE IF THE INDICATION IS DESIGNATED ORPHAN.
VERSION: 12/29/99

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. We are deferring submission of your pediatric studies until INSERT DATE (NO EARLIER THAN 12/2/00). However, you should submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

- Prava/asp
- not apply

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Note that satisfaction of the requirements at 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

**DEBARMENT CERTIFICATION
UNDER THE GENERIC DRUG ENFORCEMENT ACT OF 1992**

Bristol-Myers Squibb Company certifies that it did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this application.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

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

DATE: June 7, 2002

FROM: Robert Temple, M.D.
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Aspirin plus pravastatin, NDA 21-387; initial comments on Bristol letter of February 14, 2002

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

I find many of BMS arguments here quite credible, although I believe we were correct to think that a decision with such great implications for further "convenience" products should return to the CRAC and be the subject of an internal regulatory briefing.

Bristol has settled the dose range issue for pravastatin by agreeing to include the 20 and 80 mg doses, although they would provide the 20 mg dose reluctantly. With respect to the critical points they make:

1. Potential for continued aspirin use during surgery.

I thought this concern was exaggerated at the CRAC, but BMS makes the following points:

- There is little reason to believe patients will always know of their ASA use from OTC products, given the variety of names such products may have.
- We've allowed ASA in Rx products (Aggranox) as well as analgesic combinations.
- There is a compensating benefit, in that people will get the ASA their doctors want them to get (which they now do not, 15% of the time in the cited study).
- It is not so clear that stopping ASA before surgery is the right move. In the study cited at CRAC (I did not recall such citation, we need to check), there was at least a trend toward lower post-op stroke and MI when ASA was continued. Recommendations re ASA continuation are variable but BMS alleges that the prevailing view is that CV-directed ASA should be continued. We need to review the references and perhaps the literature more generally, but if this is correct, the CRAC's main objection to the combination will have been answered.
- Current labeling recommends stopping pravastatin before major surgery. That, of course, would stop both drugs if the label is followed. There is reason to doubt the wisdom of that recommendation, however.
- Labeling will emphasize the presence of ASA. It is not clear how much this will affect patients' knowledge of what they're taking, but presumably it will help some.

2. Dose range

All of the outcome data with pravastatin is at 40 mg, making it hard, in my view, to argue that availability of other doses is necessary. Specifically, I see little basis for providing lower doses. The 80 mg dose would help someone get to NCEP goal when 40 was not enough, which is probably reasonable behavior, if not outcome validated.

3. Compliance benefit

It is inevitably speculative to suggest better compliance from use of the combination and BMS does not allege that this is documented, but surely there might be better compliance than there is when relying on patients to find and take ASA on their own (which, as noted, there is evidence they did not do even when advised to).

4. Off-label use in primary prevention

Pravastatin has a primary prevention claim; aspirin does too in some people (angina, post angioplasty). The combination might facilitate wider use of aspirin in primary prevention, even where it is not yet indicated, although an argument could be made that anyone needing pravastatin is a candidate for ASA as well.

I have recently suggested, based on meta-analyses of 5 ASA primary prevention studies (3 besides the PHS and BMD studies) that we need to reevaluate ASA's role. Four of the 5 available studies show a pretty clear benefit.

In sum, I believe BMS has substantially supported its case. This combination, however, is a "stalking horse" for any number of CV outcome combinations of 2 or more of:

- ASA or clopidogrel
- A statin and perhaps other lipid modifiers
- Certain antihypertensives, especially ACEI's with CHF or broader (ramipril) claims
- Oral hypoglycemics
- Low dose diuretics
- Others (antidepressants, drugs for osteoporosis, etc.)

I therefore believe we should go to the CRAC (plus lipid people, perhaps supplemented further by the CV prevention crowd such as Califf, L. Friedman, Yusuf and others) and ask for a regulatory briefing. It may be that there are other convenience preparations outside CV territory and that we need broader consideration.

/s/

Robert Temple, M.D.

cc:
HFD-101/R Behrman
HFD-101/R Temple
drafted:sb/6/5/02
final:sb/6/7/02
Filename:aspirin_21387_MM_Jun02.doc

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

/s/

Sandra Benton
6/10/02 03:35:51 PM
TECHNICAL

Robert Temple
7/3/02 05:04:12 PM
MEDICAL OFFICER

The co-packaged product of pravastatin/aspirin was previously reviewed and was presented to the Cardio-Renal Advisory Committee on 18 January 2002. The advisory committee raised two objections to approval. The first was that not all doses were available in combination. In response to this objection, new formulations containing either 325 or 81 mg of aspirin will be available either with 20, 40 or 80 mg of pravastatin.

The second objection was a concern that aspirin as part of a co-packaged product, would inappropriately be continued or conversely, that the HMG CoA reductase inhibitor would be inappropriately discontinued at the time of a surgical procedure. This review consists of a summary and analysis of five publications that were submitted to the NDA on March 13, 2002. These publications are the sponsor's response to these concerns.

Publication #1

Heeschen C, Hamm CW, Laufs U, Snapinn S, Bohm M, White HD: Withdrawal of statins increases event rate in patients with acute coronary syndromes. *Circulation*; 2002; 105:1446-1452.

This was an observational study in a cohort of subjects who were enrolled in the PRISM study. These subjects had data available as to statin use at the time of entry and through the hospitalization. With respect to the PRISM study, a total of 3,232 subjects, who had evidence of unstable angina within 24 hours of study entry, received aspirin and were then randomized to additional therapy with tirofiban or heparin. The primary end point of the study was death, myocardial infarction or recurrent ischemia at each of the following time points 48-hours, 7-days and 30-days.

Of those enrolled into the PRISM study, 1,616 (50%) subjects had data available with respect to their statin use both pre-randomization as well as in-hospital. Of these subjects, 1,151 and 465 were not treated with or received statins at baseline, respectively. Of those treated with statins at baseline, 379 subjects continued statin use during hospitalization and 86 did not continue statin use. The comparison in this analysis is among those subjects whose statin usage was continued and those for whom it was discontinued.

The baseline characteristics, medical conditions and treatments did not differ in comparing those who continued and those who were discontinued from statins (data not shown here). The outcomes are shown in Table 1.

Table 1- Outcomes among those who had different statin status during the PRISM study

	No Statins N=1151	Statins continued N=369	Statins Discontinued N=86	P-value	Statins at baseline N=465*
48 Hours:					
Combined end point	68 (5.9%)	10 (2.6%)	9 (10.5%)	0.009	19 (4.1%)
Refractory ischemia	51 (4.4%)	12 (3.2%)	7 (8.1%)	0.032	19 (4.1%)
Death, MI	19 (1.7%)	2 (0.5%)	4 (4.7%)	0.21	6 (1.3%)
Death	3 (0.3%)	0	0	0.97	0
MI	16 (1.4%)	2 (0.5%)	4 (4.7%)	0.06	6 (1.3%)
Revascularization	6 (0.5%)	3 (0.8%)	1 (1.1%)	0.9	4 (0.9%)
7-Days:					
Combined end point	139 (12.1%)	36 (8.5%)	13 (15.1%)	0.25	49 (10.5%)
Refractory ischemia	122 (10.6%)	26 (6.9%)	12 (13.9%)	0.16	39 (8.2%)
Death, MI	61 (5.3%)	7 (1.9%)	8 (9.3%)	0.006	15 (3.2%)
Death	25 (2.2%)	2 (0.5%)	1 (1.2%)	0.58	3 (1%)
MI	36 (3.1%)	5 (1.6%)	7 (8.1%)	0.010	12 (2.6%)
Revascularization	235 (20.4%)	64 (17.3%)	22 (25.6%)	0.002	86 (18.5%)
30-Days:					
Combined end point	165 (14.3%)	38 (10.0%)	15 (17.4%)	0.07	53 (11.4%)
Refractory ischemia	125 (10.9%)	30 (7.9%)	13 (15.1%)	0.22	43 (9.2%)
Death, MI	86 (7.5%)	14 (3.7%)	12 (14.0%)	0.004	26 (5.6%)
Death	40 (3.5%)	6 (1.6%)	1 (1.2%)	0.31	7 (1.5%)
MI	46 (3.5%)	8 (2.1%)	11 (12.8%)	0.012	19 (4.1%)

p-values are derived from ANOVA.

*The statin at baseline group was added by this reviewer and was not included in the sponsor's calculations of p-Values.

The authors note that the outcomes among those that had their statins stopped were worse than among the subjects who had their statins continued during hospitalization. In particular, the combined end-point as well as death at 48-hours was worse than the cohort who discontinued statins when compared to the other cohorts.

(Comment: Considering those who were treated with statins at baseline (n=465), there did not appear to be a difference in outcome when compared to the no statin group (n=1151). Further subdividing the cohort into those in whom statin use was continued or discontinued must be viewed somewhat suspiciously. The cohort was not a randomized subgroup and the reason statins were discontinued is unclear. It is possible that those who were discontinued from statins were much sicker or rapidly deteriorated at baseline. They may have been made NPO because of their status during the first day of admission and therefore not given oral medication. In summary, this reviewer cannot differentiate whether the worst outcome was due to the cessation of therapy, or whether the cessation of statin therapy was due to the worsened status. In summary, this reviewer does not find this paper useful in deciding whether the short-term discontinuation of statin use is harmful).

Conclusion: This study result does not strongly support the contention that short term discontinuation of statin therapy has an acute effect on cardiovascular outcomes.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Publication # 2

Smith MS, Muir H, Hall R: Perioperative management of drug therapy, clinical considerations. *Drugs*; 1996; 51: (2) 238-259.

This publication reviews the available data on perioperative medication use. The publication does not supply any new data, but is a compendium of previous studies. These studies often rely on a surrogate marker or a very narrow population to ascertain whether the individual treatment should be discontinued or stopped at the time of a planned procedure. The treatments that were considered in the article were:

Antihypertensive medications (i.e. beta-adrenoreceptor blockers, α_1 -adrenoreceptor agonists, calcium antagonists, ACE inhibitors) and antiarrhythmic agents.

CNS agents: including therapies for affective disorders (MAO inhibitors, tricyclic antidepressants and lithium); anti-psychotics, anxiolytics, anti-epileptics and drugs for the treatment of Parkinson's disease.

Drugs affecting the coagulation system: anticoagulants (e.g. heparin and warfarin), aspirin and non-steroidal anti-inflammatory drugs as well as thrombolytic agents

Glucocorticoids:

Aspirin:

The particular relevance of the publication is to the decision to continue aspirin during the perioperative period. The publication is a compendium of previously published studies, with no new investigations by the authors. The first issue broached in this section is the utility of a bleeding time test for defining the risk of hemorrhage during surgery. This issue is of minimal relevance to the issue at hand.

The largest source of data is the randomized data derived from the CLASP study (Collaborative Low-dose Aspirin Study in Pregnancy). The study was designed to determine if low dose aspirin (60 mg daily), relative to placebo alters the development of pre-eclampsia among pregnant women. (Note: this dose is lower than the proposed dose to be included in the combination product). The charts of 1,069 women who received epidural anesthesia were examined for evidence of adverse events (de Swiet M et al.; *B. J Anaesth* 1992; 69: 109). (note: the decision to perform the epidural anesthesia was not a randomized decision but a consequence of events that occurred to these subjects post randomization).

The review of the charts found 56 adverse events. Three of these events were possible epidural hemorrhages. Two of these events were in the placebo-treated subjects and one in the aspirin treated subjects. (Note: the severity of these events was not described. Since the event rate of the epidural hemorrhage is dependent on the skill of the anesthesiologist to perform the epidural anesthesia, the event rate on and off aspirin would not be expected to differ. The safety issue would be the severity of the bleed. This information was not available.).

The publication also referred to both a retrospective study among patients who received regional anesthesia for general surgery (Horlocker TT et al., *Anesth Analg* 1990; 70: 631-4) and a prospective study in the same population (Horlocker TT et al.; *Anesth Analg* 1995, 80: 303-9). In the retrospective study, the outcome of 1,013 subjects who had a regional block prior to orthopedic surgery was collected for episodes of epidural hematoma. Of these patients, 39% were receiving preoperatively NSAID or aspirin. The review found no incidence of hematoma formation. In the prospective study by the same authors 924 subjects undergoing similar anesthesia for similar orthopedic procedures in which approximately 40% received NSAID or aspirin were examined for epidural hematoma. Again, the publication notes no increase in epidural hematoma rates.

Another study (Owens et al.; *Anesth Analg* 1986: 65:120-7) found among 33 cases of spinal hematoma one event that might have been related to post-operative use of aspirin.

For use prior to a procedure involving epidural blockade, the authors recommend albeit without data.

"Where it can be safely done without compromising patient's cardiac status, aspirin should be discontinued prior to surgery to prevent the increased risk of bleeding"

(Comment: The data base does not deal with the issues of bleeding form the infusion sites, the number of transfusions extra required or other hemorrhagic events, dehiscence of wound, stroke, gastrointestinal bleeds etc).

Conclusion: The strength of data for either stopping or continuing aspirin is not strongly supported by data as derived from this publication.

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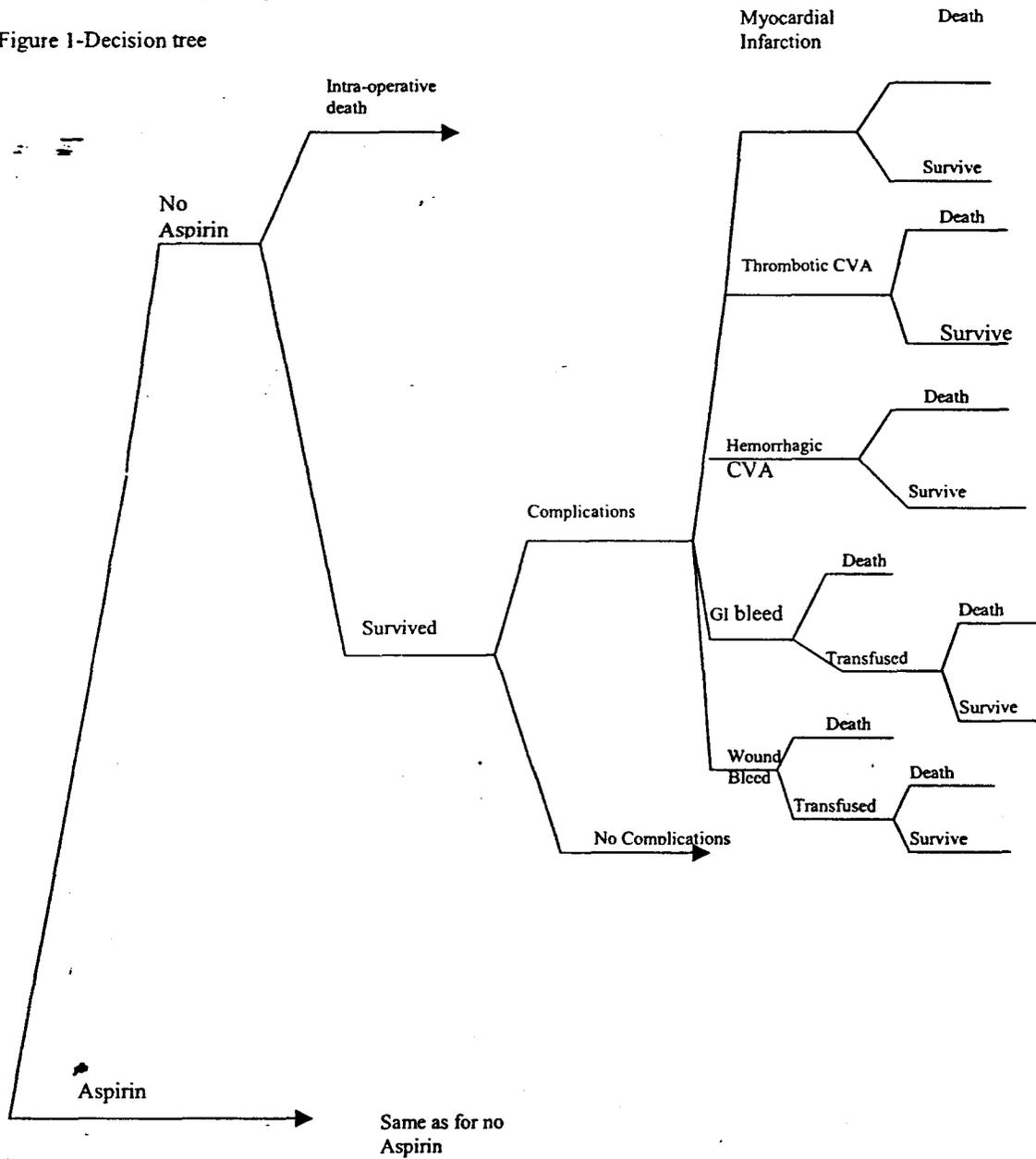
Publication # 3

Nelipovitz DT, Bryson GL, Nichol G: The effect of perioperative aspirin therapy in peripheral vascular surgery: A decision analysis. *Anesth Analg*; 2001; 93:573-80.

This publication, using a decision tree approach, explores the relative benefit of discontinuing or continuing aspirin treatment in a population undergoing an infra-inguinal revascularization procedure. There are no randomized clinical studies that specifically address the benefit/disadvantage to continue or discontinue aspirin therapy at the time of the revascularization procedure.

The decision tree analyzed by the authors is shown below.

Figure 1-Decision tree



Subjects could either receive aspirin or have aspirin discontinued at the time of surgery. Complications that are considered are myocardial infarction, thrombotic and hemorrhagic CVAs, and GI or incisional bleeds. The decision tree presumed that, for this analysis, aspirin's effect both positive and negative has completely dissipated. The frequency of these events and the resulting outcomes were derived from a series of publications culled from a MEDLINE search. The authors utilized two measures to quantify the results of a particular outcome. The first measure is the survival rates. The second is the utility value, the quantitative assessment of the subject's quality of life as a consequence of the event.

The specific values and the sources of the value are shown in Table 2. The author's included data from both randomized and cohort studies. Standardized life tables were used to assess survival after the perioperative period. Since there was no data in the literature, the authors assumed that the mortality risk from an incisional bleed was 5%. The results of the author's analysis are shown in Table 3.

Table 2. Studies, their size and the population enrolled with event rate and mortality rates as well as the relative effect of aspirin and the 95% CI

Event	Study	Type	N=	Population	Event Rate	Mortality
Myocardial Infarction	Christopherson et al.; ¹	RCT	100	PVD surgery	4%	50%
	Stuhmeier et al.; ²	RCT	297	Vascular Surgery	1.3 %	50%
	Bode et al.; ³	RCT	425	PVD surgery	4.5 %	N/A
	Iloprost Bypass Group ⁴	RCT	577	PVD surgery	4.1 %	N/A
	Sarac et al.; ⁵	RCT	56	PVD surgery	5.4 %	N/A
	Ouyang et al.; ⁶	Cohort	24	PVD surgery	8.3 %	N/A
	Mamode et al.; ⁷	Cohort	191	PVD surgery	7.3 %	57%
	Von Knorring and Lepantalo ⁸	Cohort	105	PVD surgery	2.9 %	66%
	Taylor et al.; ⁹	Cohort	207	PVD surgery	3.4 %	29%
	Cutler et al.; ¹⁰	Cohort	130	PVD surgery	5.4 %	71%
	Yeager et al.; ¹¹	Cohort	572	PVD surgery	3.5 %	25%
		Model Value (weighted mean)				3.98 %
Thrombotic CVA	Hart and Hindman ¹²	Cohort	125	PVD surgery	N/A	17.0 %
	Iloprost Bypass Group ⁴	RCT	577	PVD surgery	0.97 %	N/A
	Barnes et al.; ¹³	Cohort	125	PVD surgery	1.6 %	N/A
	Turnipseed et al.; ¹⁴	Cohort	160	PVD surgery	3.1 %	N/A
	Kelley and Kovacs ¹⁵	Cohort	171	CVA patients	N/A	20 %
	Model Value (weighted mean)				1.46 %	18.7%
Hemorrhagic CVA	Anderson et al.; ¹⁶	Cohort	492	CVA Patients	N/A	46%
	Petty et al.; ¹⁷	Cohort	339	CVA Patients	N/A	30%
	Model Value (weighted mean)				0.3 %	35.4%
GI bleed	Shina et al.; ¹⁸	Retrospective	309	PVD surgery	0.3	N/A
	Peura et al.; ¹⁹	Cohort	1235	GI bleeds	N/A	2.1%
	Model Value (weighted mean)				0.3%	2.1%
Incisional Bleed	Clyne et al.; ²⁰	RCT	70	PVD surgery	1.4 %	N/A
	Davies et al.; ²¹	Cohort	138	PVD surgery	10.1 %	N/A
	McCullum et al.; ²²	RCT	263	PVD surgery	3.4 %	N/A
	Model Value (weighted mean)				5.07%	N/A
Relative Risk of Aspirin					RR ASA	CI
Myocardial Infarction	He et al.; ²³	Systematic Review	55462	AHD	0.68	0.62-0.74
	ATC ²⁴	Systematic Review	68698	AHD	0.68	N/A
	Model Value (weighted mean)				0.68	
Thrombotic CVA	He et al.; ²³	Systematic Review	55462	AHD	0.82	0.73-0.92
	ATC ²⁴	Systematic Review	65941	AHD	0.72	N/A
	Model Value (weighted mean)				0.77	
Hemorrhagic CVA	He et al.; ²³	Systematic Review	55462	AHD	1.84	1.24-2.74
		Model Value (weighted mean)			1.84	
GI Bleed	Peura et al.; ¹⁹	Cohort	1235	GI Bleeds	2.76	2.03-3.74
	Kelly et al.; ²⁵	Case control	1752	GI bleeds	2.3	1.3-4.3
	Model Value (weighted mean)				2.53	
Incisional Bleed	ATC ²⁴	Systemic Review	3999	PVD surgery	1.52	N/A
	Model Value (weighted mean)				1.52	

RCT=Randomized clinical trial PVD=peripheral vascular disease CVA=cerebrovascular accident

¹ Christopherson R, Beatie C, Frank SM et al.: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery: Perioperative ischemia Randomized anesthesia Trial Study Group. Anesthesiology; 1993; 179: 422-34

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- ²¹. Davies AH, Pope I, Collin J, Morris PJ: Early reoperation after major vascular surgery: a four-year prospective analysis. *Br J Surg*; 1992; 79: 76-8.
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Table 3. Specific parameters used and outcomes.

Strategy	MI	Thrombotic CVA	Hemorrhagic CVA	Gastric Bleed	Incisional Bleed	All adverse events	Mortality	Crude life expectancy (yr)	Quality-adjusted life expectancy (QALYs)
- ASA	4.61 %	1.69%	0.37%	0.35 %	5.88 %	12.9 %	2.78 %	14.83	14.72
+ ASA	2.71%	1.12%	0.59 %	0.76 %	7.71 %	12.89 %	2.05 %	14.89	14.79

Based on this analysis, the authors anticipate a decrease in mortality of 0.73%. (2.78%-3.05%) at the time of the procedure.

The authors also performed a sensitivity analysis of the data. One or more of parameters was altered to determine the effect on the analyzed outcome. Based on the sensitivity analysis, the utility value of continuing aspirin exceeds the risk of bleeding from continued aspirin use as long as the risk of a myocardial infarction is approximately 1/4 that of the risk of incisional bleed (all other parameters held constant).

(Comments: The authors who devised this decision-tree analysis were well aware of its shortcomings. Below are some of the authors as well as some of the reviewer's assessment of the decision tree analysis.

- The values culled from the literature are frequently estimates derived from distantly related situations. For example, risk the reduction in myocardial infarction rate with aspirin is derived from a meta analysis of a predominantly secondary prevention population. It is unclear if the same risk reduction would occur in the peri-operative population. It is clear that some process during the perioperative period increases the frequency of myocardial infarctions and thrombotic and hemorrhagic strokes over the equivalent time from in a non-operative situation. It is, therefore, unclear if aspirin's benefits in platelet aggregation would be sufficient to mitigate the events occurring during the peri-operative period.
- The point estimates used (and the 95 % CI) are essentially meta-analyses. Each of these estimates are therefore, subject to the same limitations of any meta analyses. The uncertainty of any estimate for the overall effect is the composite of the uncertainty of each component that went into that estimate.
- Some of the estimates are derived from scant data, and with doses of aspirin that are unknown. The mid- point of the estimated effect is chosen by the authors, but may be highly inaccurate, particularly when there are few available studies which define that estimate.
- The number used in the calculations are close to but not equivalent to the numbers from the meat-analysis derived data. The values in Table 2 are weighted averages, the values used in constructing Table 3 are mean avarages (communication with the author).
- The author's presume that the risks of aspirin are limited to the frequency of events. The severity of the event is not presumed to be altered with aspirin).

In summary, the publication is of interest in its elegance. Its accuracy, however, is unknown. A proper randomized clinical study has not been performed. The relevance of the conclusion is in this reviewer's estimate, speculative.

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Publication # 4

Spell NO: Stopping and restarting medications in the perioperative period. Medical Clinics of N Amer; 85; 5 1117-1128

This is a review article that discusses the need to discontinue certain treatments prior to surgery. With respect to aspirin, no additional studies or new information is supplied. Based on the concern for the possibility of serious sequelae during certain forms of surgery e.g., neurosurgical, ophthalmological or vascular, cessation of aspirin therapy may be warranted. For cardiovascular surgeries a consensus is absent, "...although it is likely that aspirin increases perioperative mortality, evidence of significant effects on morbidity and mortality is lacking".

Conclusion: This publication adds no additional information with respect to the risk of continuing aspirin during the perioperative period.

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Publication # 5

Koch KT, Piek JJ, de Winter RAJ, Mulder K, Schorborgh CE, Tijssen GP, Lie KT: Two hour ambulation after coronary angioplasty and stenting with 6F guiding catheters and low dose heparin; Heart; 1999; 81 53:56

The purpose of the study described by the paper is to determine whether early ambulation (2 hours) after elective coronary angioplasty was safe. The study consisted of a 621 consecutive subjects treated at the Academic Medical Centre Mebergdreef, Amsterdam, Netherlands with elective angioplasty. Each of the procedures was performed using a 6F guiding catheter by the femoral approach with a standard dose of 5000 IU of heparin. Those patients given other anticoagulation were excluded from analysis. All patients were given aspirin at a dose of 100 mg/day. Patients who were stented also received ticlopidine at 250 mg daily. Haemostasis was applied by manual compression followed by the application of a manual compression bandage, after removal of the catheter sheath. Of the 621 subjects 300 patients were eligible for 2-hour ambulation. Five patients had bleeding complications at or immediately after ambulation (1.7%). A total of 9 subjects (including, one subject who had bleeding complications at ambulation). This result suggests that after low dose short-term aspirin regimens, excessive bleeding from the catheterization insertion site was not excessive.

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Overall Analysis: The supplied publications are only marginally pertinent to the safety of the continued use of aspirin during the peri-operative period. A randomized, prospective study in discontinuing or continuing aspirin in a whole series of situations defining the benefit/risk relationship has not been performed. The decision tree analysis by Nelipovitz is elegant in thought but of unknown accuracy and unknown applicability to the vast majority of situations for which the decision to discontinue aspirin would be relevant. The other publications are compendiums of data with the individual studies not really "on point".

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this page is the manifestation of the electronic signature.**

/s/

Abraham Karkowsky
6/17/02 03:08:53 PM
MEDICAL OFFICER

Teleconference Minutes

Telecon Date: August 21, 2002
Date Requested: July 27, 2002
Date Confirmed: August 12, 2002
NDA: 21-387
Sponsor: Bristol-Myers Squibb
Type: Other
Classification: C

Telecon Chair: Douglas C. Throckmorton, M.D.
Telecon Recorder: Zelda McDonald
External Participant Lead: Porter Layne, Ph.D.

FDA:

Douglas C. Throckmorton, M.D. Director, HFD-110
Zelda McDonald Regulatory Health Project Manager, HFD-110

Bristol-Myers Squibb:

Laurie Smaldone	Regulatory
Steve Bass	Regulatory (Labeling)
Porter Layne	Regulatory FDA Liaison
Mary Peters	CMC, Regulatory
Liz Yamashita	CMC, Regulatory
Betsy Hanna	US Marketing
Dan Driscoll	US Marketing
Fred Fiedorek	Clinical

Background:

A New Drug Application for co-packaged pravastatin sodium tablets and buffered aspirin tablets for use in clinical event reduction in subjects with clinically evident coronary heart disease was initially submitted on June 22, 2001 and subsequently withdrawn following a January 18, 2002 Cardiovascular and Renal Drugs Advisory Committee (CRDAC) Meeting. The application was resubmitted on May 8, 2002. The application was presented again before the CRDAC on July 18, 2002 which recommended approval of the co-packaged product. Bristol-Myers Squibb (BMS) requested this telecon (previously scheduled as a meeting) to follow-up on the Advisory Committee's recommendations.

Telecon:

BMS asked if the Division had any problems with the following assumptions that led to the questions in the briefing document:

1. The recommendation of the CRDAC is both necessary and sufficient for approval of the pravastatin/aspirin combination product when combined with the reviews of the submitted materials by the Division. Realization of this assumption is contingent on the Agency's acceptance that BMS has sufficiently met the committee's concerns which were primarily related to the packaging and labeling of the product.
2. The formal marketing approval of the product will be on or about September 2002.

- Dr. Throckmorton stated that the first assumption is correct. The second assumption he has no control over since Dr. Temple will be signing the action letter. The Agency would make every effort not to delay action any longer than necessary.

BMS asked whether the Tradename, Pravagard PAC, had been found to be acceptable by the Agency.

- Dr. Throckmorton stated the Office of Drug Safety had determined that the Pravagard PAC trade name is acceptable, however, their focus is mainly on possible prescription errors based on confusion over names. The Division is concerned that the "Pravagard PAC" trade name does not sufficiently emphasize the presence of aspirin in the product.
- BMS stated that they had explored other names through _____ Some of the names were not available because they were in use or for other reasons and some they believed would cause confusion between the Physician and the Pharmacist. BMS believed that since Pravagard PAC would be distributed as Unit-of-Use packaging, having aspirin in the name would not be an issue.
- Dr. Throckmorton agreed that the Unit-of-Use packaging may be sufficient but asked BMS to provide written arguments, that included their experience of exploring other names, to the Division. This could buttress the argument for accepting the proposed tradename. BMS agreed.

Regarding labeling and packaging for the co-packaged product, BMS' assessment is that there is general agreement that the labeling and packaging proposals made by BMS in the NDA and to the CRDAC were acceptable. BMS asked if the Agency agreed with this assessment.

- Dr. Throckmorton said the CRDAC had voiced no objection. The Division had not met to discuss the labeling and packaging, but the broad outline seemed okay.

As noted in prior discussion with the Agency, BMS continues to believe that the 40 mg and 80 mg pravastatin dosage strengths are the most appropriate dosage strengths for this combination product, which would be indicated for secondary prevention. Does the Agency intend to approve the 20 mg strength?

- Dr. Throckmorton stated that he and Dr. Temple had discussed the 20 mg strength. Clearly the CRDAC believed that the 20 mg strength is pivotal in allowing the safe and effective use of the co-packaged product as well as the combination product. The Agency will insist that the 20 mg product be available for marketing when the co-package and the combination products are launched. A difference of a week may be acceptable, but the proposed 3 month delay is unacceptable.
- BMS asked if they could make a proposal of a time frame that was in between 1 and 3 weeks for the co-packaged product. They noted that the 20 mg co-packaged product will be on the market when the fixed-combination product is ready for market and asked if there would be the same time constraints for the 20 mg fixed-dose combination product. They offered to include both proposals regarding the 20 mg strength with the information they plan to submit about the brand name.

Minutes of a teleconference

Date of teleconference:	May 9, 2002
Application:	NDA 21-387
Product:	pravastatin/aspirin co-packaged product
Sponsor:	Bristol-Myers Squibb Company
Purpose:	to discuss upcoming Advisory Committee meeting
Teleconference Chair:	Robert Temple, M.D.
Teleconference Recorder:	Colleen LoCicero
Participants:	
<u>FDA</u>	
Robert Temple, M.D.	Director, Office of Drug Evaluation I (HFD-101)
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
<u>Bristol-Myers Squibb</u>	
Todd Baumgartner, M.D., M.P.H.	Vice President, Global Regulatory Strategy
Rene Belder, M.D.	Executive Director, Metabolics Clinical Development and Life Cycle Management
Fred T. Fiedorek, M.D.	Vice President, Clinical Design and Evaluation and Exploratory Development Consultant
Elaine Klein	Vice President, Global Marketing Pravachol and Life Cycle Management
Porter Layne, Ph.D.	Group Director, FDA Liaison and Global Regulatory Strategy
Kannan Natarajan, Ph.D.	Director, Clinical Biostatistics
Laurie Smaldone, M.D.	Senior Vice President, Global Regulatory Science

Background

The Sponsor requested this teleconference to discuss the upcoming Advisory Committee meeting. In preparation for the teleconference, the Sponsor provided a list of seven issues for discussion.

The meeting

The Sponsor's issues are stated in bold below with the Agency's response following.

Issue #1: What questions/issues does the Agency intend to pose to the Advisory Committee? Is there a draft of the proposed questions that we could see and comment?

The Agency has not drafted yet the questions the Committee will be asked.

Issue #2: We would like to discuss what can be done to focus the Committee members on the questions/issues posed by the Agency for their consideration. It is our opinion that the efficacy of the combination product based on a meta-analysis, the independence-of-effect/contribution of the two components to the therapeutic effect, the relative cholesterol-lowering efficacy of pravastatin, and the proportion of pravastatin-treated patients achieving cholesterol goals are issues that were discussed/addressed in January and do not warrant further discussion. Does the Agency agree? If so, will the Committee be advised that no further discussion of these issues is necessary.

The Agency agrees that issues concerning efficacy, the contribution of the two components, the relative cholesterol-lowering effect of pravastatin, and the proportion of pravastatin-treated patients achieving cholesterol goals were adequately addressed at the January Advisory Committee meeting and do not warrant additional discussion.

The Agency plans to make an informal presentation at the meeting that summarizes the January Advisory Committee discussion and the issues we believe are settled. Additionally, we plan to phrase the questions to the Advisory Committee in a manner that does not encourage further discussion of the above issues. Although we plan to discourage further discussion of these issues, we do not usually stop the Committee from discussing issues, if they are relevant. The Sponsor should not necessarily include in their Advisory Committee background document, or plan on presenting at the meeting, any information concerning these issues, but they should be prepared to discuss any or all of these issues, should the Committee want to revisit these issues.

We believe the focus of the meeting will be the issues identified by the Advisory Committee at the January meeting, especially the safety of aspirin in the combination product and the pravastatin doses provided in the combination products.

Issue #3: Will the issue of the 20 mg pravastatin dose being included in the approved combination product be open to discussion subsequent to the Advisory Committee meeting, i.e., does the Agency reserve the right to overrule the Committee on this issue?

The Sponsor explained that although they provided in the NDA resubmission information to support 20 mg and 80 mg pravastatin co-packaged products, they would like to discuss further the need for providing 20 mg pravastatin co-packaged products. Because they did not wish the approval of this application to hinge on the availability of a 20 mg pravastatin co-packaged product, BMS included in the NDA resubmission information to support the 20 mg pravastatin combinations, but they do not agree that these combinations are necessary or appropriate. If providing 20 mg pravastatin combinations remains an issue for the Sponsor, it will likely need to be discussed at the Advisory Committee meeting. The Sponsor can certainly take the position that although they have taken the steps necessary to provide and market these combinations, they do not agree

that this is appropriate, as there are no mortality/morbidity data to support the use of these dose combinations in the proposed indication.

Finally, the Advisory Committee serves in an advisory capacity to the Agency and the Agency is not obligated to follow their recommendations.

Issue #4: Since there were several questions from the Committee in January pertaining to information on statins in general and pravastatin specifically, Bristol-Myers Squibb requests that Dr. Orloff attend the next Committee meeting so that such questions might be answered more effectively.

We will request and encourage Dr. Orloff's attendance at the meeting.

Issue #5: Will the Agency invite a consultant? If so, who might it be and what issue(s) would the consultant be invited to address?

The Agency does not plan to invite a consultant.

Issue #6: Will Dr. Hirsch again be the designated reviewer for the Committee for the July meeting?

We plan to ask Dr. Hirsch to be the designated reviewer.

Issue #7: Do you feel a presentation from BMS is needed? If so, how much time will be allotted for the Sponsor's presentation? Also, does FDA plan to make a presentation?

A presentation from BMS would be helpful. The standard 40-minute prepared presentation should suffice. As noted earlier, the Agency will likely make an informal presentation consisting of a summary of the January Advisory Committee discussion and our understanding of the issues that are settled.

Miscellaneous

At this point, the pravastatin/aspirin discussion is scheduled for the afternoon of July 18th.

The Sponsor plans to include in their background materials a discussion of their aspirin safety data, including the results of a survey they conducted regarding the use of aspirin in the peri-surgery period. They plan to include a risk benefit assessment of the use of aspirin in the peri-surgery period.

The Sponsor might want to consider including in their Advisory Committee presentation a discussion of how the co-packaged products will improve patient compliance.

Minutes of a meeting

Date of meeting:	March 8, 2002
Application:	NDA 21-387
Product:	pravastatin/aspirin co-package
Sponsor:	Bristol-Myers Squibb Company
Purpose:	follow-up to Advisory Committee meeting
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Ms Colleen LoCicero
Participants:	
<u>FDA</u>	
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, Division of Cardio-Renal Drug Products (HFD-110)
Natalia A. Morgenstern	Chief, Project Management Staff, HFD-110
David Orloff, M.D.	Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Robert Temple, M.D.	Director, Office of Drug Evaluation I (HFD-101)
Douglas C. Throckmorton, M.D.	Acting Director, HFD-110
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
<u>Bristol-Myers Squibb Company</u>	
Todd F. Baumgartner, M.D., M.P.H.	Vice President, Global Regulatory Strategy
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Fred T. Fiedorek, M.D.	Vice President, Clinical Design and Evaluation and Exploratory Development Consultant
Joan M. Kenney	Director, Regulatory Relations and Policy
Elaine Klein	Vice President, Global Marketing Pravachol and Life Cycle Management
Porter P. Layne, Ph.D.	Group Director, FDA Liaison and Global Regulatory Strategy
Kannan Natarajan, Ph.D.	Director, Clinical Biostatistics
Elliott Sigal, Ph.D., M.D.	Senior Vice President, Global Clinical and Pharmaceutical Development
Laurie Smaldone, M.D.	Senior Vice President, Global Regulatory Science

Background

The Sponsor requested this meeting in follow up to the January 18, 2002 Advisory Committee meeting in which this application was discussed. 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 is that the range of *pravastatin doses for the co-packaged products is not adequate. The second concern is* 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.

The meeting

Discussion Point #1: Sponsor's position

The Sponsor initiated the discussion by summarizing their views and understanding of the Agency's views on the pravastatin/aspirin co-package application and the Advisory Committee's recommendations. The Sponsor believes this application meets the regulatory requirement for combination products of demonstrating that the effect of the combination (A+B) is greater than the effect of either component (A or B) alone. BMS believes this application should be approved. They believe the pravastatin/aspirin co-packaged products will serve a public health need. BMS is disappointed with the January Advisory Committee discussion and recommendations. BMS believes the negative Advisory Committee recommendations are the primary obstacle to approval of this application.

In their February 14, 2002 submission to the NDA, BMS makes several proposals to address the Advisory Committee's concerns. The first is a proposal to supplement the NDA, post-approval, with 80 mg pravastatin co-packaged products. A second is to mark the co-package container labels clearly so that it is evident that the product contains aspirin.

The Sponsor understands that Dr. Temple is not prepared to sign an "Approval" or "Approvable" letter by the April 22, 2002 primary goal date, as he believes the application needs further public discussion.

Discussion Point #2: Agency's position

This combination product is the first of potentially hundreds of "convenience" combination products, i.e., combinations of products that are commonly prescribed for long term use for large numbers of people not necessarily for the same disease (e.g., diabetes and hypercholesterolemia), but sometimes, as in the present case, for two approaches to the same disease (aspirin and lipid lowering to treat coronary artery disease). (Combination antihypertensives are also created for convenience, but in these cases both drugs attempt to influence the same measure.) This application, therefore, poses the larger question of how the Agency should approach these convenience combination products in general. Provided the Agency believes such combinations should be available, we need to decide what will be required for their approval.

While it appears that pharmacokinetic/pharmacodynamic data demonstrating no interaction between the components of the combination would usually be needed, it is not

clear what clinical evidence would be required for approval. When both components are directed at the same endpoint, such as blood pressure, we ask for a study to show that the combination provides a larger effect than each component alone. However, when one drug lowers blood pressure and the other lowers cholesterol, there is usually little point in such a study. The drugs would simply have their usual and different effects. In this case, one might argue that aspirin will have its anti-platelet effect and any outcome consequences while the statin will at least lower cholesterol. Is that enough? Do we need to know that each contributes to the outcome effect? Or could that too be presumed, given their totally different mechanisms of action? Would the answer be different if one considered aspirin and a statin without outcome data? Even in cases where both drugs have outcome data, they may or may not have data on their effects in combination. In the present case, there is controlled evidence that pravastatin adds to the outcome effect in the presence of aspirin and less strong, but reasonable, evidence that aspirin contributes in the presence of pravastatin. However, this kind of evidence will only sometimes be available. Is such evidence needed when two wholly different mechanisms are combined? We certainly do not ask this question in the development of "add-on" treatments in cardiovascular and oncologic conditions; that is, we do not ask if the baseline treatment continues to contribute.

Unfortunately, the pravastatin/aspirin co-package application is caught up in our consideration of these issues.

Discussion Point #3: Need for additional discussion

Because pravastatin has outcome data with aspirin that demonstrate a contribution of both components when used together, the pravastatin/aspirin combination is in a better situation than other potential statin/aspirin combinations might be. Additionally, an aspirin/statin combination might seem sensible intuitively. However, the Agency is reluctant to ignore the rather strong objections raised by the Advisory Committee in January without asking the Committee to consider the Sponsor's rebuttal, even if we find the Sponsor's rebuttal highly persuasive. Therefore, another Advisory Committee meeting is likely, probably in July 2002.

Furthermore, the larger issue of convenience combination products in general will likely be discussed at an internal Agency meeting sometime before the July Advisory Committee meeting.

As the Advisory Committee discussion will not take place prior to the application's primary goal date, Dr. Temple is prepared to sign a "Not Approvable" letter on the April 22nd goal date.

The Sponsor asked whether the additional public discussion concerning this application could be a venue other than an Advisory Committee meeting. Dr. Temple believes it important that the Advisory Committee reconsider this application. Although the Agency is not required to follow the recommendations of the Advisory Committee and does not

always do so, we believe it important that the Committee have the opportunity to consider the rebuttal to their concerns, in light of the fact that they were fairly strong.

If the Committee recommends not approving the application again in July, we will have to consider the application further at that point.

Discussion Point #4: Advisory Committee discussion

The discussion concerning this particular application would likely focus on the safety concerns raised by the Advisory Committee at the January meeting. The Agency does not intend to ask the Advisory Committee again the questions asked at the January meeting. Issues identified at the internal meeting on convenience products might be brought to the Committee for consideration as well.

The Sponsor's background package for the July Advisory Committee meeting should consist of documents that seek to allay the concerns raised by the Advisory Committee in January, such as the articles the Sponsor references in their February 14, 2002 position paper on continued use of aspirin perioperatively.

Discussion Point #5: Dose concerns

The Sponsor asked whether their proposal to provide 80 mg pravastatin co-packaged products post approval addresses the Advisory Committee's concerns with limiting dosing. We thought it might, but could not speak for the Advisory Committee. To address the concerns with dose fully, the Sponsor should also provide an argument for not offering a 20 mg pravastatin co-packaged product.

A general question the Agency needs to address for all convenience combination products is whether these products need to offer the full dose range of all components of the combination so that they can be prescribed to outliers, such as those with compromised hepatic and renal function.

Discussion Point #6: Amending the pending application

Since providing 80 mg pravastatin co-packages will likely constitute at least part of the Advisory Committee discussion, the Sponsor asked whether it would be reasonable to submit a major amendment for an 80 mg tablet to the pending NDA. This would extend the goal date, a move the Sponsor believed might obviate the need to withdraw and resubmit the application. The primary goal date for the pending application is April 22nd. Submitting a major amendment at this time would extend the goal date to July 22nd. As the July Advisory Committee meeting is scheduled for the middle or end of July, this would not provide the Agency with sufficient time to consider the Advisory Committee's recommendations and act on the application. A better approach would be for BMS to withdraw the application and resubmit it prior to the July Advisory Committee. Barring any unforeseen circumstances, it should not take more than a couple months following

Minutes of a teleconference

Date of teleconference:	January 11, 2002
Application:	NDA 21-387
Product:	Pravastatin/aspirin co-package
Sponsor:	Bristol-Myers Squibb
Purpose:	to discuss discrepancy in analysis
Teleconference Chair:	Abraham Karkowsky, M.D., Ph.D.
Teleconference Recorder:	Colleen LoCicero
Participants:	
<u>FDA</u>	
Abraham Karkowsky, Ph.D.	Team Leader, Medical, Division of Cardio-Renal Drug Products (HFD-110)
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
<u>Bristol-Myers Squibb</u>	
Rene Belder, M.D.	Executive Director, Clinical Development & Life Cycle Management – Cardiovascular Metabolics
Porter Layne, Ph.D.	Group Director, FDA Liaison and Global Strategy Regulatory Science

Background

The Sponsor requested this teleconference to notify the Agency of a discrepancy they recently discovered in the meta-analysis used to support this application.

The teleconference

The Sponsor initiated the discussion by noting that while they do not believe the discrepancy significantly impacts the overall interpretability of the meta-analysis, they wanted to notify the Agency of their finding.

Dr. Belder noted that in the CARE study, every time a study center discovered what they believed to be a myocardial infarction (MI), they reported it to the data center as an MI. The data center subsequently categorized the event as a probable MI. Independently, the event adjudicating committee reviewed all fatal events and non-fatal MIs, applying the pre-specified definition for an MI to classify the events. An event classified as an MI by the adjudicating committee was coded a definite MI. For the primary endpoint in CARE, only definite MIs were included.

For the meta-analysis that supports this application, however, the statistician who performed the analysis included from the CARE study both definite and probable MIs.

Minutes of a teleconference

Date of teleconference:	January 8, 2002
Application:	NDA 21-387
Product:	Pravastatin/aspirin co-package
Sponsor:	Bristol-Myers Squibb
Purpose:	to discuss medical review
Participants:	
<u>FDA</u>	
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
<u>Bristol-Myers Squibb</u>	
Rene Belder, M.D.	Executive Director, Clinical Development & Life Cycle Management- Cardiovascular Consultant
Porter Layne, Ph.D.	Group Director, FDA Liaison and Global Strategy Regulatory Science
Kannan Natarajan, Ph.D.	Associate Director, Biostatistics
Andrew Walker	Manager, Clinical Research

Background

The Sponsor requested this teleconference to discuss the medical review included in the background package for the upcoming Advisory Committee Meeting regarding this application.

The teleconference

Discussion Point #1: Cholesterol levels across the meta-analysis studies

The Sponsor indicated that not all the meta-analysis studies enrolled only subjects with greater than normal cholesterol levels. They noted that the labeling approved as a result of the CARE study findings included language on use in patients with normal cholesterol levels because CARE studied subjects with average cholesterol levels. When the pravastatin labeling was subsequently revised as a result of the LIPID study findings, language on cholesterol levels was removed from the indications section. The Sponsor believes the distribution of cholesterol levels in the CARE study is similar to the distribution of cholesterol levels in the myocardial infarction patient population. The Sponsor believes the studies that support the secondary prevention indication for pravastatin cover the entire spectrum of cholesterol levels. The Sponsor does not believe it would be possible, however, to adequately address this at the Advisory Committee meeting if this topic arises.

Dr. Lipicky acknowledged that the selection of language in the medical review pertaining to the range of cholesterol levels across the meta-analysis studies might not have been the most appropriate.

So as not to elicit a discussion on this, the Division agreed not to include in the questions to the Advisory Committee any statement pertaining to cholesterol levels in the meta-analysis studies.

Discussion Point #2: Follow-up

The Sponsor expressed concern with the description of the follow-up in the CARE and LIPID studies in the medical review, noting that these studies had nearly 100% follow-up post event. CARE lost one patient, while LIPID had 100% follow up. Dr. Lipicky recommended that the Sponsor note this in their Advisory Committee presentation.

Discussion Point #3: Revised labeling

The recently approved revisions to the pravastatin labeling are not reflected in Dr. Karkowsky's review because the revised labeling was not approved until after his review was submitted to the Advisors and Consultants staff.

Discussion Point #4: Pharmacodynamic interactions

The Sponsor noted that prior to the submission of the NDA, the Agency agreed that no pharmacodynamic interaction studies would be needed for approval of this product. The Division agreed not to include in the Advisory Committee questions any that pertain to potential pharmacodynamic interactions.

Discussion Point #5: Approvability questions

If questions concerning approvability and strength of evidence are asked independently, the Sponsor believes there would be the potential for the Advisory Committee members to vote that the strength of evidence does not meet the standard two studies at a p of < 0.05 or even one study at a p of < 0.05 , but vote to approve the application. Dr. Lipicky clarified that the purpose of asking these questions independently is to compel the members to compare the benefits of this fixed-dose combination product to the risks. The Sponsor suggested that the Division first ask whether the meta-analysis data demonstrate that pravastatin plus aspirin has a greater effect than either aspirin alone or pravastatin alone and then ask about the adequacy of the level of evidence.

Discussion Point #6: Doses

Asking whether the appropriate aspirin and pravastatin doses should be determined prior to approval highlights the three conclusions that can be made with respect to the

Minutes of a teleconference

Date of teleconference:	December 11, 2001
Application:	NDA 21-387
Product:	Pravastatin/aspirin co-package
Sponsor:	Bristol-Myers Squibb
Purpose:	to discuss the Sponsor's Advisory Committee briefing document
Teleconference Chair:	Raymond Lipicky, M.D.
Teleconference Recorder:	Colleen LoCicero
Participants:	
<u>FDA</u>	
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
<u>Bristol-Myers Squibb</u>	
Rene Belder, M.D.	Executive Director, Clinical Development & Life Cycle Management-Cardiovascular
Fred Fiedorek, M.D.	Vice President, Clinical Development
Porter Layne, Ph.D.	Consultant
Kannan Natarajan, Ph.D.	Group Director, FDA Liaison and Global Strategy Regulatory Science
Andrew Walker	Associate Director, Biostatistics Manager, Clinical Research

Background

The Sponsor requested this teleconference to discuss their December 3, 2001 submitted background document for the upcoming Advisory Committee meeting.

The teleconference

Discussion Point #1: Issue of patient compliance

Dr. Lipicky started the discussion by indicating that the background document looks good. He noted, however, that it does not include data to support the Sponsor's argument that the combination product will increase patient compliance. The Sponsor may want to include information in the background document that supports this argument, as this will be one of the discussion points. The Sponsor noted that since the submission of the background document, they have added to the executive summary of the document a paragraph on patient compliance.

Discussion Point #2: Dr. Pedersen

Dr. Lipicky recently spoke with Dr. Terje Pedersen from the University of Oslo concerning ongoing European studies of an HMG-CoA reductase inhibitor ("statin") that cover a four-fold dose range of the statin. Dr. Lipicky has invited Dr. Pedersen to speak at the Advisory Committee meeting, but his participation has not yet been confirmed.

The Sponsor is aware of Dr. Pedersen's research and believes his findings, if anything, support providing only 40 mg pravastatin in the co-package products.

Another preliminary finding of Dr. Pedersen's is that there appears to be no relationship between change in cholesterol and clinical outcome.

Discussion Point #3: Sponsor's presentation

The Sponsor asked whether Dr. Lipicky still recommends limiting their presentation to 45 minutes. Dr. Lipicky does, noting that, in his experience, a planned 45-minute presentation often lasts an entire morning.

NDA 21-387 is the only item on the agenda for the January 18th meeting session.

Discussion Point #4: Questions

The Division plans to draft the questions for the Advisory Committee after Christmas. While the Division hopes to have the questions drafted before January, we could not say for certain that we would be able to do so.

Discussion Point #5: Questions from the medical reviewer

Dr. Karkowsky requested that the Sponsor provide the Division with information on the use of other antiplatelets, e.g., ticlopidine and clopidogrel, in the studies they are using to support the application. While it is not necessary to include this information in the Advisory Committee background document, this information can be provided in an amendment to the application.

Additionally, Dr. Karkowsky asked that the Sponsor address what appears to be a disparity in aspirin use among the meta-analysis studies. It is difficult to know from what was provided in the application the fraction of patients in the studies that took aspirin and whether they continued to take aspirin throughout the study. The Sponsor agreed to submit an amendment to the application that addresses this issue.

Signature, Teleconference Recorder: _____ Colleen LoCicero

Concurrence, Teleconference Chair: _____ Raymond Lipicky, M.D.

drafted: 1/2/02

finald: 1/7/02

rd:

Karkowsky/1/7/02

dfs

Minutes of a teleconference

Date of teleconference:	October 24, 2001
Application:	NDA 21-387
Product:	Pravastatin/aspirin co-package
Sponsor:	Bristol-Myers Squibb
Purpose:	to discuss upcoming Advisory Committee Meeting
Teleconference Chair:	Raymond Lipicky, M.D.
Teleconference Recorder:	Colleen LoCicero
Participants:	
<u>FDA</u>	
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
David Orloff, M.D.	Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Douglas Throckmorton, M.D.	Deputy Director, HFD-110
Mary Parks, M.D.	Medical Officer, HFD-510
William Lubas, M.D.	Medical Officer, HFD-510
John Lawrence, Ph.D.	Statistician, Division of Biometrics I (HFD-710)
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
<u>Bristol-Myers Squibb</u>	
John Bedard	Vice President, FDA Liaison and Global Strategy Regulatory Science
Rene Belder, M.D.	Executive Director, Clinical Development & Life Cycle Management – Cardiovascular Metabolics
Fred Fiedorek, M.D.	Vice President, Clinical Development
Kannan Natarajan	Consultant
Porter Layne, Ph.D.	Associate Director, Biostatistics
Chen-Sheng Lin	Group Director, FDA Liaison and Global Strategy Regulatory Science
Andrew Walker	Research Biostatistician Manager, Clinical Research

Background

This teleconference was scheduled at both the Division and Sponsor's request to discuss the upcoming Advisory Committee Meeting.

The teleconference

Discussion Point #1: Focus of the Advisory Committee discussion

Dr. Lipicky started the discussion by stating that the purpose of the Advisory Committee discussion will not be to address co-packaging, as we realize this will be a temporary arrangement for this combination product. The co-packaging policy will be discussed minimally, if at all. At this time, we believe the Advisory Committee discussion will focus on the following issues:

1. Convenience packaging, in general, and whether combining products for the sake of convenience is sensible. The discussion will likely include to what degree the combination policy requirement that the effect of A + B be greater than the effect of either A or B alone must be met. Additionally, the range of doses of the individual drug products the convenience package product must cover will also likely be discussed.
2. Whether the rudiments the Division outlined for the pravastatin/aspirin co-package product application are reasonable and whether our interpretation of the convenience package policy, based on what we required for the application, is accurate.
3. Whether the information and data the sponsor has provided in the application conforms to 1 and 2 above.

The discussion will be highly philosophical and we are not exactly sure how it will be executed. The details will be important, however, we cannot provide details at this time. As our review of the application progresses, we will be able to provide additional details.

This is the Division's first application for a combination therapy product of two drugs that are not in the same drug group, i.e., these are not two anti-hypertensive drug products. As our response to this application will likely be precedent setting, we believe it prudent to hold a public discussion of the concept and whether the data provided conform to the policy.

Dr. Orloff reminded the sponsor that the burden will be on them to address the doses they elected to include in the co-package application and why they excluded the other marketed pravastatin doses.

Discussion Point #2: Advisory Committee Participants

Although the Division is considering inviting members of the Metabolic and Endocrine Advisory Committee to participate in the January meeting, this needs further internal discussion. Dr. Orloff noted that it might be better to obtain outside consultants for the meeting, rather than Metabolic and Endocrine Advisory Committee members. Drs. Throckmorton and Orloff will work on this. BMS agreed to send via facsimile the list of consultants they plan to use for the Advisory Committee discussion.

drafted: 11/5/01

finald: 11/9/01

rd:

Orloff/11/6/01

Parks/11/7/01

Lawrence/11/6/01

Throckmorton/11/6/01

FILING SUMMARY/MEETING MINUTES

Date of filing meeting:	July 31, 2001
Application #:	NDA 21-387
Product:	Pravastatin/Aspirin Co-Package
Sponsor:	Bristol-Myers Squibb
Meeting Chair:	Raymond Lipicky, M.D.
Meeting Recorder:	Colleen LoCicero
Participants:	
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Douglas Throckmorton, M.D.	Deputy Director, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, Division of New Drug Chemistry (HFD-810)
Florian Zielinski, Ph.D.	Chemist, HFD-810
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I (HFD-860)
James Hung, Ph.D.	Team Leader, Statistical, Division of Biometrics I (HFD-710)
John Lawrence, Ph.D.	Statistician, HFD-710
Sriram Subramaniam, Ph.D.	Physiologist, Division of Scientific Investigation (HFD-340)
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
Colleen LoCicero	Regulatory Health Project Manager, HFD-110

Application Information

Indication: C

J

Therapeutic Classification: 4S

Date of Application: June 22, 2001

Date of Receipt: June 22, 2001

User Fee Goal: April 22, 2002 (primary); June 22, 2002 (secondary)

User Fee Status: Paid

Submission Complete As Required Under 21 CFR 314.50? YES

Patent Information Included? YES

Exclusivity Requested? NO

Debarment Statement Included? YES

Pediatric Rule addressed? N/A (Per Ms. Terri Crescenzi and Dr. Rosemary Roberts of PdIT, this application is not subject to the pediatric rule.)

Pre-NDA Meeting(s)? YES (Minutes are attached.)

Assigned Reviewers:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Dr. Pelayo
Secondary Medical:	Dr. Stockbridge
Pharmacology:	N/A (The application does not include a pharmacology/toxicology section as both products are approved and marketed. However, Dr. Resnick has indicated that a pharmacology review of the proposed labeling may be needed, as the pharmacology information from the aspirin monograph does not comply with the Rx labeling requirements and therefore may need to be modified.)
Chemist:	Dr. Zielinski
Environmental Assessment:	N/A
Statistician:	Dr. Lawrence
Biopharmacist:	Dr. Dorantes
Microbiologist:	N/A
DSI:	N/A
Project Manager:	Ms. LoCicero

Background

Documents relevant to the review of this application include:

1. Minute of October 31, 2000 meeting with BMS to discuss a pravastatin/aspirin combination product (fixed-dose, single tablet combination) and other pravastatin combination products.
2. April 11, 2001 response from DCRDP (Division of Cardio-Renal Drug Products) to the sponsor's February 14, 2001 proposal for a pravastatin/aspirin co-package application.
3. Minutes of the April 5, 2001 CMC pre-NDA meeting (attached).
4. Minutes of the May 8, 2001 pre-NDA meeting (attached).
5. Minutes of the June 12, 2001 internal meeting to discuss this application.

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. The Division's April 11, 2001 response to the sponsor's February 14, 2001 proposal stated that a meta-analysis of the data on subjects on both pravastatin and aspirin from studies in the proposed indication, secondary prevention of coronary events, would be needed to support approval of the application. The letter specified further that the point estimates and confidence intervals for this analysis would need to be included in the NDA.

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.

Prior to the submission of the application, there was considerable internal debate, as well as discussion with the sponsor, as to the range of pravastatin doses this application should cover. From the outset, the sponsor has proposed to provide for pravastatin 40 mg co-packaged products only (i.e., pravastatin 40 mg/aspirin 325 mg and pravastatin 40 mg/aspirin 81 mg). The sponsor claims that the pravastatin data they have in the setting in which they are seeking an indication for the co-packaged products, secondary prevention of coronary events, is of 40 mg pravastatin only. At the May 8, 2001 meeting, the Agency told BMS that we would decide whether the co-package application would need to include also pravastatin 20 mg co-packaged products, pending a decision by DMEDP on a supplemental application for pravastatin currently under review. This supplemental application proposes eliminating the 10 and 20 mg recommended starting doses for pravastatin, leaving a single 40 mg recommended starting dose. At the June 12, 2001 internal meeting, it was agreed that if DMEDP decides that eliminating the 10 and 20 mg recommended starting doses for pravastatin is acceptable, the co-package application will not need to include pravastatin 20 mg co-package products for approval. ☐

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It was decided at the June 12, 2001 internal meeting that DCRDP would file this application, provided there were no unexpected deficiencies with the application (i.e., we would not refuse to file because the application does not cover the full pravastatin dose range, etc.).

The meeting

Medical

Dr. Pelayo identified no unexpected deficiencies in the application that would be reason to refuse to file the application.

The medical review will consist of a review of the meta-analysis of data the sponsor has provided from five previously submitted studies. As per the combination product policy/co-package draft

decision tree, in order for the application to be approved, it will be necessary for the data to show that the effect of the combination in this setting is greater than the effect of either component individually. Dr. Pelayo estimated that he will finish his review no later than mid- February 2002.

Statistical

It is not clear whether a statistical review will be needed and none was requested. However, once Dr. Pelayo's review is under way and he has discussed his preliminary findings and impressions with Drs. Stockbridge and Lipicky, Dr. Lipicky may request a statistical review at that time.

Clinical Pharmacology/Biopharmaceutics

Dr. Marroum identified no filing concerns and expects that Dr. Dorantes will be finished with her review of this application by October 31, 2001.

Chemistry

Although the CMC section of the NDA is incomplete, Drs. Zielinski and Srinivasachar expect, based on previous agreements with the sponsor, that the needed CMC information will be submitted within a reasonable period of time and identified no filing concerns. The timing of the completion of Dr. Zielinski's review will depend on when the sponsor submits the outstanding CMC information. Dr. Zielinski expects, however, to complete his review within nine months of the submission of the original NDA (March 2002).

Bristol Myers-Squibb included in the original NDA submission an environmental assessment (EA) for aspirin. An EA is not required for Pravachol, as Pravachol is covered under NDA 19-898.

An Establishment Evaluation Request (EER) was submitted to the Office of Compliance on August 16, 2001.

DSI

Dr. Lipicky stated that no audits by the Division of Scientific Investigation will be needed for this application.

DDMAC

Dr. Haffer of DDMAC declined to attend this meeting. The sponsor's proposed labeling was sent electronically to Dr. Haffer by Ms. LoCicero on June 26, 2001.

OPDRA

The sponsor did not include in the original NDA submission a tradename for review.

Per Ms. Kathleen Bongiovanni of OPDRA, a pre-approval safety conference for this application will not be required, although OPDRA would be willing to have one if the Division believes one warranted.

Miscellaneous

Dr. Lipicky indicated that Dr. Temple will sign the action letter for this application.

Signature, Minutes Recorder: _____ Colleen LoCicero

Concurrence, Meeting Chair: _____ Raymond Lipicky, M.D.

drafted: 8/7/01

finalized: 8/27/01

rd:

Zielinski/8/16/01

Srinivasachar/8/16/01

Lawrence/8/18/01

Hung/8/20/01

Marroum/8/20/01

Pelayo/8/20/01

Stockbridge/8/27/01

Throckmorton/8/27/01

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Minutes of an internal meeting

Date of meeting:	June 12, 2001
Application:	<u> </u>
Product:	Pravastatin/aspirin co-package
Sponsor:	Bristol-Myers Squibb
Purpose:	to discuss pending supplement in HFD-510 and its implications on requirement for lower dose pravastatin co-packaged products
Teleconference Chair:	Robert Temple, M.D.
Teleconference Recorder:	Colleen LoCicero
Participants:	
Robert Temple, M.D.	Director, Office of Drug Evaluation I (HFD-101)
David Orloff, M.D. (by telephone)	Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Douglas Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products (HFD-110)
Norman Stockbridge, M.D., Ph.D.	Medical Team Leader, HFD-110
William Lubas, M.D. (by telephone)	Medical Officer, HFD-510
Mary Parks, M.D. (by telephone)	Medical Officer, HFD-510
Howard Lee, M.D.	Staff Fellow, Medical, HFD-110
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
Margaret Simoneau (by telephone)	Regulatory Health Project Manager, HFD-510
Colleen LoCicero	Regulatory Health Project Manager, HFD-110

Background

This teleconference was scheduled to discuss further the sponsor's anticipated pravastatin/aspirin co-package application, specifically, what will be required for approval with respect to the pravastatin doses provided for in the application. C

On the pravastatin doses required for the co-package application were to be the primary focus of the discussion.

The meeting

Dr. Orloff noted that although 40 mg pravastatin is an appropriate starting dose for most patients, there are subgroups of patients for whom a lower starting dose is appropriate. The sponsor did not provide any rationale or support for _____

While all the efficacy data from the long-term studies are derived from subjects on 40 mg pravastatin, these studies excluded patients with renal and/or hepatic dysfunction, and patients on cyclosporine. Additionally, enrollment was limited to certain age groups.

The question that HFD-510 faces is whether evidence that 40 mg pravastatin is as safe as 10 and 20 mg pravastatin is needed to justify the elimination of the two lower doses from the pravastatin starting dose recommendations. Although data are available from the long-term pravastatin studies from ~10,000 patients starting at 40 mg, none of these patients had significant renal and/or hepatic dysfunction or were taking cyclosporine. Dr. Orloff believes it unlikely, however, that switching from 20 mg to 40 mg pravastatin would be problematic, noting that it has never been demonstrated that less pravastatin is safer. When the "statins" came to market, they were all titrated to a desired effect as a precautionary measure only, as there are no data that demonstrate that lower statin doses are safer. Furthermore, Dr. Orloff noted that Lipitor's lowest marketed dose (10 mg) produces 35% lowering of lipids from baseline, which is approximately equivalent to the lipid-lowering effect of 40 mg pravastatin.

At the May 8th meeting with BMS, BMS stated that they did not intend to discontinue marketing of their single entity 10 and 20 mg pravastatin products, as they recognize that there are patients for whom a lower pravastatin dose is appropriate. It was noted that since patients with significant renal and/or hepatic dysfunction require close monitoring of their medications, they are generally not considered good candidates for convenience-packaged products, such as co-packaged products, combination products, etc. Language discouraging the use of co-packaged products in patients who require a lower pravastatin dose can be included in the co-package labeling. Historically, the Agency has required combination products to cover the full dose range of each of the individual components as it has applied to the general population, but not for special populations, such as those with hepatic impairment.

HFD-510 revised recently the recommendations for hepatic monitoring in the pravastatin labeling, recommending less rigorous monitoring. The new language recommends monitoring hepatic function at baseline, prior to increasing the pravastatin dose, and if found to be clinically indicated during treatment. The previous labeling recommended monitoring at baseline and at 12 weeks, and the labeling prior to that recommended monitoring at six, 12, 18 weeks and six months. It is not known whether pravastatin is hepatotoxic.

Those in attendance agreed that if HFD-510 determines that eliminating the 10 and 20 mg starting doses from the pravastatin label is appropriate

10 and 20 mg pravastatin co-packaged products will not be required for approval of the co-package application. The need for an 80 mg pravastatin co-packaged product, if the 80 mg "safe and effective" dose is approved, was discussed,

Minutes of a meeting

Date of meeting:

May 8, 2001

Application:

Product:

Pravastatin/Aspirin Co-package

Sponsor:

Bristol-Myers Squibb

Purpose:

pre-NDA

Meeting Chair:

Robert Temple, M.D.

Meeting Recorder:

Colleen LoCicero

Participants:

FDA

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Background

On February 14, 2001, the sponsor submitted to the Division of Metabolic and Endocrine Drug Products a proposal for an application for a co-packaged pravastatin/aspirin product for use in preventing cardiac events and stroke in patients with clinically evident coronary heart disease. After some internal discussion, it was decided that this application would be reviewed in the Division of Cardio-Renal Drug Products (DCRDP). On April 11, 2001, DCRDP issued a letter to the sponsor that responded to some of the issues identified in the February 14, 2001 submission and encouraged the sponsor to meet with the Division to discuss further the proposed co-package application. A separate Chemistry, Manufacturing and Controls (CMC) meeting was held on April 5, 2001 to discuss the CMC issues concerning the proposed application.

The meeting

Discussion Point #1: Dose range

Available pravastatin data seem to indicate that certain subpopulations of pravastatin users, particularly the elderly, are as responsive to 20 mg pravastatin as they are to 40 mg. If this is the case, an application for co-packaged pravastatin/aspirin products should provide for both 20 mg pravastatin and 40 mg pravastatin doses.

believe it premature to consider whether the co-packaged products should also include 80 mg pravastatin. If the co-package application provides for a 40 mg pravastatin dose only, the sponsor will need to justify the unavailability of the 20 mg pravastatin dose. We have said that we do not believe co-packaging should alter the practice of medicine, e.g., by forcing everyone to use 40 mg when some would have used 20 mg.

The sponsor acknowledged that there are subsets of the pravastatin population for which 10 and 20 mg pravastatin are appropriate doses. For this reason, they do not intend to discontinue marketing of these single entity products. However, it is not the sponsor's intention that the co-packaged products be used in these populations. The sponsor proposed specifying in detail in the co-package labeling that the co-packaged products are not intended for use in patients who require a lower pravastatin dose.

The sponsor reported

The Agency noted, however, that this is not currently and has never been pointed out in the pravastatin labeling.

The sponsor reported

1, Dr. Temple believed we should reconsider our position on the need for a 20 mg pravastatin/aspirin co-packaged product. As the Agency's decision on this application might set precedent for similar future co-package applications, Dr. Temple believed it important that we consider carefully this point. The Agency committed to follow up with the sponsor on this point.

Discussion Point #2: Need for a pharmacodynamic study

The design of the pharmacokinetic study BMS has conducted is acceptable. No pharmacodynamic study will be necessary, provided BMS reviews the available data and documents an effect for both co-packaged components in the presence of the other. First, BMS should be able to show that pravastatin is effective both in patients on aspirin and not on aspirin. That will establish the effect of pravastatin when added to aspirin. As there are few, if any, data examining the effect of aspirin added to a "statin", the Agency believed data from studies of other anti-platelet drugs (IIB/IIIA inhibitors, clopidogrel, etc.) plus a statin could be used to assess whether, in principle, adding an anti-platelet drug to a statin provides an added benefit. If it seems to do so, we would be prepared to conclude that aspirin is effective in the presence of a statin.

BMS presented information on comparative C_{max} and AUC for pravastatin alone versus pravastatin plus aspirin and aspirin alone versus aspirin plus pravastatin that appears to demonstrate no significant difference between the single entities and the combinations. BMS presented also findings from the meta-analyses they've done of the patients on pravastatin alone, aspirin alone, and pravastatin plus aspirin in the pravastatin secondary prevention studies that included a significant number of patients on both pravastatin and aspirin. They presented a Cox Analysis and Bayesian Analysis. Both analyses suggested that the pravastatin plus aspirin arms fared better than the pravastatin alone and aspirin alone arms on both fatal/nonfatal myocardial infarction (MI) and stroke.

Although the Agency found these findings reassuring, we believed information from the anti-platelet studies would provide additional support.

BMS was not sure they could access the anti-platelet data, but agreed to perform a literature search, search the FOI database for relevant anti-platelet data, ask Sanofi-Synthelabo for access to the relevant clopidogrel data, and gather and submit what data they can.

Discussion Point #3: Financial disclosure

For the NDA, the sponsor proposes to reference the previously submitted financial disclosure information for the more recent pravastatin studies included in the meta-analysis and attempt to obtain documentation for the older studies. The Agency found this proposal acceptable.

Discussion Point #4: Clinical/Statistical data

The sponsor proposes to merge substantially the clinical and statistical sections of the NDA into the application summary, but to submit report text for each of the studies included in the meta-analysis. Report appendices and supplemental tables will be available on request. The sponsor does not intend to include additional summaries of clinical data or other documentation (e.g., curriculum vitae, etc.) in the NDA. The Agency found the proposal acceptable.

Discussion Point #5: Annotated blank case report forms

Provided all datasets that support the meta-analysis are included in the application, the Agency found the proposal not to include annotated blank case report forms in the NDA acceptable.

Discussion Point #6: Case report forms for deaths and discontinuations due to AEs

The sponsor reported that case report forms (crfs) for all deaths and discontinuations due to adverse events (AEs) have been previously submitted to the Agency for all the studies included in the meta-analysis. Therefore, the sponsor proposes to submit crfs for deaths and discontinuations due to AEs, if any, from the pravastatin/aspirin interaction study only. The Agency found this proposal acceptable.

Discussion Point #7: Timeframe

The sponsor anticipates a June 2001 submission of the co-package application.

Conclusion

1. If the sponsor plans to provide 40 mg pravastatin co-packaged products only, they will need to provide justification in the application for not providing co-packaged products containing the other major pravastatin dose, 20 mg.

The Agency will follow up with the sponsor on our position on the need for 20 mg pravastatin co-packaged products.

2. A pharmacodynamic study will not be necessary, provided the sponsor can show in outcome studies that a statin is effective in the presence of aspirin and that anti-platelet drugs are effective in the presence of a statin. The sponsor agreed to do a literature search of the anti-platelet studies, search the FOI database for relevant anti-platelet data, ask Sanofi-Synthelabo for the relevant clopidogrel data, and gather and submit what data they can.
3. The sponsor's proposal for the submission of the financial disclosure information is acceptable.