CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-387

Chemistry Review(s)

Chemistry Review Data Sheet

NDA 21-387
(Resubmission)
Aspirin/ Pravastatin sodium

Ramsharan D. Mittal
Review Chemist
Division of Cardio-Renal Drug Products

Chemistry Review Data Sheet

1. NDA 21-387

2. REVIEW #: 3

3. REVIEW DATE: 06-June-2003

4. REVIEWER: Ramsharan D. Mittal

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	**Document Date**
Original NDA	June 22, 2001
Amendment	August 20, 2001
Amendment	December 14, 2001
Submission(s) Reviewed	Document Date
N000-BC	07-FEB-2002
N000-BC	14-FEB-2002
N000 (RS)	08-MAY-2002
N000-BC	28-MAY-2002
N000-BC	22-AUG-2002
N000-BC	06-SEP-2002
N000-BC	25-OCT-2002

6. SUBMISSION (S) BEING REVIEWED :

Submission(s) Reviewed	Document Date
N000-AC	03-JUN-2003

7. **NAME AND ADDRESS OF APPLICANT:**

Name: Bristol Myers Squibb Company
Address: PO Box 4000, Princeton, NJ 08543-4000
Representative: Porter Lane, Group Director
Telephone: (609) 252-4722

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name Pravigard PAC
   b) Non- Proprietary Name (USAN): Aspirin /Pravastatin Sodium
   c) Code Name/# (ONDC only): aspirin/SQ 31,000
   d) Chem. Type /Submission Priority (ONDC only):
      - Chem. Type: 4
      - Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION: N/A**

10. **PHARMACOL. CATEGORY:**

Pravachol is a lipid lowering statin. Bufferin (buffered aspirin) is an anti-platelet drug. The co-packaged product is indicated for long-term management of patients with clinically evident coronary heart disease to reduce the risk of death, nonfatal myocardial infarction, myocardial revascularization procedures and ischemic stroke

11. DOSAGE FORM: Tablets (Aspirin/Pravastatin co-package)

12. STRENGTH/POTENCY: 81 mg /20 mg; 325 mg/20 mg; 81 mg/40 mg; 325 mg/40 mg; 81 mg/80 mg; 325 mg/80 mg (Aspirin/Pravastatin sodium)

13. ROUTE OF ADMINISTRATION: Oral

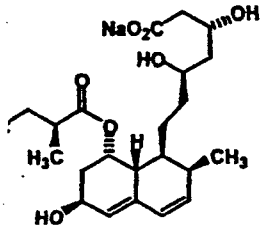
14. **Rx/OTC DISPENSED:** _X_Rx ___OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):** No

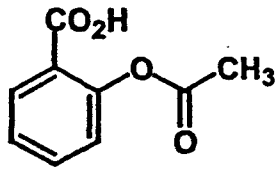
16. CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA,

Pravastatin Sodium: Hexahydro-β,δ-6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxyl)-1-naphthaleneheptanoic acid, monosodium salt, $C_{23}H_{35}NaO_7$, MW 446.52

Aspirin: Acetyl salicylic acid, $C_9H_8O_4$, MW 180.16



Pravastatin Sodium



Aspirin

17. RELATED/SUPPORTING DOCUMENTS:

DMFs: As per Review # 1.

DMF #	TYPE	HOLDER	ITEM	Code	Status	Date Completed	Comments
	II		Pravastatin Sodium	1	Adequate	2/26/02	
	II			1	Adequate	2/26/02	
	IV			1	Adequate	2/26/02	
	IV			1	Adequate	2/26/02	
	IV			1	Adequate	2/26/02	

DMF Sections 107, 113 and 136) for primary-packaging components was not reviewed because the components are routinely used for packaging pharmaceutical products

Action codes for DMF Table: 1 = DMF Reviewed.

Other Documents:	Number	Description
Approved NDA	NDA 19-898	Pravachol Tablets
Commercial IND	IND	

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	06/04/2003	S. Ferguson
Pharm/Tox	N/A		
Biopharm	(a) dissolution specs OK (b) Bio waiver for 81 mg Bufferin	12/20/2001	A Dorantes
LNC			
Methods Validation	Not needed because no new methods are used.	12/19/2001	FW Zielinski
DMETS	Pravigard PAC name is acceptable	08/14/2002	Kevin Dermanoski
EA	FONSI	11/14/2001	N. Sager & M. Maust
Microbiology	N/A		

Chemistry Review Data Sheet

The Chemistry Review for NDA 21-387

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Review # 2 recommended Not Approvable because of a withhold recommendation from the Office of Compliance. The status of this withhold was resolved by applicant withdrawing the [redacted] facility, for manufacturing Pravachol tablets. The NDA provides for the BMS facility in Humacao, Puerto Rico as an alternate site for manufacture of Pravachol tablets. The Overall recommendation from the Office of Compliance is ACCEPTABLE. A copy of the EER is attached at the end of this review.

From the CMC standpoint, the application is recommended for approval because the WITHHOLD by the Office of Compliance has been changed to ACCEPTABLE.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This application is a resubmission. Advisory Committee discussed the original application on January 18, 2002. Although the Committee agreed overall that the combination meets the efficacy standard for approval, they raised two safety concerns with the application.

- The first concern was that the range of the pravastatin doses for the co-packaged product was not adequate.

- The second concern was that the combination pravastatin/aspirin would present bleeding risk, as patients might not realize that they are taking a product which contains aspirin and fail to discontinue the product prior to dental, surgical or other invasive procedures.

In February 14, 2002 amendment, the applicant provided updated container labels for the blister and carton. The container labels now include the proposed trade name Pravigard PAC. In addition the applicant proposes the product to clearly indicate the presence of aspirin. The applicant proposed that the non-proprietary name will

lead with aspirin instead of pravastatin and the container label will bear the notion "This product contains aspirin".

Based on the Advisory Committee recommendations the applicant was required to include additional strengths and submitted the co-packaged product containing 20 mg, 40 mg, and 80 mg pravastatin tablets each co-packaged separately with 81 mg and 325 mg aspirin tablet. The applicant would have missed the Advisory Committee meeting which was to take place after the goal date of this NDA, therefore, the applicant withdrew the application and resubmitted it prior to the July Advisory Committee meeting.

The drug product is a co-package blister card containing Bufferin Tablets (OTC) and Pravachol Tablets (Approved NDA 19-898). Pravachol and Bufferin Tablets are placed into separate cavities in cold-form foil blisters. There is no contact between the Pravachol and Bufferin Tablets in the blisters. Co-packaging was developed to provide the patient with two tablets that are used together. This co-packaged drug product is expected to be more convenient to use than two individual containers (Pravachol and Bufferin). The patient compliance is expected to improve because the patient will be presented with both tablets in the co-package configuration.

Pravachol: CMC data for drug substance pravastatin sodium and drug product Pravachol (pravastatin sodium) Tablets 20 mg, 40 mg, and 80 mg are provided by reference to approved NDA 19-898. The current approved expiry data for Pravachol Tablets in foil pouch is 3 years.

Bufferin Aspirin: The drug substance aspirin, is well known and has a USP monograph. Buffered aspirin tablets comply with the OTC Tentative Final Monograph (CFR 310, 343 and 369) and USP for "Buffered Aspirin Tablets." Bristol Myers Squibb (BMS) currently markets the 325-mg buffered aspirin Tablets (OTC) but not the 81-mg buffered aspirin Tablets. The 81-mg buffered aspirin tablet is made from the same formulation as the 325-mg tablet but, obviously, it is ¼ the weight. Shape and de-bossing are different. The current approved expiry data for 325-mg buffered aspirin Tablets in foil pouch is 3 years. Based on the stability and expiry date of 325-mg buffered aspirin tablets, it is reasonable to expect the stability of the 81-mg tablets to be identical to the 325-mg tablets packaged in essentially impermeable cold-form foil blisters.

Stability data confirm that cold-form foil blisters do not transmit moisture and light. Therefore, statements concerning protection from light and moisture are eliminated from labeling

Available stability data for Bufferin Tablets are within specifications and expectations. Based on supportive data, known decomposition mechanisms and protective packaging concepts, 3-year expiration dating is granted.

Analytical methods validation will not be requested because no new analytical methods are involved in the approval of the co-packaged product.

Nancy Sager and Melissa Maust reviewed the Environmental Assessment for aspirin and its metabolite, salicylic acid. They determined that adverse environmental effects are not expected.

B. Description of How the Drug Product is Intended to be Used

The patient is expected to take a single Bufferin Tablet and a single Pravachol Tablet each day.

The expiration date proposed for the co-packaged product is 3 years. This is acceptable based on the stability of individual products, Buffered aspirin and Pravachol in similar package.

C. Basis for Approvable or Not-Approvable Recommendation

N/A

III. Administrative

A. Reviewer's Signature
B. Endorsement Block
C. CC Block

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 21387/000	Action Goal:	
Stamp:	22-JUN-2001	District Goal:	08-JAN-2003
Regulatory Due:	09-MAR-2003	Brand Name:	PRAVACHOL(ASPIRIN/PRAVAS
Applicant:	BRISTOL MYERS SQUIBB CO PHARMA 5400 PRINCETON, NJ 08540	Estab. Name:	TATIN SODIUM)
		Generic Name:	ASPIRIN/PRAVASTATIN SODIUM
Priority:	4S	Dosage Form:	(TABLET)
Org Code:	110	Strength:	81 OR 325 MG / 40 MG

Application Comment: THIS NDA DESCRIBES CO-PACKAGING OF PRAVACHOL TABLETS (NDA19-898) WITH BUFFERIN TABLETS. THE VARIOUS SITES LISTED IN THIS EER ARE RESPONSIBLE FOR [redacted] DRUG SUBSTANCES, DRUG PRODUCTS, PACKAGING OR TESTING. PLEASE CALL FLORIAN ZIELINSKI, FDA REVIEW CHEMIST AT (301) 594-5348 FOR ADDITIONAL INFORMATION AND / OR CLARIFICATION. (on 16-AUG-2001 by ZIELINSKIF)

FDA Contacts:	C. LOCICERO	(HFD-101)	301-594-6758	, Project Manager
	R. MITTAL	(HFD-110)	301-594-5353	, Review Chemist
	K. SRINIVASACHAR	(HFD-110)	301-594-5376	, Team Leader

Overall Recommendation:
ACCEPTABLE on 04-JUN-2003 by S. FERGUSON (HFD-322) 301-827-9009
WITHHOLD on 05-MAR-2003 by S. FERGUSON (HFD-322) 301-827-9009
ACCEPTABLE on 26-JUN-2002 by J. D AMBROGIO (HFD-322) 301-827-9049
ACCEPTABLE on 04-MAR-2002 by J. D AMBROGIO (HFD-322) 301-827-9049
WITHHOLD on 30-NOV-2001 by S. FERGUSON (HFD-322) 301-827-9009

Establishment: CFN 1819504 FEI 1819504
BRISTOL MYERS SQUIBB CO
2400 WEST LLOYD EXPY.
EVANSVILLE, IN 477210001

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE MANUFACTURER
Profile: CTL OAI Status: NONE

Estab. Comment: THIS FACILITY CONFIRMS [redacted] RESULTS PROVIDED BY [redacted] FOR ASPIRIN (on 15-AUG-2001 by ZIELINSKIF)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-AUG-2001				ZIELINSKIF
OC RECOMMENDATION	16-AUG-2001			ACCEPTABLE BASED ON PROFILE	FERGUSONS
REQUEST CANCELLED	09-APR-2002			APPLICATION WITHDRAWN	EES_PROD
SUBMITTED TO OC	13-DEC-2002				FERGUSONS
OC RECOMMENDATION	13-DEC-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Profile: TCM OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-AUG-2001				ZIELINSKIF
REQUEST CANCELLED	16-AUG-2001			IRRELEVANT FACILITY/PROFILE	FERGUSONS
SUBMITTED TO OC	21-JUN-2002				MITTALR
SUBMITTED TO DO	24-JUN-2002	10D			DAMBROGIOJ
DO RECOMMENDATION	26-JUN-2002			ACCEPTABLE BASED ON FILE REVIEW	MROBINSO
GMP & PAI EI 1/22-2/13/2002 WAS CLASSIFIED VAI FOR DEVIATIONS NOT LIKELY TO AFFECT FINAL PRODUCT QUALITY.					
OC RECOMMENDATION	26-JUN-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: CFN 1825662 FEI 1825662
BRISTOL MYERS SQUIBB CO
HWY 62 WEST BLDG 122
MOUNT VERNON, IN 47620

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM OAI Status: NONE

Estab. Comment: DET-DO FACTS ASSIGNMENT 231266 CALLS FOR A GMP AND PAI EI OF TABLETS & CAPSULES WITH A TARGET DUE DATE OF FEBRUARY 21, 2002, AND A ROUTINE PRIORITY. (on 16-AUG-2001 by M. ROBINSON (HFR-CE740) 313-226-6260)
MFG BUFFERED ASPIRIN (on 15-AUG-2001 by ZIELINSKIF)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-AUG-2001				ZIELINSKIF
SUBMITTED TO DO	16-AUG-2001	GMP			FERGUSONS
ASSIGNED INSPECTION T	16-AUG-2001	PS			MROBINSO
INSPECTION PERFORMED	30-NOV-2001		02-NOV-2001		MROBINSO
DO RECOMMENDATION	30-NOV-2001			ACCEPTABLE INSPECTION	MROBINSO
PAI EI 10/24-11/2/2001 COVERED THIS PRODUCT AND WAS CLASSIFIED NAI.					
OC RECOMMENDATION	30-NOV-2001			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS
REQUEST CANCELLED	09-APR-2002			APPLICATION WITHDRAWN	EES_PROD
SUBMITTED TO OC	13-DEC-2002				FERGUSONS
SUBMITTED TO DO	16-DEC-2002	10D			DAMBROGIOJ
DO RECOMMENDATION	16-DEC-2002			ACCEPTABLE BASED ON FILE REVIEW	MROBINSO
GMP & PAI EI 10/24-11/2/2001 WAS CLASSIFIED NAI AND PROFILED ACCEPTABLE.					
OC RECOMMENDATION	17-DEC-2002			ACCEPTABLE	DAMBROGIOJ

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DISTRICT RECOMMENDATION

Establishment: CFN FEI

DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TCM OAI Status: NONE

Estab. Comment: PACKAGES PRAVASTATIN AND BUFFERED ASPIRIN TOGETHER (CO-PACKAGING) (on 15-AUG-2001 by ZIELINSKIF)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-AUG-2001				ZIELINSKIF
OC RECOMMENDATION	16-AUG-2001			ACCEPTABLE BASED ON PROFILE	FERGUSONS
REQUEST CANCELLED	09-APR-2002			APPLICATION WITHDRAWN	EES_PROD
SUBMITTED TO OC	13-DEC-2002				FERGUSONS
OC RECOMMENDATION	13-DEC-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN FEI

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment: MFG ASPIRIN, "NOR INFO IN DMF (on 15-AUG-2001 by ZIELINSKIF)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-AUG-2001				ZIELINSKIF
OC RECOMMENDATION	16-AUG-2001			ACCEPTABLE BASED ON PROFILE	FERGUSONS
REQUEST CANCELLED	09-APR-2002			APPLICATION WITHDRAWN	EES_PROD
SUBMITTED TO OC	13-DEC-2002				FERGUSONS

Redacted 4

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/s/

Ramsharan Mittal
6/6/03 02:48:44 PM
CHEMIST

Kasturi Srinivasachar
6/6/03 02:56:09 PM
CHEMIST

Chemistry Review Data Sheet

NDA 21-387
(Resubmission)
Aspirin/ Pravastatin sodium

Ramsharan D. Mittal
Review Chemist
Division of Cardio-Renal Drug Products

Chemistry Review Data Sheet

1. NDA 21-387

2. REVIEW #: 2

3. REVIEW DATE: 06-March-2003

4. REVIEWER: Ramsharan D. Mittal

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original NDA	June 22, 2001
Amendment	August 20, 2001
Amendment	December 14, 2001

6. SUBMISSION (S) BEING REVIEWED :

Submission(s) Reviewed	Document Date
N000-BC	07-FEB-2002
N000-BC	14-FEB-2002
N000 (RS)	08-MAY-2002
N000-BC	28-MAY-2002
N000-BC.	22-AUG-2002
N000-BC	06-SEP-2002
N000-BC	25-OCT-2002

7. **NAME AND ADDRESS OF APPLICANT:**

Name: Bristol Myers Squibb Company
Address: PO Box 4000, Princeton, NJ 08543-4000
Representative: Porter Lane, Group Director
Telephone: (609) 252-4722

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name Pravigard PAC
   b) Non- Proprietary Name (USAN): Aspirin /Pravastatin Sodium
   c) Code Name/# (ONDC only): aspirin/SQ 31,000
   d) Chem. Type /Submission Priority (ONDC only):
      - Chem. Type: 4
      - Submission Priority: S

Chemistry Review Data Sheet

9. **LEGAL BASIS FOR SUBMISSION: N/A**

10. **PHARMACOL. CATEGORY:**

Pravachol is a lipid lowering statin. Bufferin (buffered aspirin) is an anti-platelet drug. The co-packaged product is indicated for long-term management of patients with clinically evident coronary heart disease to reduce the risk of death, nonfatal myocardial infarction, myocardial revascularization procedures and ischemic stroke

11. DOSAGE FORM: Tablets (Aspirin/Pravastatin co-package)

12. STRENGTH/POTENCY: 81 mg /20 mg; 325 mg/20 mg; 81 mg/40 mg; 325 mg/40 mg; 81 mg/80 mg; 325 mg/80 mg (Aspirin/Pravastatin sodium)

13. ROUTE OF ADMINISTRATION: Oral

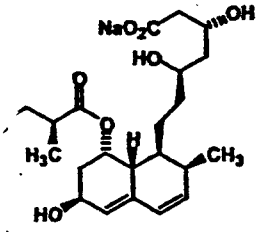
14. **Rx/OTC DISPENSED:** _X_ Rx ___OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):** No

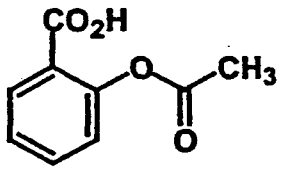
16. CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA,

Pravastatin Sodium: Hexahydro-β,δ-6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxyl)-1-naphthaleneheptanoic acid, monosodium salt, $C_{23}H_{35}NaO_7$, MW 446.52

Aspirin: Acetyl salicylic acid, $C_9H_8O_4$, MW 180.16



Pravastatin Sodium



Aspirin

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

DMFs: As per Review # 1.

DMF #	TYPE	HOLDER	ITEM	Code	Status	Date Completed	Comments
	II		Pravastatin Sodium	1	Adequate	2/26/02	
	II			1	Adequate	2/26/02	
	IV			1	Adequate	2/26/02	
	IV			1	Adequate	2/26/02	
	IV			1	Adequate	2/26/02	

DMF(Sections 107, 113 and 136) for primary-packaging components was not reviewed because the components are routinely used for packaging pharmaceutical products

Action codes for DMF Table: 1 = DMF Reviewed.

Other Documents:	Number	Description
Approved NDA	NDA 19-898	Pravachol Tablets
Commercial IND	IND( )	

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	03/05/2003	S. Ferguson
Pharm/Tox	N/A		
Biopharm	(a) dissolution specs OK (b) Bio waiver for 81 mg Bufferin	12/20/2001	A Dorantes
LNC			
Methods Validation	Not needed because no new methods are used.	12/19/2001	FW Zielinski
DMETS	Pravigard PAC name is acceptable	08/14/2002	Kevin Dermanoski
EA	FONSI	11/14/2001	N. Sager & M. Maust
Microbiology	N/A		

Chemistry Review Data Sheet

The Chemistry Review for NDA 21-387

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Review # 1 recommended Not Approvable because of a withhold recommendation from the Office of Compliance. The status of this withhold was resolved by withdrawing the facility for [redacted] and submitting a new facility. The Overall recommendation from the Office of Compliance is still WITHHOLD because of the withhold status of the tablet manufacturing facility at [redacted] All pending CMC issues have been addressed. A copy of the EER is attached at the end of this review.

From the CMC standpoint, the application is not approvable because of the Overall Recommendation of Withhold by the Office of Compliance. The application may be approved only after an overall recommendation of Acceptable by the Office of Compliance, is issued.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This application is a resubmission. Advisory Committee discussed the original application on January 18, 2002. Although the Committee agreed overall that the combination meets the efficacy standard for approval, they raised two safety concerns with the application.

- The first concern was that the range of the pravastatin doses for the co-packaged product was not adequate.

- The second concern was that the combination pravastatin/aspirin would present bleeding risk, as patients might not realize that they are taking a product which contains aspirin and fail to discontinue the product prior to dental, surgical or other invasive procedures.

In February 14, 2002 amendment, the applicant provided updated container labels for the blister and carton. The container labels now include the proposed trade name Pravigard PAC. In addition the

applicant proposes the product to clearly indicate the presence of aspirin. The applicant proposed that the non-proprietary name will lead with aspirin instead of pravastatin and the container label will bear the notion "This product contains aspirin".

Based on the Advisory Committee recommendations the applicant was required to include additional strengths and submitted the co-packaged product containing 20 mg, 40 mg, and 80 mg pravastatin tablets each co-packaged separately with 81 mg and 325 mg aspirin tablet. The applicant would have missed the Advisory Committee meeting which was to take place after the goal date of this NDA, therefore, the applicant withdrew the application and resubmitted it prior to the July Advisory Committee meeting.

The drug product is a co-package blister card containing Bufferin Tablets (OTC) and Pravachol Tablets (Approved NDA 19-898). Pravachol and Bufferin Tablets are placed into separate cavities in cold-form foil blisters. There is no contact between the Pravachol and Bufferin Tablets in the blisters. Co-packaging was developed to provide the patient with two tablets that are used together. This co-packaged drug product is expected to be more convenient to use than two individual containers (Pravachol and Bufferin). The patient compliance is expected to improve because the patient will be presented with both tablets in the co-package configuration.

Pravachol: CMC data for drug substance pravastatin sodium and drug product Pravachol (pravastatin sodium) Tablets 20 mg, 40 mg, and 80 mg are provided by reference to approved NDA 19-898. The current approved expiry data for Pravachol Tablets in foil pouch is 3 years.

Bufferin Aspirin: The drug substance aspirin, is well known and has a USP monograph. Buffered aspirin tablets comply with the OTC Tentative Final Monograph (CFR 310, 343 and 369) and USP for "Buffered Aspirin Tablets." Bristol Myers Squibb (BMS) currently markets the 325-mg buffered aspirin Tablets (OTC) but not the 81-mg buffered aspirin Tablets. The 81-mg buffered aspirin tablet is made from the same formulation as the 325-mg tablet but, obviously, it is ¼ the weight. Shape and de-bossing are different. The current approved expiry data for 325-mg buffered aspirin Tablets in foil pouch is 3 years. Based on the stability and expiry date of 325-mg buffered aspirin tablets, it is reasonable to expect the stability of the 81-mg tablets to be identical to the 325-mg tablets packaged in essentially impermeable cold-form foil blisters.

Stability data confirm that cold-form foil blisters do not transmit moisture and light. Therefore, statements concerning protection from light and moisture are eliminated from labeling

Available stability data for Bufferin Tablets are within specifications and expectations. Based on supportive data, known decomposition mechanisms and protective packaging concepts, 3-year expiration dating is granted.

Analytical methods validation will not be requested because no new analytical methods are involved in the approval of the co-packaged product.

Nancy Sager and Melissa Maust reviewed the Environmental Assessment for aspirin and its metabolite, salicylic acid. They determined that adverse environmental effects are not expected.

B. Description of How the Drug Product is Intended to be Used

The patient is expected to take a single Bufferin Tablet and a single Pravachol Tablet each day.

The expiration date proposed for the co-packaged product is 3 years. This is acceptable based on the stability of individual products, Buffered aspirin and Pravachol in similar package.

C. Basis for Approvable or Not-Approvable Recommendation

The Overall recommendation from Office of the Compliance is WITHHOLD because of the withhold status of the tablet manufacturing facility at [redacted] where cGMP violations were uncovered during recent inspection.

III. Administrative

A. Reviewer's Signature
B. Endorsement Block
C. CC Block

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/s/

Ramsharan Mittal
3/6/03 12:08:02 PM
CHEMIST

Kasturi Srinivasachar
3/6/03 12:23:48 PM
CHEMIST

Chemistry Review Data Sheet

NDA 21-387

Pravachol / Bufferin

Florian Zieliński, Review Chemist
Division of Cardio-Renal Drug Products

Original NDA dated June 22, 2001 with Amendments dated August 20 and Dec 14, 2001

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-387

2. REVIEW #1

3. REVIEW DATE: February 27, 2002

4. REVIEWER: Florian Zielinski

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Original NDA	June 22, 2001
Amendment	August 20, 2001
Amendment	December 14, 2001

7. NAME & ADDRESS OF APPLICANT:

Name:	Bristol Myers Squibb Company
Address:	PO Box 4000 Princeton, NJ 08543-4000
Representative:	Porter Lane, Group Director
Telephone:	(609) 252-4722

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Pravachol / Bufferin
   b) Non-Proprietary Name (USAN): Pravastatin Sodium / Aspirin
   c) Code Name/# (ONDC only): SQ 31,000 / aspirin
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 4
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Pravachol is a lipid lowering statin. Bufferin (buffered aspirin) is an anti-platelet drug. The co-packaged product is indicated for long-term management of patients with clinically evident coronary heart disease to reduce the risk of death, nonfatal myocardial infarction, myocardial revascularization procedures and ischemic stroke

Chemistry Review Data Sheet

11. DOSAGE FORM: Tablets for oral administration

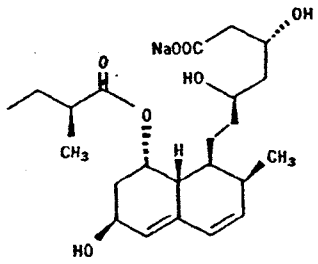
12. STRENGTH/POTENCY: 40 mg Pravachol co-packaged with an 81-mg or 325-mg Bufferin

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

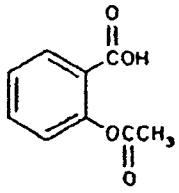
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{23}H_{35}NaO_7$ MW 446.52

Pravastatin sodium is hexahydro-β,δ-6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxyl)-1-naphthaleneheptanoic acid, monosodium salt.



Aspirin is acetyl salicylic acid

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

DMFs:

DMF #	TYPE	HOLDER	ITEM	Code	Status	Date Completed	Comments
[redacted]	II	[redacted]	Pravastatin Sodium	1	Adequate	2/26/02	
	II		[redacted]	1	Adequate	2/26/02	
	IV			1	Adequate	2/26/02	
	IV			1	Adequate	2/26/02	
	IV			1	Adequate	2/26/02	

DMF [redacted] Sections 107, 113 and 136) for primary-packaging components was not reviewed because the components are routinely used for packaging pharmaceutical products

Action codes for DMF Table: 1 = DMF Reviewed

Other Documents:	**Number**	**Description**
Approved NDA	NDA 19-898	Pravachol Tablets
Commercial IND	IND [redacted]	[redacted]

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	11/30/2001	S. Ferguson
Pharm/Tox	N/A		
Biopharm	(a) dissolution specs OK (b) Bio waiver for 81 mg Bufferin	12/20/01	A Dorantes
LNC			
Methods Validation	Not needed because no new methods are used.	12/19/01	FW Zielinski
OPDRA	N/A Trade name not submitted yet		
EA	FONSI	11/14/2001	N. Sager & M. Maust
Microbiology	N/A		

Chemistry Review Data Sheet

The Chemistry Review for NDA 21-387

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not approvable because:

(1) The overall establishment evaluation for CGMP compliance is WITHHOLD. This recommendation is based on significant CGMP deficiencies.

(2) The container/ closure section of the application is incomplete. Please refer to the List of Chemistry Deficiencies and Comments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is a co-package blister card containing Bufferin Tablets (OTC) and Pravachol Tablets (Approved NDA 19-898). Pravachol and Bufferin Tablets are placed into separate cavities in cold-form foil blisters. There is no contact between the Pravachol and Bufferin Tablets in the blisters. Co-packaging was developed to provide the patient with two tablets that are used together. This co-packaged drug product is expected to be more convenient to use than two individual containers (Pravachol and Bufferin). The patient compliance is expected to improve because the patient will be presented with both tablets in the co-package configuration.

Pravachol: CMC data for drug substance pravastatin sodium and 40 mg Pravachol (pravastatin) Tablets are provided by reference to approved NDA 19-898.

Bufferin: Bufferin tablets comply with the OTC Tentative Final Monograph (CFR 310, 343 and 369) and USP for "Buffered Aspirin Tablets." Bristol Myers Squibb (BMS) currently markets the 325-mg Bufferin Tablets (OTC) but not the 81-mg Bufferin Tablets. The 81-mg Bufferin tablet is made from the same formulation as the 325-mg tablet but, obviously, it is ¼ th the weight. Shape and debossing are different.

The OTC monograph describes the daily administration of 75 to 325 mg aspirin for the prevention of recurrent myocardial infarct.

Complete stability data is provided for the 325-mg Bufferin Tablet. Data confirm that cold-form foil blisters do not transmit moisture and light. Therefore, statements concerning protection from light and moisture are eliminated from labeling. Furthermore, it is reasonable to expect the stability of the 81-mg Bufferin tablets to be identical to the 325-mg tablets packaged in essentially impermeable cold-form foil blisters.

Available stability data for Bufferin Tablets are within specifications and expectations. Based on supportive data, known decomposition mechanisms and protective packaging concepts, 3-year expiration dating is granted.

Analytical methods validation is not requested because no new analytical methods are involved in the approval of the co-packaged product.

Nancy Sager and Melissa Maust reviewed the Environmental Assessment for aspirin and its metabolite, salicylic acid. They determined that adverse environmental effects are not expected.

Chemistry Review Data Sheet

B. Description of How the Drug Product is Intended to be Used

The patient is expected to take a single Bufferin Tablet and a single Pravachol Tablet each day.

C. Basis for Not-Approval Recommendation

The overall establishment evaluation for CGMP compliance is WITHHOLD. As a result, this NDA can not be approved at this time. The recommendation is based on significant CGMP deficiencies.

In addition, the applicant should adequately document information on the container closure requested in the list of Deficiencies and Comments.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist's Name / Date: Florian Zielinski / February 27, 2002
Chemistry Team Leader's Name / Date: Kasturi Srinivasachar
Project Manager's Name / Date:

C CC Block

Redacted 20

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confidential

commercial

information

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

/s/

Florian Zielinski
2/27/02 10:19:01 AM
ENV ASSESSMENT

Kasturi Srinivasachar
2/27/02 04:02:15 PM
CHEMIST