CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-387

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

NDA 21-387 **SUBMISSION DATE:** June 22, 2001

Pravastatin 40 mg Tablets co-packaged with
Aspirin 81 mg or Buffered Aspirin 325 mg Tablets
Bristol-Myers Squibb Pharm. Res. Institute
Princeton, NJ **REVIEWER:** Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Original New Drug Application

TABLE OF CONTENTS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-387	Brand Name	NA
OCPB Division (I, II, III)	DPEI	Generic Name	Pravastatin/Aspirin Tab
Medical Division	DCRDP	Drug Class	Lipid-lowering agent & analgesic
OCPB Reviewer	Angelica Dorantes, Ph.D.	Indication(s)	Reduce risk of cardiovascular events
OCPB Team Leader	Patrick Marroum, Ph.D.	Dosage Form	40/81 mg & 40/325 mg
		Dosing Regimen	Once a day
Date of Submission	June 22, 2001	Route of Administration	Oral
OCPB Estimated Due Date	September 2001	Sponsor	Bristol-Myers Squibb
PDUFA Due Date	April 22, 2002	Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data,	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vitro effects on primary drug:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request	X			
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2	2	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments to be sent to the firm ?	X	Filing Comment: • A biowaiver request to support the lower proposed strength of pravastatin 40 mg/aspirin 81 mg and supportive dissolution data were not included in the NDA. Therefore, the sponsor needs to provide such information.
QBR questions (key issues to be considered)		1. Is there a clinically relevant interaction between pravastatin and aspirin when they are administered concomitantly? 2. Is the bio-waiver request for the lower proposed strength of pravastatin 40 mg/aspirin 81 mg acceptable? 3. Is the clinical pharmacology and biopharmaceutic information included in the proposed labeling acceptable to OCPB?
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

EXECUTIVE SUMMARY

Background:

Cardiovascular disease is the major cause of death in the United States. The AHA Consensus Panel provided guidelines in 1995 for the reduction of risk in patients with coronary artery disease. These guidelines included the use of aspirin 80-325 mg and a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (a statin) along with other risk reducing medications (i. e., antihypertensives), where appropriate.

Statins such as pravastatin, are competitive inhibitors of HMG-CoA reductase, have become the lipid-lowering therapy of choice. Pravastatin reduces cardiovascular clinical events in primary prevention and in secondary prevention populations. The ability of pravastatin, given as an oral 40 mg dose once a day, to reduce these total cardiovascular risks is appropriately described in the approved labeling by various worldwide regulatory authorities.

Aspirin treatment has also been shown to be effective in reducing fatal and non-fatal myocardial infraction (MI) or sudden death in patients with chronic stable angina. The use of aspirin as a therapeutic agent in the management of patients with cardiovascular and cerebrovascular diseases has been widely supported by the professional medical societies.

As these two therapies for cardiovascular risk reduction, aspirin and pravastatin, work by such different mechanisms, i.e., impairing thrombus formation and reducing LDL-C respectively, it was considered probable that they would show an independence of effect in man. Although the combined administration of these two agents seems logical, to date, there are no published data demonstrating the independence of effect of these two agents, which would justify the clinical use of the combination.

Submission:

Original NDA 21-387 for Pravastatin sodium 40 mg tablets co-packaged with either aspirin tablets 81 mg or buffered aspirin tablets 325 mg was filed on June 22, 2001. This product is indicated [redacted]

The central objective of this application was to assess the efficacy of the combination of pravastatin 40 mg and aspirin compared with the individual components alone. In this Application, existing databases from five (5) pravastatin secondary prevention studies submitted to original NDA 19-898 for Pravachol Tablets, were retrospectively analyzed to assess the efficacy of these two agents when taken concomitantly The five pravastatin studies were LIPID (Protocol 27,201-095, Long Term Intervention with Pravastatin in Ischemic Disease), CARE (Protocol 27,201-067, Cholesterol and Recurrent Events), PLAC I (Protocol 27,201-026, Pravastatin Limitation of Atherosclerosis in the Carotids), PLAC II (Protocol 27,201-50, Pravastatin, Lipids and Atherosclerosis in the Carotids), and REGRESS (Protocol 27,201-82, Regression Growth Evaluation Statin).

The main elements included in this submission are; proposed labeling, an Application Summary, Integrated Summaries of Efficacy and Safety (i.e., meta-analysis of data from studies PLAC I, PLAC II, REGRESS, CARE, and LIPID), a copy of the text of the report for each of the five studies included in the meta-

analysis, a Human Pharmacokinetic and Bioavailability section containing information on a not previously submitted pravastatin-aspirin interaction study (CV123-234), a Chemistry, Manufacturing and Controls section, and electronic data sets for both the Human Pharmacokinetic and Bioavailability, and Clinical/Statistical sections.

From the clinical pharmacology and biopharmaceutic viewpoint, study CV123-2347 was submitted in support of the pravastatin (40 mg) and buffered aspirin (325 mg) co-package application. The purpose of this study was to assess the potential pharmacokinetic interaction of pravastatin and aspirin given concomitantly. The results of this study showed that the 90% confidence intervals of AUCinf and Cmax for serum pravastatin and plasma salicylate were within the 80-125% equivalence criteria recommended by the Agency. Therefore, it was concluded that buffered aspirin has no effect on the pharmacokinetics of pravastatin and pravastatin has no effect on the pharmacokinetics of buffered aspirin when administered concurrently.

Additionally, dissolution data were provided to support a bio-waiver request of the requirement for the submission of bioequivalence data for the new 81 mg lower strength of buffered aspirin tablet. This tablet will be included in the pravastatin (40 mg) and buffered aspirin (81 mg) co-package that the sponsor is seeking approval for.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the information included in original NDA 21-387 dated June 22, 2001 for pravastatin sodium tablets and buffered aspirin tablets co-packaged product and has the following Comments:

- ***Waiver Request:*** Based on the review of the submitted dissolution information, OCPB is of the opinion that the sponsor has provided appropriate data to support their request for a bio-waiver for the requirement of the submission of in vivo bioequivalence data for the 81 mg strength of buffered aspirin. Therefore, a bio-waiver for this lower strength of buffered aspirin is granted.
- ***Dissolution:*** With respect to the currently approved dissolution methods and specifications for pravastatin and buffered aspirin individual tablets, no dissolution changes are recommended for the pravastatin tablets co-packaged with buffered aspirin tablets.
- ***Labeling:*** The clinical pharmacology and biopharmaceutic information for pravastatin and buffered aspirin included in the proposed labeling is appropriate and acceptable.

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Patrick Marroum, Ph.D. _____

Briefing Day: 12/20/01 (Mehta, Sahajwalla, Marroum, Dorantes, Wei)

cc: NDA 21-387, HFD-110, HFD-860 (Dorantes, Mehta), and CDR (Biopharm).

QUESTION BASED REVIEW

How will the drug product be presented?

Pravastatin sodium tablets and buffered aspirin tablets will be presented as either a PRAVACHOL® 40 mg tablet and BUFFERIN® 325 mg tablet or PRAVACHOL® 40 mg tablet and BUFFERIN® 81 mg tablet co-packaged products.

PRAVACHOL® 40 mg tablets and the current tri-buffered formulation for BUFFERIN® 325-mg tablets have been available on the market individually for more than 10 years by prescription and OTC, respectively. The BUFFERIN 81-mg tablet is not currently marketed but is in development; the 81-mg tablet will have identical composition (same drug/excipient ratio) to the 325-mg tablet and will differ only in tablet weight, shape and debossing.

Composition and Dosage Form

PRAVACHOL® (pravastatin sodium) 40 mg Tablets

Information pertaining to the identity, quality and manufacture of PRAVACHOL® (pravastatin sodium) 40 mg tablets is referenced to Bristol-Myers Squibb's NDA 19-898 for PRAVACHOL® (pravastatin sodium) Tablets, 10 mg, 20 mg and 40 mg.

Buffered Aspirin 325 and 81 mg Tablets

The quantitative compositions of the two strengths of buffered aspirin 325 and 81 mg tablets are shown in Table 1. The tablets comprise an aspirin layer and an alkaline layer presented as a bilayer tablet which is film-coated for aesthetic purposes. The buffered aspirin tablets, 81 mg and 325 mg, are quantitatively identical with the lower strength tablet compressed at approximately one quarter of the weight of the 325 mg product.

Quantitative Composition of Buffred Aspirin Tablets, 81 mg and 325 mg

COMPONENT	FUNCTION	81 MG/TABLET	325 MG/TABLET
Aspirin Layer		-	-
Aspirin	Active		
Alkaline Layer			
Magnesium Stearate			
Total Weight Uncoated		**165.14**	**662.61**
Film Coat Composition		-	-
Purified water		q.s.	q.s.
		-	

Investigational Formulations

Buffered aspirin 325-mg tablets Batch 007502 was used in the drug-interaction study (CV123-234). In addition, this batch of buffered aspirin 325-mg tablets is the reference product used to generate *in vitro* dissolution data presented in this submission to support a bio-waiver request for the lower

strength buffered aspirin tablet. Batch 007502 is representative of a typical lot of BUFFER1N® 325-mg tablets that is currently available on the market as an OTC product.

Buffered aspirin 81-mg tablets Batch 8MEM247 is the test product used to generate in vitro dissolution data presented in the NDA to support a bio-waiver request for the lower strength buffered aspirin tablet. This batch is one of the process justification batches that have been manufactured to support the launch of the buffered aspirin 81-mg tablets in the pravastatin sodium tablets and buffered aspirin tablets co-packaged product. All stages of manufacture of Batch 8MEM247 have been conducted at [redacted] employing the commercial procedures and the commercial scale ([redacted]

Is the requested bio-waiver acceptable?

In this submission Bristol-Myers Squibb is requesting a bio-waiver for the new lower strength buffered aspirin 81 mg tablets. In support of their request the following information was provided:

- Comparative dissolution data in three different pH media,
- Formulation data showing that the lower strength tablet is proportionally similar in its active and inactive ingredients to the higher strength 325 mg tablet used in the in vivo study, and
- Published data showing that the absorption and elimination kinetics of aspirin are linear over the dose range covered by this submission.

Dissolution Data

Dissolution testing of aspirin was conducted in three different pH media across the physiological range [redacted] In all cases the dissolution test conditions employed the USP Type 2 apparatus (paddles) and a media volume of 500 mL as described in the USP monograph for buffered aspirin tablets. The sponsor employed a slower paddle rotation speed ([redacted]) than that defined in the USP monograph (75 rpm) to generate the drug release profiles for the comparison calculations.

The individual in vitro dissolution results at 5, 10, 15, and 20 minutes in the three media are shown below for the 325 mg and 81 mg buffered aspirin tablets. The dissolution profiles in each media, were compared by calculating the similarity factors (f2). The results showed that the similarity factors are in the 50-100 range, thereby demonstrating equivalence of in vitro drug release from the two strength buffered aspirin tablets. A summary of the dissolution data is presented in the next table.

DISSOLUTION MEDIUM	% DISSOLVED (N=12) BUFFERED ASPIRIN 325 MG				% DISSOLVED (N=12) BUFFERED ASPIRIN 81 MG				
	5min	10 min	15min	20min	5min	10 min	15min	20min	f_2
/	48.9 (44-56)	67.6 (61-74)	75.6 (68-83)	80.4 (73-88)	54 (45-65)	72.4 (62-84)	80.4 (71-92)	85.6 (79-96)	65
/	64.9 (51-74)	81.1 (66-93)	87.3 (73-97)	90.5 (76-99)	72.5 (65-80)	88.3 (82-94)	94.9 (87-99)	98.1 (90-102)	56
/	47.9 (29-61)	67.5 (46-80)	76.3 (56-87)	81.7 (64-91)	56.9 (43-65)	77.2 (65-85)	86.2 (76-93)	91.0 (82-99)	51

Reviewer Comment:

- *Although a different rotation speed was used to generate the dissolution profiles, this reviewer is of the opinion that a slower speed may discriminate better the dissolution profiles. Therefore, the provided dissolution information can be used to support their request and a bio-waiver for the 81 mg buffered aspirin tablet is granted.*

What are the highlights of the pharmacokinetics of pravastatin and aspirin?

- ***Pravastatin:*** In clinical pharmacology studies in man, pravastatin is rapidly but incompletely absorbed, with peak plasma levels of the parent compound attained 1 to 1.5 hours following oral ingestion. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. In vitro studies demonstrated that pravastatin is transported into hepatocytes but there is substantially less uptake into cells of other tissues. In view of pravastatin's apparently extensive first-pass hepatic metabolism, plasma levels may not necessarily correlate perfectly with lipid-lowering efficacy. Pravastatin plasma concentrations [including: area under the concentration-time curve (AUC), peak (Cmax), and steady-state minimum (Cmin)] are directly proportional to administered dose, over the approved dosage range. Approximately 50% of the circulating drug is bound to plasma proteins.

  The biotransformation pathways elucidated for pravastatin include: (a) isomerization to 6-epi pravastatin and the 3α-hydroxyisomer of pravastatin (SQ 31,906), (b) enzymatic ring hydroxylation to SQ 31,945, (c) ω-1 oxidation of the ester side chain, (d) β-oxidation of the carboxy side chain, (e) ring oxidation followed by aromatization, (f) oxidation of a hydroxyl group to a keto group, and (g) conjugation. The major degradation product is the 3α-hydroxy isomeric metabolite, (SQ 31,906) which has one-tenth to one-fortieth the HMG-CoA reductase inhibitory activity of the parent compound. Following oral ingestion, SQ 31,906 is formed by an acid catalyzed process in the stomach. Given intravenously to man, 64% of dose of pravastatin is recovered as unchanged pravastatin. This absence of significant oxidative metabolism distinguishes pravastatin from other HMG-CoA reductase inhibitors, such as lovastatin, simvastatin and atorvastatin, which are subject to extensive oxidative metabolism, particularly by the cytochrome CYP3A4.

- ***Aspirin:*** Aspirin is well and completely absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1-2 hours of dosing. The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents), and other physiologic factors. Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is concentration-dependent. At low concentrations (< 100 micrograms per milliliter), approximately 90 percent of plasma salicylate is bound to albumin while at higher concentrations (> 400 mcg/mL), only about 75 percent is bound.

  Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide.

  The elimination of salicylic acid follows zero order pharmacokinetics; (i.e., the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5 percent to > 80 percent. Alkalinization of the urine is a key concept in the management of salicylate overdose.

Is there a drug-interaction between pravastatin and aspirin?

Two studies have been conducted to explore the potential for a drug interaction with aspirin. The first study was provided with the original submission (NDA 19-898). This study compared the pharmacokinetics of pravastatin (20 mg) in twenty-four (24) healthy male subjects in an open,

balanced, randomized, incomplete-block study. Each subject received 3 of 4 treatments, which were a 20 mg dose given either (1) alone, (2) concomitantly with 1 g of nicotinic acid, (3) 30 minutes after a single 324-mg dose of aspirin, or (4) concomitantly with 1 g of nicotinic acid 30 minutes after a single 324-mg dose of aspirin. Comparison of the pharmacokinetic data of pravastatin alone and with aspirin given 30 minutes prior to dosing showed that administration of aspirin did not affect the pharmacokinetics of pravastatin.

The second study (CV123-234), was an open-label, single dose, randomized, 3-period, 3-treatment crossover study in 30 subjects comparing the pharmacokinetics of pravastatin (40 mg) and buffered aspirin (325 mg) when they were given separately, to when given concomitantly. The analytes chosen for evaluation of a potential interaction were pravastatin and salicylic acid (measured as salicylate). The 90% confidence intervals for Cmax and AUCinf for pravastatin and salicylate are listed in the next table.

Summary Statistics for Pravastatin and Salicylate

	PRAVASTATIN			SALICYLATE		
Parameter	Comparison	Point Estimate**	90% CI	Comparison	Point Estimate**	90% CI
AUC_{inf} (ng.h/ml)	C:A	0.95	85-105	C:B	1.02	99-104
C_{max} (ng/ml)	C:A	0.92	82-103	C:B	1.02	95-108

Regimen A: Pravastatin 40 mg alone. **Regimen B**: Buffered Aspirin 325 mg alone. **Regimen C**: Pravastatin 40 mg + Buffered Aspirin 325 mg

The ratios of the geometric means and the 90% confidence intervals for the ln-transformed parameters AUCinf and Cmax for serum pravastatin and plasma salicylate are within the 80-125% equivalence intervals recommended by FDA. Therefore, this study showed that buffered aspirin has no effect on the pharmacokinetics of pravastatin when administered concurrently and pravastatin has no effect on the pharmacokinetics of buffered aspirin (as measured by salicylate) when administered concurrently. A summary report of this study is included in Attachment I.

Reviewer Comment:

- *It should be noted that the major metabolite SQ-31906 and aspirin were not evaluated from a pharmacokinetic interaction viewpoint due to the relatively low concentrations of SQ-31906 and aspirin in comparison to pravastatin and salicylate, respectively.*
- *Study CV123-23 showed that pravastatin and aspirin do not present a pharmacokinetic interaction when given concomitantly. However, it should be noted that the pharmacodynamic interaction of these drug was not evaluated.*

Is the clinical pharmacology information included in the proposed labeling acceptable?

A copy of the proposed labeling is included in Attachment II.

Reviewer Comment:

- *Due to the fact that the overall format of the proposed labeling is similar to the format of previously approved combination products and to the fact that the proposed labeling does not include any new clinical pharmacology information, this reviewer is of the opinion that the proposed labeling is appropriate and acceptable.*

Attachment I

Includes

NDA 21-387

- **Summary of Study No. CV123-234**
- **Summary of the Analytical Information for Pravastatin and Salicylic acid**
- **Summary of the Dissolution Data submitted to support the Bio-waiver**

Study Report Summary

Study No. CV123-234

Study Title: Randomized, Open-Label, Single Dose, Drug Interaction Study of Pravastatin and Aspirin.

Principal Investigator/Investigation Site:

Primary Objectives:

- To assess the effects of 325 mg buffered aspirin on the pharmacokinetics of 40 mg pravastatin administered concurrently.
- To assess the effects of pravastatin on the pharmacokinetics of aspirin (as measured by salicylate) administered concurrently.

Secondary Objective:

- To assess the safety and tolerability of single oral doses of pravastatin and aspirin given alone and concurrently.

Study Population:

A total of 30 healthy volunteers (25 males and 5 non-nursing, non-pregnant and not of childbearing potential females) enrolled in and completed the clinical phase of the study. The demographic characteristics of all normal subjects randomized in the Clinical Pharmacology study, are presented in the next Table.

Demographics	Number (%) of Subjects
	Clinical Pharmacology Studies with Normal Healthy Volunteers (N = 30)
Age, years n (%)	
≤ 20	1 (3)
20-30	7 (23)
31-40	12 (40)
41-50	8 (27)
51-64	2 (7)
Mean (sd)	36.5 (8.3)
Range	20 – 56
Gender, n (%)	
Male	25 (83)
Female	5 (17)
Race, n (%)	
White	30 (100)
Body Weight, kg	
Mean (sd)	73.8 (7.8)
Range	55.7 – 83.8

Study Design:

This was an open-label, single-dose, randomized, three-period, three-treatment crossover study;

performed on 30 volunteers. In each period, subjects were housed from the evening prior to dosing until approximately 24 hours post-dose. Doses were separated by washout periods of 7 days. Subjects were administered the following three treatments with 240 mL of water according to the randomization scheme.

Treatment A: A single 40 mg oral dose of pravastatin (Pravachol®)

Treatment B: A single 325 mg oral dose of buffered aspirin (Bufferin®)

Treatment C: Concurrent administration of a single 40 mg oral dose of pravastatin (Pravachol®) and a single 325 mg oral dose of buffered aspirin (Bufferin®).

A complete set of vital signs (temperature, respiratory rate, seated blood pressure, and heart rate) were recorded during screening visit, Day -1 of Period 1 only, Study Day 1 of each period, and prior to study discharge. Vital signs were performed at other times when deemed necessary.

Clinical Supplies:

- ***Treatment A:*** Bristol-Myers Squibb Company; (Pravachol®) 40 mg pravastatin sodium tablets; Lot No. OJ31343; Exp. Date: SEP 2003.
- ***Treatment B:*** Bristol-Myers Squibb Company; (Bufferin®) 325 mg buffered aspirin tablets; Lot No. 007502; Exp. Date: JUN 2003.
- ***Treatment C:*** Bristol-Myers Squibb Company; (Pravachol®) 40 mg pravastatin sodium tablets; Lot No. OJ31343; Exp. Date: SEP 2003, and (Bufferin®) 325 mg buffered aspirin tablets; Lot No. 007502; Exp. date: JUN 2003.

Collection of Samples:

Blood samples were collected at the following times pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 16 hours post-dose.

Analytical Methods:

Serum pravastatin and SQ-31906 were analyzed using a validated —— method developed at —— The analytical range for serum pravastatin and SQ-31906 was —— ng/mL. Plasma aspirin (acetylsalicylic acid) and salicylate (measured as salicylic acid) were analyzed using a validated —— method developed at —— The analytical ranges for plasma aspirin and salicylate were —— —— mcg/mL and —— ncg/mL, respectively.

DATA ANALYSIS:

- ***Safety:*** Blood pressure, pulse rate, and clinical laboratory data were reviewed on an ongoing basis during the study to evaluate the safety of subjects. Any clinically relevant abnormalities or values of potential clinical concern were described.

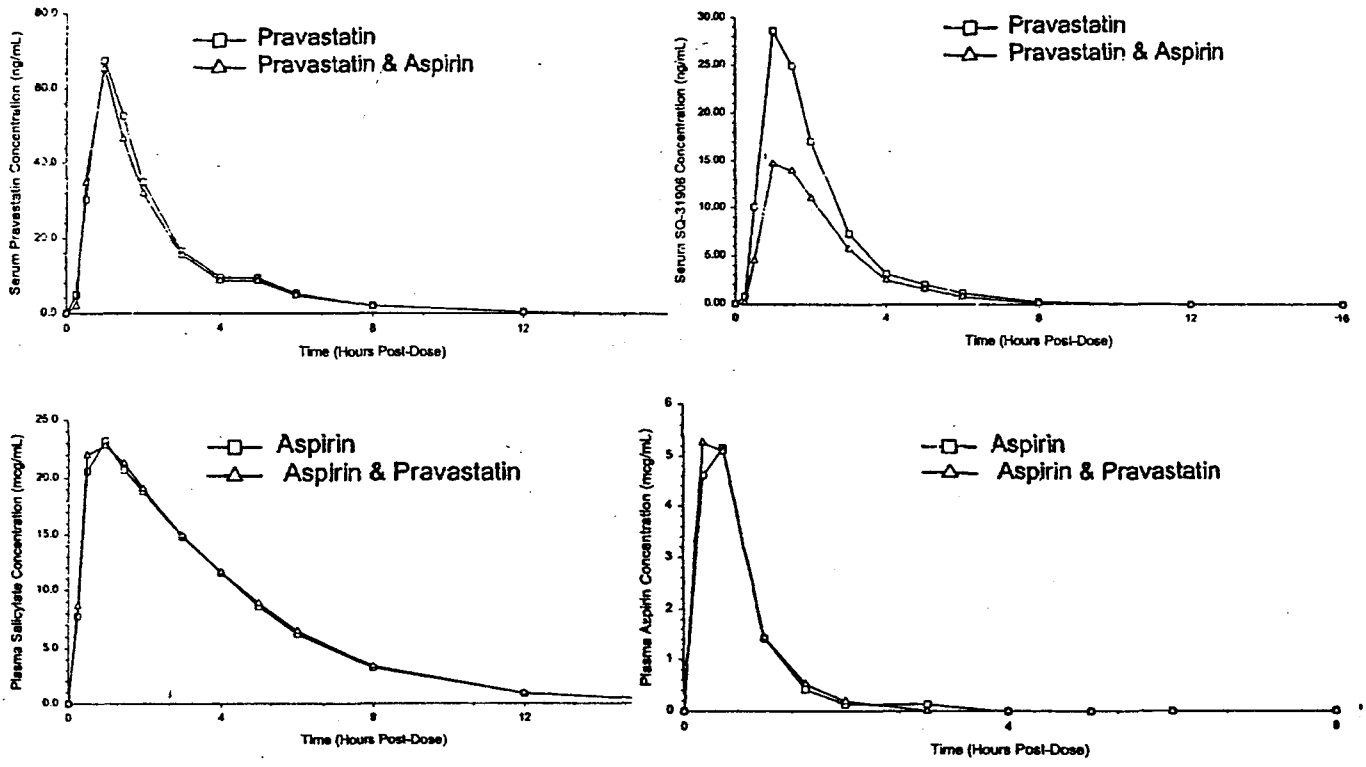
- ***Pharmacokinetics:*** Pharmacokinetic parameters AUC0-t, AUCinf, Cmax, Tmax, T1/2, and Kel were calculated for serum pravastatin and SQ-31906 and plasma aspirin and salicylate.

- ***Statistics:*** Arithmetic means, standard deviations and coefficients of variation were calculated on the individual pharmacokinetic parameters.

Analyses of variance (ANOVA) were performed on ln-transformed parameters AUCinf and Cmax for serum pravastatin and plasma salicylate. The ANOVA model included sequence group, period, formulation and first-order carryover as fixed effects and subject nested within sequence as a random effect. No carryover was observed for ln-transformed parameters AUCinf and Cmax and this term was removed from the final model. The sequence effect was tested with subject nested within sequence as the error term. Each analysis of variance included calculations of least-squares means (LSM), differences between adjusted formulation means and the standard error associated with these differences. Point estimates and 90% confidence intervals for treatment differences on the log scale were exponentiated to obtain estimates of ratios of least-squares means on the original scale for the parameters AUCinf and Cmax for serum pravastatin and plasma salicylate, The confidence intervals are expressed as a percentage relative to the least-squares mean of the reference treatment.

RESULTS:

- ***Pharmacokinetics:*** Mean concentration-time profiles for pravastatin, SQ-31906, aspirin, and salicylate following administration of treatments A, B, and C are illustrated in the next Figure.



Mean Plasma Pravastatin and Salicylate Concentrations Following a Single Dose of Pravastatin 40 mg (—□—Treat A) or Buffered Aspirin 325 mg (—□—Treat B) or Concurrent Administration of a Single Dose of Pravastatin 40 mg and a Single Dose of Buffered Aspirin 325 mg (—▲—Treat C)

The next Table presents a summary of the mean (SD) pharmacokinetic values for pravastatin, SQ-31906, aspirin, and salicylate.

PHARMACOKINETIC PARAMETERS				
	PRAVASTATIN		**SQ-31906**	
Parameter	Pravastatin	Pravastatin+ Aspirin	Pravastatin	Pravastatin+ Aspirin
AUC_{inf} (ng.h/ml)	122.16 (79.4)	115.39 (73)	47.98 (79.6)	27.37 (101.9)
C_{max} (ng/ml)	55.15 (90.3)	50.76 (86)	25.63 (84.2)	13.3 (98.2)
*T_{max} (hour)	1.17 (0.5-2.0)	1.09 (0.5-2.0)	1.07 (0.5-2.0)	1.18 (0.5-2.0)
$T_{1/2}$ (hour)	2.05 (39.3)	2.07 (39.5)	1.62 (52)	1.49 (53)
	ASPIRIN		**SALICYLATE**	
Parameter	Pravastatin	Pravastatin+ Aspirin	Pravastatin	Pravastatin+ Aspirin
AUC_{inf} (ng.h/ml)	4.17 (15.1)	4.38 (17.8)	101.23 (26.2)	103.1 (28.5)
C_{max} (ng/ml)	5.79 (26.3)	5.99 (39.3)	23.57 (17.8)	23.93 (25.4)
*T_{max} (hour)	0.408 (0.25-0.5)	0.413 (0.25-1.0)	0.883 (0.5-2.0)	0.92 (0.5-2.0)
$T_{1/2}$ (hour)	0.300 (15.4)	0.336 (26.6)	2.08 (15.1)	2.09 (14.5)

From a pharmacokinetic interaction point of view, only pravastatin and salicylate data were considered for evaluation of interaction potential. The next Table presents the summary statistics for pravastatin and salicylate

Summary Statistics for Pravastatin and Salicylate

	PRAVASTATIN			**SALICYLATE**		
Parameter	Comparison	Point Estimate**	90% CI	Comparison	Point Estimate**	90% CI
AUC_{inf} (ng.h/ml)	C:A	0.95	85-105	C:A	1.02	99-104
C_{max} (ng/ml)	C:A	0.92	82-103	C:A	1.02	95-108

Regimen A: Pravastatin 40 mg alone
Regimen B: Buffered Aspirin 325 mg alone
Regimen C: Pravastatin 40 mg + Buffered Aspirin 325 mg

For SQ-31906, the quantity in serum ranged from 23.7% (Treatment C) to 39.3% (Treatment A) relative to that of pravastatin. This along with the relatively low HMG-CoA reductase inhibitory activity supported the rationale for not evaluating this analyte for pharmacokinetic interaction. For aspirin, the relative quantity in plasma was determined to be approximately 3% that of salicylate.

Safety:

Clinical Adverse Events

- No SAEs, deaths, or discontinuations due to AEs were reported during this study.
- A total of 11 AEs was reported in 7/30 (23.33%) treated subjects. Two (2) pravastatin treated subjects reported 5 AEs, three Bufferin-treated subjects reported 3 AEs and two subjects treated with both pravastatin and Bufferin® reported 3 AEs.
- The most commonly reported AE was braising at the venipuncture site, which occurred in one Bufferin®-treated subject and in one subject treated with both pravastatin and Bufferin®. Five (5) AEs in two subjects were considered to be possibly associated with study drug: one Bufferin-treated subject complained of a headache and one pravastatin-treated subject experienced clinically significant laboratory abnormalities

Clinical Laboratory Evaluation

- Of the 30 healthy subjects in the study, one subject treated with pravastatin in the third leg of the study had elevations of AST, ALT, CK and LDH, which normalized in 4 days. He had previously received pravastatin with aspirin and aspirin alone uneventfully.

Special Interest in Adverse Events

It appears that the only area of special interest is where the adverse events of the hematological body system events may increase due to the concomitant use of aspirin with pravastatin. Even here aspirin's effect may be restricted to minor hematological events (AEs) because SAEs are not increased by the concomitant use of aspirin. In the 3 other body systems of special interest (gastrointestinal, musculoskeletal and hepato-biliary) the concomitant use of pravastatin and aspirin appears to actually decrease the frequency of the more serious events (SAEs and discontinuations). One possible explanation for this is that the patients receiving aspirin tended to be slightly younger, presumably as a result of clinicians reluctance to give aspirin to the elderly, because of the perceived poorer risk/benefit ratio in these patients. Thus the reduced rates of GI, M/S and H/B events in aspirin-treated patients could simply be an artifact of the lack of aspirin randomization. Whatever the reason, these comparisons of adverse events in special interest body systems do not suggest an additivity of side-effect of pravastatin and aspirin. If anything, the expected event rate when pravastatin and aspirin are given concomitantly appears to be lower than the event rate observed for either treatment given alone.

CONCLUSIONS:

- The clinical and laboratory data safety profile in this single dose study demonstrated that the combination of pravastatin 40 mg and aspirin 325 mg is well tolerated and safe, relative to pravastatin and aspirin given separately.
- In summary, it appears that the concomitant administration of pravastatin 40 mg with aspirin is well tolerated. None of the analyses reported here suggest an additivity of side-effect of pravastatin and aspirin and the expected event rates may even be lower than those observed for either treatment given alone.
- The relatively low concentrations of the metabolite SQ-31906 and aspirin in comparison to pravastatin and salicylate, respectively, supports the rationale for not evaluating SQ-31906 and aspirin from a pharmacokinetic interaction point of view.
- The ratios of the least-squares means and the 90% confidence intervals derived from the analysis

of the ln-transformed parameters AUCinf and Cmax for serum pravastatin and plasma salicylate were within the 80-125% equivalence intervals recommended by the FDA in their Guidance for Industry document.

- Based on these results, it is concluded that buffered aspirin has no effect on the pharmacokinetics of pravastatin when administered concurrently and pravastatin has no effect on the pharmacokinetics of buffered aspirin (as measured by salicylate) when administered concurrently.

REVIEWER COMMENTS:

1. *Overall, the provided analytical validation reports and quality control data showed adequate validation and assay precision/accuracy for both drugs.*

2. *The sponsor's approach of evaluating the statistical interaction of only pravastatin and salicylate is appropriate and acceptable.*

VALIDATION SUMMARY

The next table presents a summary of the analytical methodologies used to determine pravastatin and salicylic acid in study CV123-234.

IN VIVO ANALYTICAL METHODS				
Study No.	**Type of Biological Fluid**	**Method**	**Sensitivity of Method/ Range (ng/ml)**	**linearity**
Pravastatin and SQ-31906				
CV123-234	Serum	[redacted]	—ng/mL	range from — ng/mL
Acetylsalicylic Acid and Salicylic Acid				
CV123-234	Plasma	[redacted]	—ncg/mL	range from — mcg/mL

Analysis of Acetylsalicylic Acid and Salicylic Acid in Human Plasma by —
Validation Report: A sensitive and rapid method for the analysis of acetylsalicylic acid (ASA) and salicylic acid (SA) in human plasma (acidified with 5% phosphoric acid) has been validated, using methylparaben as the internal standard. Proteins are precipitated using trichloroacetic acid, and a portion of the extract is then injected onto a — column. The analytes are determined by —

The peak height ratio data were fitted using a 1/x weighted linear regression. The standard curves were linear (— in the range from — mcg/mL to — mcg/mL for acetylsalicylic acid and in the range from — mcg/mL to — ncg/mL for salicylic acid. The lower limit of quantitation was established at — mcg/mL for both analytes. The assay demonstrated acceptable inter-day precision and accuracy for all levels of the quality control (QC) samples. The ability to accurately dilute and quantitate a high concentration QC sample was demonstrated. The stability of both analytes over — was demonstrated. The analytes were not stable over 24 hours when maintained at room temperature but were stable at — over the same period. Similarly, the analytes were not stable in extracts from plasma over 24 hours at room temperature but were stable over the same period when held in — maintained at —

Anaiysis of Pravastatin and SQ-31906, in Human Serum by —
Validation Report: A sensitive and rapid method for the analysis of pravastatin and its major metabolite SQ-31906 in human serum has been validated. The method involves the extraction of pravastatin and

its internal standard, D3-pravastatin, SQ-31906 and its internal standard, D5-SQ-31906, from acidified human serum using ——— ———. After evaporation and reconstitution, the extract is analyzed by
; ——— for pravastatin,
pravastatin, respectively.

The peak area ratio data were fitted using a 1/x weighted linear regression. The standard curves were linear — in the range from — ng/mL to — ng/mL for pravastatin and SQ-31906. The lower limit of quantitation was established at — ng/mL for all three analytes. The assay demonstrated good inter-day precision and accuracy for all levels of the quality control (QC) samples. The ability to accurately dilute and quantitate a high concentration QC sample was demonstrated.

Reviewer Comment:

- *Appropriate validation data were provided for the analytical methodology used to assay pravastatin and salicylic acid in the submitted drug-interaction study (see validation summaries in Attachment I). Also, this submission included Quality Control data for the determination of pravastatin in serum and salicylic acid in plasma. These Quality Control data showed that the accuracy and precision for both pravastatin and salicylic acid are in the expected range for the analytical methodologies that were used.*

BIOWAIVER REQUEST

Background: It should be noted that the currently approved dissolution methodologies for pravastatin and buffered aspirin are as follows:

- *Pravastatin:*
  Specification: No less than ___ % (Q) at 30 minutes.
- *Buffered Aspirin:* Apparatus: 2 (paddle), 75 rpm; Medium: 500 ml of acetate buffer pH 4.5
  Specification: No less than 80% (Q) at 30 minutes.

Submission: In this submission Bristol-Myers Squibb is requesting a bio-waiver for the new lower strength of buffered aspirin 81 mg tablets under 21 CFR 320.22 (d)(2). In support of this request, the sponsor provided the following information:

- Comparative in vitro dissolution data in three different pH media.
- Formulation data showing that the 81 mg tablet is similar in its active and inactive ingredients to the higher strength 325 mg tablet used in the in vivo study. The only exception is the polishing agent carnauba wax, a very small quantity of which ___ mg per tablet may be applied to the 325 mg strength tablet.
- Published data showing that the absorption and elimination kinetics of aspirin have been reported to be linear over the dose range covered by this submission.

Buffered aspirin 325 mg tablets Batch 007502 was used in the pharmacokinetic study (CVI23-234) and is the reference product used to generate in vitro dissolution data presented in this section. Batch 007502 is representative of a typical lot of BUFFERIN® 325 mg tablets produced from the commercial facility at ___ that is currently available on the market as an OTC product.

In vitro dissolution data has been generated for the Buffered aspirin 81 mg tablet using Batch 8MEM247 as the test product. This is a process justification batch manufactured employing the commercial image and the commercial scale ___ tablets) and was manufactured to support the launch of the buffered aspirin 81 mg tablet in the pravastatin sodium tablets and buffered aspirin tablets co-packaged product.

Dissolution Methodology: For the Dissolution testing of aspirin was conducted in three different pH media across the physiological range

___ In all cases the dissolution test conditions employed the USP Type II apparatus (paddle) and a media volume of 500 mL as described in the USP monograph for buffered aspirin tablets. A slower paddle rotation speed ___ was employed than that defined in the USP monograph (75 rpm) to provide suitable drug release profiles for the comparison calculations.

The individual in vitro dissolution results at 5, 10, 15, and 20 minutes in the three media are shown in Tables 1-3 for buffered aspirin tablets 325 mg and 81 mg. The dissolution profiles for aspirin from each strength product, generated in each media, were compared by calculating a similarity factor (f_2).

Similarity Factors for Buffered Aspirin tablets

65	56	51

The results showed that the similarity factors (f_2) fall within the typical acceptable Guidance range of 50-100, thereby demonstrating equivalence of in vitro drug release from the two strength buffered aspirin tablets.

Conclusion:

The dissolution profile data presented in tables 1-3 together with the similarity factors presented in table 4 are considered to demonstrate the equivalence of drug release from the 325 mg and 81 mg buffered aspirin products. Therefore, a bio-waiver is requested for the 81 mg tablet.

TABLE 1

Dissolution of Buffered Aspirin Tablet, 325 mg
(500 mL — Type II apparatus, paddles at — rpm)

	% Dissolved Aspirin			
Time (minutes)	5	10	15	20
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Mean	48.9	67.6	75.6	80.4
RSD (%)	7.9	6.4	5.8	5.4
Range (min - max)	44.0 - 56.0	60.5 - 73.7	68.2 - 82.8	72.9 - 87.7

Dissolution of Buffered Aspirin Tablet, 81 mg
(500 mL — Type II apparatus, paddles at — rpm)

	% Dissolved Aspirin			
Time (minutes)	5	10	15	20
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Mean	54.0	72.4	80.4	85.6
RSD (%)	9.6	7.9	6.7	5.6
Range (min - max)	44.6 - 65.1	62.4 - 84.3	71.3 - 92.1	78.6 - 96.3

TABLE 2

Dissolution of Buffered Aspirin Tablet, 325 mg
(500 mL — Type II apparatus, paddles at — rpm)

	% Dissolved Aspirin			
Time (minutes)	**5**	**10**	**15**	**20**
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Mean	64.9	81.1	87.3	90.5
RSD (%)	10.0	8.7	7.5	6.8
Range (min - max)	51.3 - 73.6	66.2 - 92.8	72.5 - 97.1	75.5 - 98.7

Dissolution of Buffered Aspirin Tablet, 81 mg
(500 mL — Type II apparatus, paddles at — rpm)

	% Dissolved Aspirin			
Time (minutes)	**5**	**10**	**15**	**20**
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Mean	72.5	88.3	94.9	98.1
RSD (%)	6.6	4.1	3.5	3.5
Range (min - max)	64.9 - 79.9	81.9 - 93.7	87.4 - 99.3	90.4 - 102.3

TABLE 3

Dissolution of Buffered Aspirin Tablet, 325 mg (500 mL ——— Type II apparatus, paddles at —— m)

	% Dissolved Aspirin			
Time (minutes)	5	10	15	20
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Mean	47.9	67.5	76.3	81.7
RSD (%)	24.0	17.4	13.1	9.9
Range (min - max)	28.5 - 61.1	45.5 - 79.9	55.8 - 87.4	63.9 - 90.7

Dissolution of Buffered Aspirin Tablet, 81 mg (500 mL ——— Type II apparatus, paddles at —— m)

	% Dissolved Aspirin			
Time (minutes)	5	10	15	20
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Mean	56.9	77.2	86.2	91.0
RSD (%)	10.9	7.4	6.6	5.8
Range (min - max)	42.7 - 64.8	65.4 - 84.8	76.4 - 93.1	82.0 - 99.1

Attachment II

Includes

NDA 21-387

Proposed Labeling for Pravachol®/Bufferin® Compliance Pack

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

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

/s/

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12/21/01 02:25:54 PM
BIOPHARMACEUTICS

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