CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-855

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-855	SUBMISSION DATE:
Loperamide HCl	07/01/05 (BC)
1 and 2 mg Soft Gelatin Capsules	07/12/05 (BC)

GENERIC NAME: Loperamide Softgel

SPONSOR: Banner Pharmacaps Inc.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Response to CMC IR Letter (dated 06/16/05)

Addendum

The original CPB review of this NDA was completed on 6/24/05. OCPB recommended dissolution specifications of Q= [redacted] at 30 minutes (min) for both 1 and 2 mg soft gelatin capsules (SGC) in lieu of Q= [redacted] at [redacted] as proposed by the sponsor. This recommendation along with other CMC comments were discussed with the sponsor in a telecon on 06/27/05. On 07/01/05, the sponsor submitted additional dissolution data to support the stability up to 18 months and the data was reviewed by both CMC and CPB review teams.

In the 7/12/05 submission, sponsor agreed to tighten the specifications of Q= [redacted] at 30 min for the 2 mg SGC, [redacted]. After consultation with the CMC review team, it was agreed by the CPB review team that the sponsor suggested specifications for the 1 mg strength be adopted on an interim basis. Data should be acquired over the course of next 12 months and if that data does not show any problems, then the sponsor should revert to the specifications originally proposed by the Agency, i.e., Q= [redacted] at 30 min. In a telecon on 7/20/05, sponsor agreed to this proposal.

Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

Team Leader
Suresh Doddapaneni, Ph.D. _____

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/s/

Tien-Mien Chen
7/22/05 01:17:27 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
8/1/05 07:36:50 AM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-855
Generic Name:	Loperamide HCl
Dosage form and Strength:	Soft Gelatin Capsules, 1 and 2 mg
Route of Administration:	Oral
Proposed Indication:	Control symptoms of diarrhea, including Travelers' diarrhea
Proposed Dosage Regimen:	For Adults and Children 12 years and older: Two 2 mg softgels after the first loose bowel movement; one 2 mg softgel after each subsequent loose bowel movement; but no more than four 2 mg softgels a day (OR four 1 mg softgels after the first loose bowel movement; two 1 mg softgels after each subsequent loose bowel movement; but no more than eight 1 mg softgels a day) Children 9 - 11 years (60 - 95 lbs): Two 1 mg softgels after the first loose bowel movement; one 1mg softgel after each subsequent loose bowel movement; but no more than six 1 mg softgels a day Children 6 – 8 years (48 - 59 lbs): Two 1 mg softgels after the first loose bowel movement; one 1 mg softgel after each subsequent loose bowel movement; but no more than four 1 mg softgels a day Children under 6 years old (up to 47 lbs): Ask a doctor (not intended for use in children under 6 years old)
Sponsor:	Banner Pharmacaps Inc.
Type of Submission:	Original
Clinical Division:	Gastrointestinal and Coagulation Drug Products (HFD-180)
OCPB Division:	DPE II (HFD-870)
Priority:	Standard

Submission Date:	10/01/04, 12/12/04
Reviewer:	Tien-Mien Chen, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.

I. Executive Summary

Currently, there is no soft gelatin capsules (SGC) dosage form of loperamide on the market. On 10/01/04, Banner Pharmacaps Inc. (BPI) submitted original NDA 21-855 under 505(b)(2) seeking approval for loperamide 1 and 2 mg SGC and for direct over-the-counter (OTC) marketing.

A bioequivalence (BE) study conducted under fasting conditions in 30 healthy male and female subjects comparing loperamide 2 mg SGC with the reference listed drug (RLD), Imodium A-D 2 mg caplet, demonstrated BE of the two products. A biowaiver for the lower strength, 1 mg SGC, can be granted since both 1 and 2 mg strengths of loperamide are compositionally proportional and show similar dissolution characteristics.

The proposed indications and dosing regimen for loperamide SGC are the same as Imodium A-D caplet. The partial waiver request for pediatric study in children from birth to 2 years old can be granted.

A. Recommendations

From the view point of the Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation II (OCPB/DPE II), NDA 21-855 for loperamide 1 and 2 mg SGC, submitted on 10/01/04 is acceptable provided that a mutually satisfactory agreement can be reached on the dissolution specification. The following dissolution specification is recommended by the Agency; **NLT [redacted] at 30 minutes.**

B. Phase IV Commitments: None

II. Table of Contents

III. Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

On 10/01/04, BPI submitted original NDA 21-855 under 505(b)(2) regulations seeking approval of loperamide 1 and 2 mg SGC. One BE study was conducted comparing loperamide 2 mg SGC with the RLD, Imodium A-D 2 mg caplet. The proposed indications and dosing regimen for loperamide SGC are the same as Imodium A-D caplet. To support a biowaiver for the lower strength, loperamide 1 mg SGC, *in vitro* comparative dissolution data between loperamide SGC 1 and 2 mg was submitted.

The BE study No. R03-724 was a randomized, single-dose, open-label, 2x2 crossover study comparing test product, loperamide 2 mg SGC (Treatment A) and RLD, Imodium A-D 2 mg caplet (Treatment B) under fasting conditions with a washout period of 2 weeks in 30 healthy subjects (17 males and 13 females). Twenty eight subjects completed the study.

The results of the BE study demonstrated that loperamide 2 mg SGC is bioequivalent to the currently marketed Imodium A-D 2 mg caplet under fasting conditions based on the Agency's two one-sided tests procedure acceptance criteria.

The *in vitro* dissolution comparisons also showed comparable dissolution data between loperamide 1 and 2 mg SGC. Biowaiver for the lower strength of loperamide, 1 mg SGC can therefore be granted. The partial waiver request for pediatric study in children from birth to 2 years old can be granted.

IV. Question Based Review

A. General Attributes

Loperamide 2 mg capsule was originally approved by the Agency prior to January 1, 1982 as a prescription product. In 1984, the liquid loperamide (1 mg/5 mL) for prescription use was also approved (but now discontinued). McNeil's loperamide 2 mg caplet (under NDA 19-860) was approved as the first OTC loperamide product (Imodium A-D) in 1989. Other OTC approvals include liquid dosage forms, capsules, and chewable tablets. Currently, there is no SGC dosage form of loperamide available on the market either by a prescription or OTC.

BPI is seeking approval for loperamide 1 and 2 mg SGC under 505(b)(2) provisions. A pre-IND meeting between the sponsor and the Agency was held in July, 03. This NDA relies on the Agency's finding of safety and efficacy of Imodium A-D caplet. There are no proposed changes to the indications and dosage and administration sections. In support of the NDA, a single-dose BE study (R03-724) comparing the currently marketed OTC drug, Imodium A-D 2 mg caplet (reference) and loperamide SGC 2 mg was conducted.

A biowaiver with supportive *in vitro* dissolution data is sought for loperamide 1 mg SGC as the 1 mg and 2 mg strengths are compositionally proportional. A waiver for pediatric study in children from birth to 2 years old was also requested.

B. General Clinical Pharmacology

Loperamide HCl is a synthetic piperidine opioid, used as an antidiarrheal agent. It acts predominately on opiate (μ) receptors in the GI tract. Loperamide slows intestinal transmit time (permitting more time for absorption) and reduces secretion. It produces antidiarrheal effects at doses that produce few CNS effects since it penetrates poorly into the CNS.

C. Intrinsic Factors: Not Applicable

D. Extrinsic Factors: Not Applicable

E. General Biopharmaceutics:

Q: Is Loperamide 2 mg SGC bioequivalent to Imodium A-D 2 mg Caplet?

Four loperamide 2 mg SGCs is bioequivalent to that of four Imodium A-D 2 mg caplets under fasting conditions.

Study R03-724 was a randomized, single-dose, open-label, 2x2 crossover study with a washout period of 2 weeks in 30 healthy subjects (17 males and 13 females) under fasting conditions with the following treatments:

Treatment A: 4 x 2 mg loperamide SGCs swallowed with 240 mL water (Test)
Treatment B: 4 x 2 mg Imodium A-D caplets swallowed with 240 mL water (Reference)

Twenty eight subjects completed the study. Four x 2 mg loperamide SGCs is bioequivalent to 4 x 2 mg Imodium A-D caplets based on the Agency's recommended acceptance criteria using two one-sided tests procedure (Table 1).

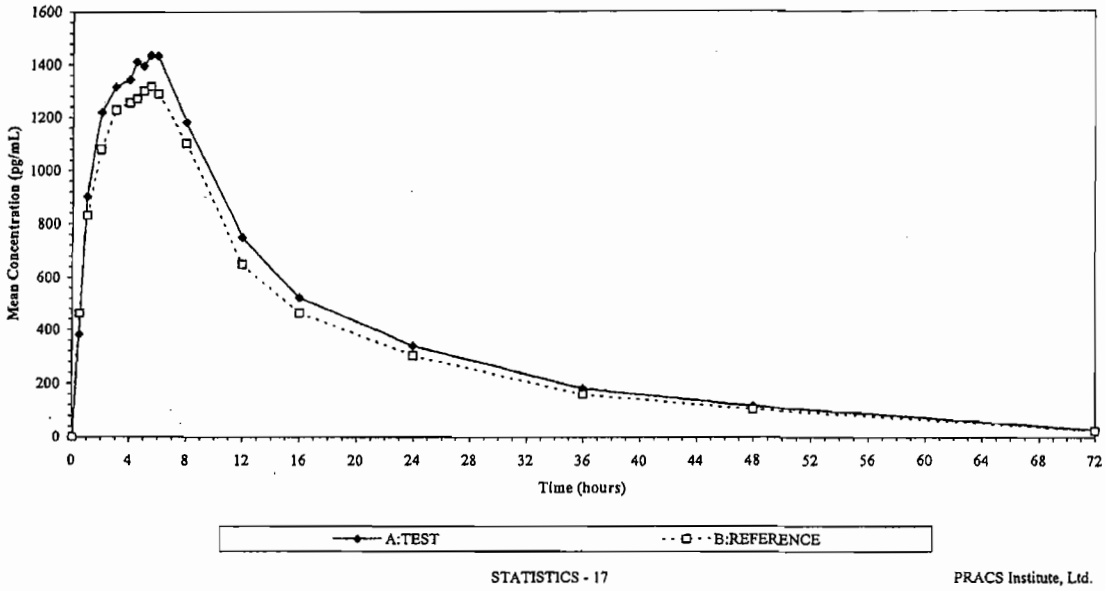
Table 1. Results of BE Assessment for Treatment A (Test) vs. Treatment B (Reference)

PK Parameters Mean (SD)	Treatment A (Test)	Treatment B (Reference)[1]	A vs. B Point Estimate	90% CI
C_{max} (pg/ml)[2]	1589.9 (936.8)	1456.8 (750.1)	-----	-----
T_{max} (hr)[2]	4.45 (1.90)	4.93 (1.64)	-----	-----
$T_{1/2}$ (hr)	15.7 (5.7)	17.0 (4.6)	-----	-----
$AUC_{0\text{-last}}$[2] (pg-hr/ml)	25220.2 (17566.2)	22845.1 (12287.8)	-----	-----
$AUC_{0\text{-}\infty}$[2] (pg-hr/ml)	27854.2 (20910.3)	25757.8 (12800.9)	-----	-----
Ln (C_{max})[3]	7.16 (0.75)	7.11 (0.70)	106.1	99.4-113.2
Ln ($AUC_{0\text{-last}}$)[3]	9.89 (0.88)	9.84 (0.77)	104.8	96.6-113.7
Ln ($AUC_{0\text{-}\infty}$)[3]	10.0 (0.78)	10.0 (0.49)	106.7	99.7-115.4

1. Biolot No. XPP0308002A (250,000 SGC manufactured on 09/02/03).
2. Arithmetic mean (± standard deviation, SD).
3. Log-transformed geometric mean (± SD).

The mean plasma concentration time profiles of three treatments are shown in Figure 1

Figure 1.1
Mean Plasma Concentration (0 - 72 hours)
N=28



STATISTICS - 17 PRACS Institute, Ltd.

Food effect:

It was agreed upon in the pre-IND meeting on July, 03 between the Agency and BPI that a food effect study was not needed since the labeling of the currently marketed loperamide products does not contain information regarding a food effect.

Inspection:

The Division of Scientific Investigations (DSI) had conducted an audit on the BE study R03-724 (see DSI review written by Dr. Nilufer Tampal, saved in DFS on 06/21/05, and appended in appendix 3). With respect to the acceptability of data, DSI made the following recommendations;

- Plasma concentrations for subjects 1 and 10 be excluded from the bioequivalence determination (item 1).

- Data for subjects 4, 5, and 6 not be accepted unless adequate bench top stability is demonstrated (item 2).

This reviewer conducted a reanalysis for BE assessment by deleting data of the above 5 subjects as a worst case scenario. The reanalysis still demonstrated BE between loperamide 2 mg SGC and Imodium A-D 2 mg caplet.

Formulation Composition:

The composition and formulation of the loperamide HCl SGC 1 and 2 mg are shown in Table 3. The two strengths are compositionally proportional.

Table 3. The Composition and Formulation of Loperamide HCl, 1 and 2 mg SGC

Description Component	Function	Amount per Capsule (1 mg Strength)	Amount per Capsule (2 mg Strength)
Capsule Fill			
Loperamide hydrochloride, USP	Active	1.000 mg	2.000 mg
Butylated hydroxyanisole, NF			
Glyceryl caprylate			
Polyoxyl 40 hydrogenated castor oil, NF			
Theoretical Total Fill Weight			
Capsule Shell			
Gelatin, NF			
Glycerin, USP			
Purified water, USP			
FD&C blue #1			
Edible ink			
Theoretical Total (Dry) Shell Weight			
Total Capsule Weight		234.641 mg	234.642 mg

Dissolution Data:

The proposed dissolution methodology and specification are as follows:

Medium: **pH 4.7, acetate buffer 500 mL at 37°C**
Apparatus: **USP Apparatus 1 (basket)**
Speed: **100 rpm**
Sample Size: **n=12**
Sampling at: **30, [redacted] min**
Specifications: NLT [redacted] min

The dissolution data is shown in Table 4 below:

Table 4. Mean (± SD) Initial Dissolution Data of Loperamide 1 and 2 mg SGC Lots (n=12/lot)

Time (min)	% Released		
	1 mg SGC (XPP0309011A)[1]	2 mg SGC (XPP0309009A)[2]	Remarks 2 mg SGC [redacted]
[redacted]			
30	[redacted]		
[redacted]			

1. Obtained from stability lot No. XPP0309011 ([redacted] SGC manufactured on 10/07/03).
2. Obtained from stability lot No. XPP0309009 ([redacted] SGC manufactured on 10/09/03).
3. Obtained from stability test (n=6).

Upon manufacture, for both 1 and 2 mg SGC lots ([redacted] and other stability lots), the initial dissolution is essentially complete [redacted] minutes as shown above. When the stability lots of soft gelatin products are stored under accelerated conditions (25°C/60%RH and 40°C/75%RH), [redacted] was added (NMT [redacted]) to the dissolution medium (as described in the USP 25 <711>) due to possible cross-linking of gelatin. However, most of the loperamide 1 and 2 mg stability lots when stored under accelerated conditions for [redacted] months still failed the dissolution tests even after the addition of [redacted] Note: Additional dissolution data on stability lots at [redacted] months were submitted on 12/12/04.

Large variations were observed between 2 and 1 mg SGC lots and also among 2 mg SGC lots as shown below in the dissolution testing (with [redacted] added to the medium):

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

NDA 21-855 for Loperamide HCl
1 and 2 mg SGC

Appendix 1

Sponsor's Proposed Labeling
(10/04 Version)

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_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-2

NDA 21-855 for Loperamide HCl
1 and 2 mg SGC

Appendix 2

Study Synopsis (No. R03-724)

A RELATIVE BIOAVAILABILITY STUDY OF 2 MG LOPERAMIDE HYDROCHLORIDE SOFT GELATIN CAPSULES VERSUS IMODIUM® A-D CAPLETS UNDER FASTING CONDITIONS

INTRODUCTION

A randomized, two-way crossover design was used in this study to compare the relative bioavailability (rate and extent of absorption) of two products under fasting conditions. In this study, a single dose of Loperamide HCl 2 mg Soft Gelatin Capsules manufactured by Banner Pharmacaps, Inc. was compared with Imodium® A-D 2 mg Caplets by McNeil Consumer Healthcare (Division of McNeil-PPC, Inc.).

METHODOLOGY

Thirty healthy volunteers were randomly assigned a sequence (AB or BA) of the following products:

Test Product (A):	Loperamide HCl 2 mg Soft Gelatin Capsules by Banner Pharmacaps, Inc. Lot No. XPP0308002-A; Exp. Date: None Shown; Mfg. Date: 09/2/03
Reference Product (B):	Imodium® A-D 2 mg Caplets by McNeil Consumer Healthcare (Division of McNeil-PPC, Inc.) Lot No. HAA092; Exp. Date: 11/05

A single oral dose of the test or reference product was administered to volunteers on two separate occasions under fasting conditions with a fourteen day washout between doses. Food and fluid intake were controlled during each confinement period.

Blood samples (17 per subject each period) were obtained within one hour prior to dose administration (0 hour) and after dose administration at 0.5, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 12, 16, 24, 36, 48, and 72 hours for drug content analysis. The concentrations at each sampling time are included in this report. Deviations from these sample collection times were as follows:

	Subject No.	Scheduled (hr:min)	Actual (hr:min)	+/-
Period I	17	0:30	0:32	+0:02
	20	5:00	5:03	+0:03
	10	72:00	No Sample - Schedule Conflict	
	29	72:00	No Sample - Schedule Conflict	
Period II	13	Subject elected to withdraw prior to Period II dosing		
	17	Subject elected to withdraw prior to Period II dosing		
	01	1:00	1:05	+0:05
	08	1:00	1:01	+0:01
	01	4:30	4:34	+0:04
	01	5:00	5:05	+0:05
	12	5:00	5:02	+0:02
	29	36:00	37:48	+1:48

PHARMACOKINETIC PARAMETERS

The bioanalytical laboratory of [redacted] determined the loperamide plasma concentrations and sent the data to the Statistical Division of [redacted]. The pharmacokinetic parameters were calculated using WinNonlin™, Version 3.1, software designed specifically for analyzing pharmacokinetic data. WinNonlin™ [redacted] for extravascular input was utilized. All other computations were completed using SAS®, Version 8.2 for Windows. Microsoft® Excel® 97 was used to produce tables and graphs.

The following pharmacokinetic parameters were computed from the plasma concentration data using the actual sample collection times:

- AUC_{0-t} Area under the plasma concentration-time curve (pg-hr/mL) from time zero to the time of the last quantifiable concentration (t), calculated using the linear trapezoidal rule:
  $\Sigma_i(t_i-t_{i-1})(C_i+C_{i-1})/2$, i=1 to t,
  where C_i is the plasma concentration at time t_i.

- AUC_{inf} Area under the plasma concentration curve from time zero extrapolated to infinity (pg-hr/mL), calculated by $AUC_{0-t} + (C_{last}/k_{elim})$, where C_{last} is the last quantifiable concentration and k_{elim} is the terminal elimination rate constant.

- C_{max} Maximum or peak concentration, obtained by inspection (pg/mL).
- T_{max} Time of maximum or peak concentration, obtained by inspection (hr).
- k_{elim} Terminal elimination rate constant (1/hr). This value was estimated by linear regression on the terminal phase of the semi-logarithmic concentration versus time curve.
- $t_{1/2}$ Half life of the product (hr), calculated by $\ln(2)/k_{elim}$.

Natural logarithmic (ln) transformations were computed for AUC_{0-t}, AUC_{inf}, and C_{max}. The time points used to calculate the elimination rates (k_{elim}) are presented in Appendix A (pages 49 – 53 of the statistical report).

STATISTICAL ANALYSIS

An analysis of variance (ANOVA) was performed on each of the pharmacokinetic parameters using SAS® software. The ANOVA model containing factors for sequence of products, subjects within sequence, periods and products was utilized in comparing the effects between the test and reference products. Differences were declared statistically significant at the 5% level.

A 90% confidence interval about the ratio of the mean test value to mean reference value was calculated for all of the pharmacokinetic parameters. The power of the ANOVA to detect a difference equal to 20% of the reference mean was also calculated with the SAS® software. The calculations for the power and confidence interval used the least squares means (LSMEANS) and the standard error of the estimate, both generated by the SAS® software. The ratio of the geometric means for the ln-transformed data and the corresponding 90% confidence intervals were calculated for AUC_{0-t}, AUC_{inf}, and C_{max}, as well.

The lower limit of quantitation for loperamide was [redacted]. For statistical analysis, subject sample values below the lower limit of quantitation (BLQ) were reported as zero.

The statistical analysis was done using SAS®, Version 8.2 for Windows, using code based on Chow and Liu pp. 559-562.

RESULTS

Plasma concentration data from 28 of 30 subjects were used in the statistical analysis. Subjects 13 and 17 elected to withdraw prior to Period II dosing.

Tables 1.1 and 1.2 display the individual concentration data for the test and reference products, respectively. Descriptive statistics (mean, standard deviation, coefficient of variation, minimum, and maximum) are computed for each scheduled observation time.

The pharmacokinetic parameters for each subject are displayed by product in Tables 2.1 and 2.2. Calculations of the mean, standard deviation, and coefficient of variation are included in these tables.

Tables 3.1 – 3.3 summarize C_{max} and ln-transformed C_{max}, AUC_{0-t} and ln-transformed AUC_{0-t}, and AUC_{inf} and ln-transformed AUC_{inf}, respectively. Along with the values for the pharmacokinetic parameters, the differences and ratios between products are calculated. The natural logarithms for the test and reference values are given, as well as the difference. The descriptive statistics in these tables include the mean, standard deviation, coefficient of variation, and geometric mean.

Figures 1.1 and 1.2 show the mean plasma concentration from time 0 to 72 hours after dosing on original and semi-logarithmic scales (log_{10}), respectively. Figures 2.1 and 2.2 represent an overlaying of individual concentration-time profiles for the test and reference products, respectively. The concentration versus time curves for each individual subject are shown in Figures 3.1a – 3.28a on a linear scale. Figures 3.1b – 3.28b represent the individual curves on semi-logarithmic scale (log_{10}).

The following tables summarize the results of the analyses performed on the pharmacokinetic parameters.

Loperamide	Ln-Transformed C_{max}	Ln-Transformed AUC_{0-t}	Ln-Transformed AUC_{inf}
Test Product Geometric Mean	1292.62	19723.23	22153.05
Reference Product Geometric Mean	1218.59	18817.17	20658.67
% Ratio	106.07	104.82	107.23
90% Confidence Interval	(99.38, 113.22)	(96.59, 113.74)	(99.65, 115.4)

Loperamide	C_{max}	AUC_{0-t}	AUC_{inf}
Test Product Least Squares Mean	1589.89	25220.17	27854.16
Reference Product Least Squares Mean	1456.77	22845.11	24822.76
% Ratio	109.14	110.40	112.21
90% Confidence Interval	(100.75, 117.53)	(99.38, 121.41)	(98.89, 125.54)

Loperamide	T_{max}	k_{elim}	$t_{1/2}$
Test Product Least Squares Mean	4.45	0.0489	15.71
Reference Product Least Squares Mean	4.93	0.0459	16.61
% Ratio	90.22	106.59	94.59
90% Confidence Interval	(76.04, 104.39)	(97.94, 115.24)	(84.99, 104.18)

The statistical analyses are presented in Table 4. With a 5% significance level, the ANOVA did not detect any statistically significant differences between the products, between periods, or between sequences. The powers for all pharmacokinetic parameters were above 80%, with the exception of AUC_{inf} and T_{max}.

There were no statistically significant differences between products at any of the draw times.

The 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean are within the 80% and 125% limits for the pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{inf} of the ln-transformed data.

Complete details of the statistical analysis can be found in the SAS® output included in Appendix B (pages 54 – 106 of the statistical report).

As additional information, the statistical analysis using original concentration values where pharmacokinetic repeats were identified is included in Appendix C (pages 107 – 143 of the statistical report).

CONCLUSION

The results of this study indicate bioequivalence between the test and reference products under fasting conditions.

NDA 21-855 for Loperamide HCl
1 and 2 mg SGC

Appendix 3

DSI Audit Report for the BE Study
No. R03-724 (in DFS on 06/21/05)

4 Page(s) Withheld

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Withheld Track Number: Clin Pharm/Bio 3

NDA 21-855 for Loperamide HCl
1 and 2 mg SGC

Appendix 4

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-855**	**Brand Name**	
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Loperamide**
Medical Division	**GI and Coagulation**	**Drug Class**	**Anti-diarrhea**
OCPB Reviewer	**Tien-Mien Chen, Ph.D.**	**Indication(s)**	**Controls symptoms of diarrhea, including Traveler's diarrhea**
OCPB Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Soft Gelatin Capsules**
		Dosing Regimen	
Date of Submission	**10/01/04**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**06/23/05**	**Sponsor**	**Banner Pharmaceuticals Inc.**
Medical Division Due Date	**06/23/05**	**Priority Classification**	**3 S**
PDUFA Due Date	**08/04/05**		

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, etc.	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:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
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:	X	1	1	
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1	1	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is loperamide 2 mg SGC bioequivalent to Imodium A-D 2 mg caplet?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**06/23/05**	
Secondary reviewer Signature and Date	**06/23/05**	

CC: NDA 21-855, HFD-850 (Electronic Entry or Lee), HFD-180 (S. Daugherty), HFD-870 (S. Doddapaneni, H. Malinowski, J. Hunt)

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/s/

Tien-Mien Chen
6/23/05 12:37:22 PM
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Suresh Doddapaneni
6/26/05 09:25:05 AM
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