

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-140

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-140

SUBMISSION DATE: 10/29/99

LOPERAMIDE HCl 2 MG AND
SIMETHICONE 125 MG CAPLETS
IMODIUM® ADVANCED CAPLETS

McNEIL CONSUMER HEALTHCARE
7050 CAMP HILL ROAD
FORT WASHINGTON, PA 19034-2299

REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: ORIGINAL NDA

SUBMISSION CODE: 3S

CONTENT	PAGE
I. Synopsis/Background	1
II. Summary of Information on Pharmacokinetics and Bioequivalence, etc.	4
III. Labeling Comments	12
IV. Recommendation	13
V. Proposed Labeling	27

I. SYNOPSIS/BACKGROUND

What is the Drug? This NDA is submitted for loperamide 2 mg/simethicone 125 mg (Imodium® Advanced) caplet, an over-the-counter (OTC) drug product.

What is the Drug Product Composition? The composition of Imodium® Advanced caplet stated in the NDA is presented in Table 1.

Table 1. The Composition of the Proposed Market Formulation of Imodium® Advanced Caplet (C-826-15 and 16)

Ingredients	Unit Weight (mg)	
Loperamide HCl, USP	2.0	
Simethicone, USP	[Redacted]	
Dibasic calcium Phosphate, [Redacted]		
[Redacted] Cellulose, NF		
Sodium Starch Glycolate, NF		
Acesulfame K		
[Redacted]		
Stearic Acid, NF		
Total Tablet Weight		960.0
[Redacted]		

What is the Proposed Indication? Imodium® Advanced caplet is proposed for controlling the symptoms of diarrhea plus bloating, pressure and cramps, commonly referred to as gas, in adults and children six years old or older.

What is the Mechanism of Drug Action? Loperamide decreases gastrointestinal motility and transit time by inhibiting peristalsis. It also exhibits antisecretory activities in the gastrointestinal tract.

What is the Scientific Rationale for the Proposed Indication? The sponsor states that the loperamide/simethicone combination of Imodium® Advanced Caplet is more effective in relieving acute diarrhea and associated gas related discomfort (bloating, pressure and cramps) as compared to loperamide and simethicone given separately for the relief of diarrhea and gas related discomfort, respectively. The sponsor further states that Imodium® Advanced caplet would be an alternative convenient dosage form of the loperamide-simethicone combination to Imodium® Advanced chewable tablet for the above indication.

What is the Recommended Dosage of Imodium® Advanced Caplet? The proposed dosage regimen of Imodium® Advanced caplet is as follows:

Adults and Children 12 Years Old or Older: Two caplets after the first loose stool; one caplet after each subsequent loose stool but no more than four caplets per day (i.e., maximum daily dose = 8 mg loperamide and 500 mg simethicone).

Children 9-11 Years Old (60-95 pounds): One caplet after the first loose stool; half a caplet after each subsequent loose stool but no more than three caplets per day (i.e., maximum daily dose = 6 mg loperamide and 375 mg simethicone).

Children 6-8 Years Old (48-59 pounds): One caplet after the first loose stool; half a caplet after each subsequent loose stool but no more than two caplets per day (i.e., maximum daily dose = 4 mg loperamide and 250 mg simethicone).

Children Under 6 Years Old (up to 47 pounds): Ask a doctor.

The sponsor is requested to exclude children's weight and children under 6 years old from the labeling as covered under **Labeling Comments 1 and 2** (page 12).

What Are the Clinical Efficacy Endpoints? The efficacy of the loperamide 2 mg-simethicone 125 mg combination has already been established in the approved OTC drug product, Imodium® Advanced chewable tablet (NDA 20-606). Accordingly, efficacy endpoints were not assessed in this NDA submission.

What is the Adverse Event Profile? In the study assessing the bioequivalence of Imodium® Advanced caplet formulation and the currently marketed Imodium® Advanced chewable tablet formulation, the maximum adult daily dose (8 mg loperamide and 500 mg simethicone) was administered, in each regimen, to each of 29 adult subjects. Adverse events were observed as follows:

Two adverse events occurred in three subjects (lightheadedness [n=1], and vasovagal episode n=2) receiving Imodium® Advanced caplet. Five adverse events occurred in four subjects (cold symptoms [n=2], headache and dizziness [n=1], fever and abdominal cramps [n=1]) receiving Imodium® Advanced chewable tablet. The sponsor states that all adverse events were mild in intensity.

What is the Purpose of this NDA Submission? The purpose of this NDA is to establish bioequivalence of the proposed market formulation of Imodium® Advanced loperamide 2 mg/simethicone 125 mg caplet and the current market formulation of Imodium® Advanced loperamide 2 mg/simethicone 125 mg chewable tablet.

What is the Nature of the Bioequivalence Studies Submitted in the NDA? Two bioequivalence studies, (Protocols 98-051 and 989-051), conducted by the sponsor, are submitted in this NDA. Protocol 98-051 utilized the initial, pilot study caplet formulation of Imodium® Advanced loperamide 2 mg/simethicone 125 mg caplet, which is different from the proposed market caplet formulation. Since this NDA compares the proposed market caplet formulation and the currently marketed chewable tablet formulation of Imodium® Advanced loperamide 2 mg/simethicone 125 mg, the findings of Protocol 98-051 are not considered in the recommendation related to the approval of this NDA.

Is Adequate Information Provided on the Methods of Sample Analysis? The submitted bioequivalence studies utilized adequately validated radioimmunoassay (RIA) methods.

Summary of Bioequivalence Study: Based on the data provided in the submitted bioequivalence study (Protocol 98-068), the proposed market formulation of Imodium® Advanced loperamide 2 mg/simethicone 125 mg caplet and the currently marketed formulation of Imodium® Advanced loperamide 2 mg/simethicone 125 mg chewable tablet are bioequivalent.

What is the Recommendation? The submitted bioequivalence data are deemed acceptable for consideration in the NDA approval process.

**APPEARS THIS WAY
ON ORIGINAL**

II. SUMMARY OF INFORMATION ON PHARMACOKINETICS AND BIOEQUIVALENCE

1. *Is Adequate Plasma Pharmacokinetic Information Provided?*

The pharmacokinetics of the proposed market formulation (Formulation C-826-15F) of Imodium[®] Advanced caplet and the currently marketed formulation of Imodium[®] Advanced chewable tablet was evaluated in 29 healthy, adult subjects in a crossover study (Protocol 98-068). In this study, each subject received two single-dose treatment regimens of 8 mg of loperamide and 500 mg of simethicone as four Imodium[®] Advanced caplets (Treatment A) and as four Imodium[®] Advanced chewable tablets (Treatment B). Twenty-six subjects (14 males and 12 females) were evaluable. Three subjects were not evaluable due to problems with sample analysis. The mean plasma concentration profiles of loperamide for both treatments are presented in Table 2. Individual subject plasma concentrations of loperamide are presented in Appendix I (pages 14-15). The mean semi-logarithmic plots are not provided in the NDA. The mean linear plots and typical individual subject semi-logarithmic plots of plasma loperamide concentration versus time are presented in Figs. 1 and 2, respectively. The pharmacokinetic parameters are summarized in Table 3. Individual subject pharmacokinetic parameters are presented in Appendix I (pages 16-17).

Table 2. Mean Values and Standard Deviations of Plasma Concentrations (ng/mL) of Loperamide and Coefficients of Variation (CV%) Following Administration of 8 mg Loperamide and 500 mg Simethicone as a Single Dose of Imodium Advanced Caplets (A) and as Imodium Advanced Chewable Tablets (B) to Twenty-six Healthy Subjects

Time (h)	0	0.5	1	1.5	2	3	4	5	6	7	8	10	12	16	24	28	32	36	48
A																			
Mean	0	0.304	0.532	0.743	0.868	1.27	1.43	1.78	1.78	1.75	1.53	1.19	1.00	0.800	0.529	0.478	0.372	0.300	0.227
sd	0	0.288	0.376	0.508	0.847	1.07	0.96	0.95	0.98	1.17	0.75	0.51	0.45	0.403	0.268	0.223	0.199	0.178	0.129
cv%	0	95	71	79	88	84	66	53	54	67	49	43	45	50	51	47	53	59	57
n	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26
B																			
Mean	0.007	0.259	0.543	0.732	0.970	1.28	1.36	1.62	1.87	1.52	1.34	1.08	0.928	0.734	0.505	0.437	0.350	0.278	0.220
sd	0.035	0.138	0.313	0.412	0.634	0.85	0.88	0.88	0.81	0.73	0.63	0.48	0.419	0.372	0.244	0.207	0.188	0.152	0.134
cv%	510	53	58	56	55	75	65	54	54	48	47	43	45	51	48	47	54	55	61
n	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26

**APPEARS THIS WAY
ON ORIGINAL**

Fig. 1 Plots of Mean \pm SD Loperamide Plasma Concentration Versus Time in Twenty-six Healthy Subjects Following Administration of a Single dose of 8 mg Loperamide and 500 mg Simethicone as Four Imodium[®] Advanced Caplets and as Four Imodium[®] Advanced Chewable Tablets

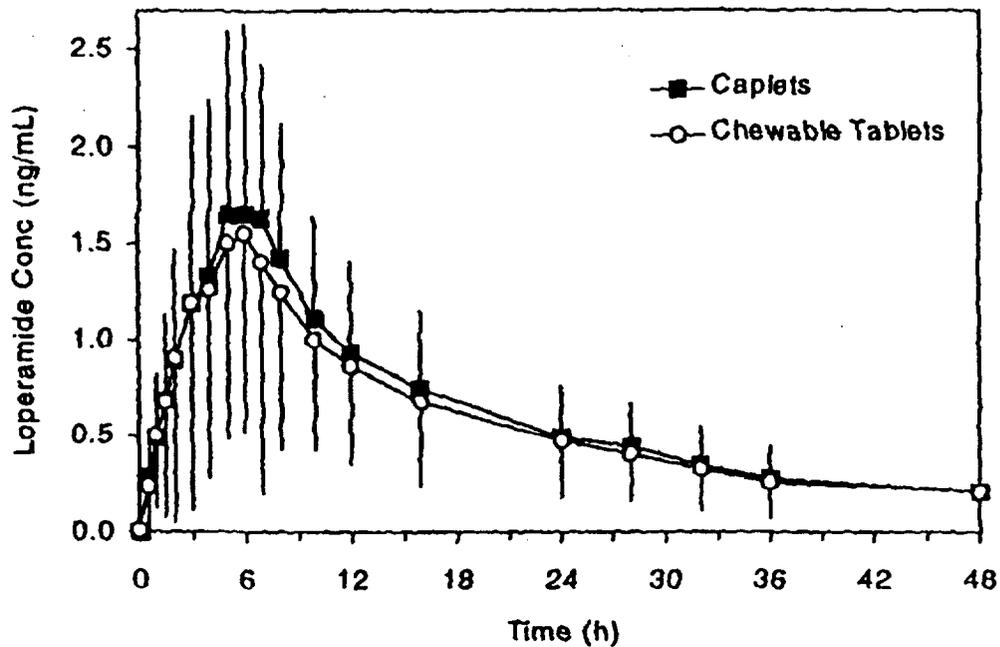


Fig. 2 Typical Individual Subject Semi-logarithmic Plots of Plasma Loperamide Concentration Versus Time in Healthy Subjects Following Administration of a Single Dose of 8 mg Loperamide and 500 mg Simethicone as Four Imodium[®] Advanced Caplets and as Four Imodium[®] Advanced Chewable Tablets

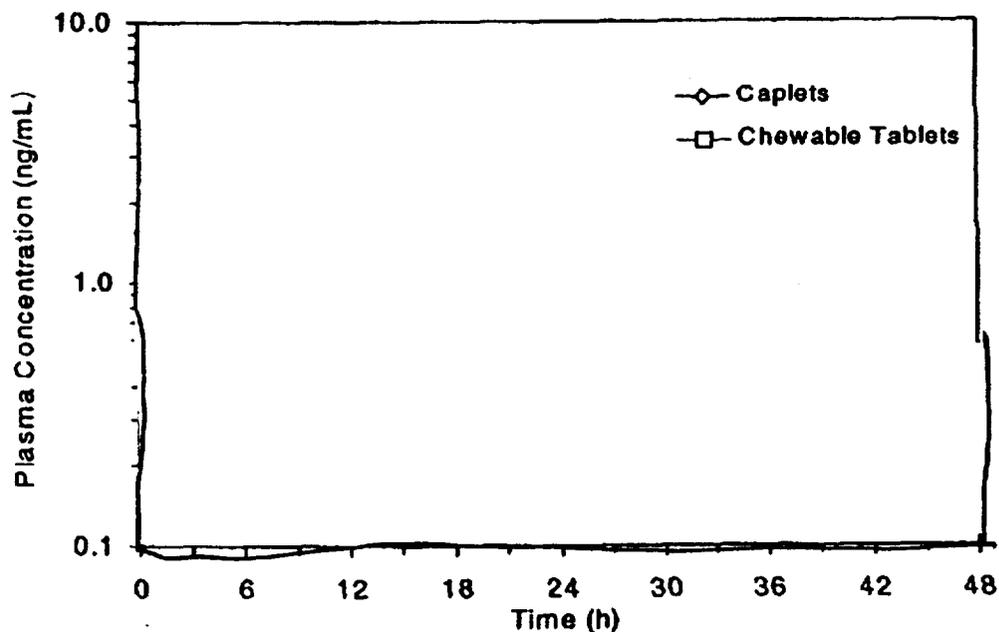


Table 3. Mean Values, (SD) and %CV of Pharmacokinetic Parameters of Loperamide in Twenty-six Healthy Subjects Following Administration of a Single dose of 8 mg Loperamide and 500 mg Simethicone as Four Imodium® Advanced Caplets and as Four Imodium® Advanced Chewable Tablets

Product	AUC (ng-h/mL)	AUC _{0-∞} (ng-h/mL)	C _{max} (ng/mL)	T _{max} (h)	k _{el} (1/h)	t _{1/2} (h)
Loperamide-Simethicone Caplet (Treatment A)	32.4 (16.6) 51%	37.8 (19.7) 52%	1.94 (1.20) 62%	5.7 (0.8) 14%	0.045 (0.009) 20%	16.3 (4.3) 26%
Imodium® Advanced Chewable Tablet (Treatment B)	30.0 (14.8) 49%	35.3 (18.4) 52%	1.74 (0.91) 52%	5.9 (0.9) 16%	0.044 (0.008) 19%	16.2 (3.2) 20%

Based on these findings, the mean pharmacokinetic parameters of loperamide for the proposed Imodium® Advanced Caplet formulation and the currently marketed Imodium® Advanced Chewable Tablets are similar. For both Imodium® Advanced formulations, AUC and C_{max} are highly variable among individuals whereas inter-individual variability in t_{max} and t_{1/2} is low to moderate.

2. Do Imodium® Advanced Caplet and Imodium® Advanced Chewable Tablet Exhibit Pharmacokinetic Differences in Males or in Females?

In the study described in item 1 above, the pharmacokinetic data were re-analyzed by gender. The results are presented in Table 4.

Table 4. Comparative Pharmacokinetic Analysis of Imodium® Advanced Caplet and Imodium® Advanced Chewable Tablet in Males and in Females Receiving a Single dose of 8 mg Loperamide and 500 mg Simethicone as Four Imodium® Advanced Caplets and as Four Imodium® Advanced Chewable Tablets

Gender	Product	AUC (ng-h/mL)	AUC _{0-∞} (ng-h/mL)	C _{max} (ng/mL)	T _{max} (h)	k _{el} (1/h)	t _{1/2} (h)
Men (n = 14)	Loperamide-Simethicone Caplets	31.1 (9.2) 29%	35.9 (9.7) 27%	1.84 (0.75) 41%	5.9 (0.9) 16%	0.046 (0.010) 21%	15.9 (5.2) 33%
	Imodium® Advanced Chewable Tablets	27.4 (7.3) 26%	32.2 (9.1) 28%	1.55 (0.43) 28%	5.7 (1.2) 21%	0.045 (0.008) 19%	16.0 (3.1) 20%
Women (n = 12)	Loperamide-Simethicone Caplets	33.9 (22.9) 68%	39.9 (27.6) 69%	2.06 (1.61) 78%	5.6 (0.7) 12%	0.043 (0.008) 18%	16.6 (3.2) 19%
	Imodium® Advanced Chewable Tablets	32.9 (20.4) 62%	39.0 (25.4) 65%	1.96 (1.25) 64%	6.1 (0.5) 8%	0.044 (0.008) 19%	16.4 (3.3) 20%

Based on these results, the proposed market formulation of Imodium® Advanced caplet and the currently marketed formulation of Imodium® Advanced chewable tablet are similar in pharmacokinetic characteristics in males as well as in females. In general, males and females are comparable in pharmacokinetic parameters for the two formulations. However, regardless of drug formulation inter-individual variability in drug exposure (AUC and C_{max}) appears to be higher in females as compared to males.

3. *Is the Bioequivalence of Imodium® Advanced Caplet and Imodium® Advanced Chewable Tablet Adequately Evaluated?*

The bioequivalence of the proposed market formulation (Formulation C-826-15F) of Imodium® Advanced caplet (Treatment A) and the currently marketed Imodium® Advanced chewable tablet formulation (Treatment B) was evaluated in 26 healthy subjects in the crossover study described in item 1 above (Protocol 98-068). Bioequivalence was assessed using the Two One-sided t-test procedure at the 90% confidence level, with Treatment A as test and Treatment B as reference. The results are summarized in Table 5. A more comprehensive summary of the results is presented in Appendix I (page 18).

Table 5. Bioequivalence of Loperamide in Twenty-six Healthy Subjects Following Administration of a Single dose of 8 mg Loperamide and 500 mg Simethicone as Four Imodium® Advanced Caplets and as Four Imodium® Advanced Chewable Tablets

Geometric Mean	Treatment A	Treatment B	A/B ^a (%)	90% C.I. ^b	In. V ^c (CV%)	P-value	Power (%)
AUC _{inf} (ng/mL*h)	34.2	32.0	107	102-113	11.0	0.0253	100
C _{max} (ng/mL)	1.70	1.58	108	102-115	12.9	0.0342	100

^aRatio of least square means, ^bConfidence interval, ^cIntra-individual variability

The 90% confidence intervals for AUC_{infinity} (AUC_{inf}) and C_{max}, 102-113% and 102-115%, respectively, are within the range of 80-125% required for bioequivalence. Based on these findings, the proposed market formulation of Imodium® Advanced loperamide 2 mg/simethicone 125 mg caplet and the currently marketed formulation of Imodium® Advanced loperamide 2 mg/ simethicone 125 mg chewable tablet are bioequivalent.

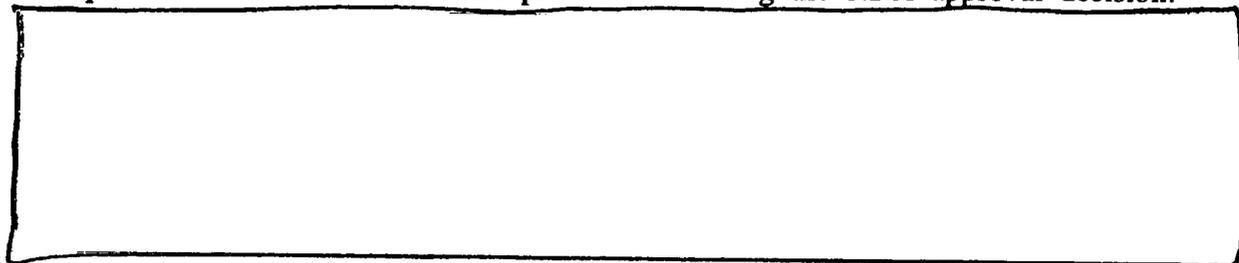
4. *Is Adequate Information Provided on Drug Product Dissolution?*

The dissolution profile of the proposed Imodium® Advanced loperamide 2 mg/simethicone 125 mg caplet formulation was evaluated in 500 mL of 0.1N hydrochloric acid (HCl) and in 500 mL of acetate buffer (pH=4.5), each maintained at

5 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

VI. RECOMMENDATION

NDA 21-140 submitted for loperamide 2 mg/simethicone 125 mg Imodium® Advanced caplet, by the sponsor, on October 29, 1999, has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The bioequivalence information provided by the sponsor is acceptable for consideration in the process of making the NDA approval decision.



/S/

07/14/00

David G. Udo, Ph.D.

Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D.

/S/

7/14/00

Clinpharm/Biopharm Briefing: 07/14/00 at 2.30 p.m. (Attendees: Huang, Hunt and Doddapaneni [all of HFD-870]).

cc: NDA 21-140, HFD-180, HFD-180 (Levine), HFD-870 (M. Chen, Huang, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

17 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.