

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-855**

**MEDICAL REVIEW**

## CLINICAL REVIEW

Application Type NDA  
Submission Number 21-855  
Submission Code 000

Letter Date October 1, 2004  
Stamp Date October 4, 2004  
PDUFA Goal Date August 4, 2005

Reviewer Name Eric Brodsky, MD  
Review Completion Date July 21, 2005

Established Name Loperamide Hydrochloride  
(Proposed) Trade Name None  
Therapeutic Class Anti-diarrheal  
Applicant Banner Pharmacaps Inc.

Priority Designation Standard  
Formulation Oral Soft Gelatin Capsule  
Over-the-counter Indication Control symptoms of diarrhea, including  
Travelers Diarrhea

Proposed Dosing Regimen for the 2 mg Loperamide dose: For adults and children 12 years and older — 2 capsules after the first loose stool; 1 capsule after each subsequent loose stool; but no more than 4 capsules in 24 hours.

Proposed Dosing Regimen Table for the 1 mg Loperamide dose:

Age group	Loperamide 1 mg Dose
Adults and children 12 years old and over	4 capsules (4 mg) after the first loose stool; 2 capsules (2 mg) after each subsequent loose stool; but no more than 8 capsules (8 mg) in 24 hours
Children 9-11 years old	2 capsules (2 mg) after the first loose stool; 1 capsule (1 mg) after each subsequent loose stool; but no more than 6 capsules (6 mg) in 24 hours
Children 6-8 years old	2 capsules (2 mg) after the first loose stool; 1 capsule (1 mg) after each subsequent loose stool; but no more than 4 capsules (4 mg) in 24 hours

**TABLE OF CONTENTS:**

	<b>PAGE NUMBER(S)</b>
<b>1.0 EXECUTIVE SUMMARY -----</b>	<b>2</b>
<b>2.0 BACKGROUND -----</b>	<b>3</b>
<b>2.1 Introduction -----</b>	<b>3</b>
<b>2.2 Product Information -----</b>	<b>3-4</b>
<b>2.3 Currently Available Treatments -----</b>	<b>4-5</b>
<b>2.4 Highlights of Regulatory Experience in the United States -----</b>	<b>5</b>
<b>2.5 Highlights of Safety Experience in the United States -----</b>	<b>5</b>
<b>2.6 Pre-submission Regulatory Activity -----</b>	<b>6</b>
<b>3.0 BIOEQUIVALENT STUDY -----</b>	<b>7-11</b>
<b>4.0 PHARMACOKINETICS RESULTS -----</b>	<b>11</b>
<b>5.0 SAFETY RESULTS -----</b>	<b>11-12</b>
<b>6.0 LABELING -----</b>	<b>12-15</b>
<b>7.0 PEDIATRIC ISSUES -----</b>	<b>15</b>
<b>8.0 CONCLUSIONS -----</b>	<b>16-17</b>
<b>9.0 RECOMMENDATIONS -----</b>	<b>17</b>

**1.0. EXECUTIVE SUMMARY:**

Banner Pharmacaps Inc. submitted a 505(b)(2) new drug application to support the approval of oral **loperamide soft gelatin capsules** in the over-the-counter treatment of diarrhea in adults and children over 12 years old (NDA 21-855). To support the approval of loperamide, Banner submitted one bioequivalent study (Study R03-724) in 30 healthy adult men and adult women.

From a clinical standpoint, the loperamide soft-gelatin capsules appears bioequivalent to Imodium A-D caplets. In the 30 subject bioequivalent study, there were no deaths, no serious adverse events, and no significant adverse events associated with the use of loperamide soft-gelatin capsules. Two patients withdrew from the study; however, their discontinuations were not related to study treatment. In the bioequivalent study, the safety of loperamide soft-gelatin capsules appeared similar to Imodium A-D caplets, the reference listed drug product. Furthermore, loperamide has not demonstrated significant safety signals as an approved drug product for the treatment of diarrhea in the United States in the past 30 years (including 17 years as an over-the-counter drug).

From a clinical perspective, this medical officer recommends an **approval** action for the 1 mg loperamide soft gelatin capsule dose in the over-the-counter treatment of diarrhea in adults and pediatric patients over 6 years old. Also, this medical officer recommends an **approval** action for the 2 mg loperamide soft gelatin capsule dose in the over-the-counter treatment of diarrhea in adults and pediatric patients over 12 years old. Additionally, this medical officer recommends a partial waiver for the assessment of loperamide soft-gelatin capsules in the OTC treatment of diarrhea in pediatric patients from birth to two years old, under the Pediatric Research Equity Act of 2003.

## 2.0. BACKGROUND:

### 2.1 Introduction:

Banner Pharmacaps Inc. (Banner) submitted this 505(b)(2) new drug application to support the approval of oral **loperamide soft gelatin capsules** in the over-the-counter treatment of diarrhea in adults and children over 12 years old (NDA 21-855). Loperamide, a  $\mu$ -opioid agonist, has been approved in the United States for almost 30 years (including 17 years as an over-the-counter drug). Multiple loperamide formulations are approved for the over-the-counter treatment of diarrhea. Since no soft gelatin capsule loperamide formulation is available, Banner decided to investigate and request approval for this new loperamide formulation.

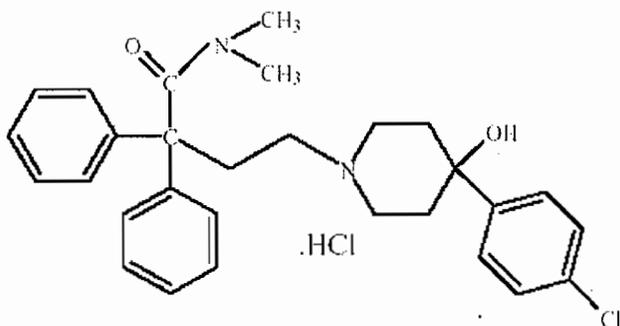
Banner requested the approval of two loperamide doses — 1 mg and 2 mg — in the over-the-counter treatment of diarrhea. To support the approval of the 2 mg loperamide dose, Banner submitted one bioequivalent study (Study R03-724) in 30 healthy adult men and adult women. To support the approval of the 1 mg loperamide dose, Banner submitted *in vitro* comparative dissolution data between the 1 mg and 2 mg loperamide doses and submitted a biowaiver request.

The single bioequivalent study (R03-724) was a randomized, open-label, single dose, 2-way crossover phase 1 study. A single 8 mg (4 pills of 2 mg) dose of loperamide caplets (Imodium® A-D), the RLD (Reference Product), by McNeil Consumer Healthcare was compared to a single 8 mg (4 pills of 2 mg) dose of the soft gelatin loperamide capsules (Test Product) by Banner.

### 2.2 Product Information:

**Proposed Trade Name:** None

**Established name:** Loperamide Hydrochloride Soft Gelatin Capsules



**Proposed Over-The-Counter Indication:** “controls symptoms of diarrhea, including Travelers’ Diarrhea”

**Pharmacologic Class:** Anti-diarrheal

**Route of Administration, Description, and Formulation:** Oral soft gelatin capsules (liquid-filled capsules) are oval and have a light blue color.

**Chemical Class:** New formulation

**Proposed Treatment Regimen and age groups for the 1 mg Loperamide Soft Gelatin Capsule:**

<b>Age group</b>	<b>Dose</b>
<b>Adults and children 12 years old and over</b>	4 capsules (4 mg) after the first loose stool; 2 capsules (2 mg) after each subsequent loose stool; but no more than 8 capsules (8 mg) in 24 hours
<b>Children 9-11 years old</b>	2 capsules (2 mg) after the first loose stool; 1 capsule (1 mg) after each subsequent loose stool; but no more than 6 capsules (6 mg) in 24 hours
<b>Children 6-8 years old</b>	2 capsules (2 mg) after the first loose stool; 1 capsule (1 mg) after each subsequent loose stool; but no more than 4 capsules (4 mg) in 24 hours

**Proposed Treatment Regimen and age groups for the 2 mg Loperamide Soft Gelatin Capsule:**

For adults and children 12 years old and older take 2 capsules (4 mg) after the first loose stool; 1 capsule (2 mg) after each subsequent loose stool; but no more than 4 capsules (8 mg) in 24 hours

**Molecular Formula:** C<sub>29</sub>H<sub>33</sub>ClN<sub>2</sub>O<sub>2</sub>•HCl

**Chemical Name:** 4-(4-Chlorophenyl)-4-hydroxy-N,N-dimethyl- $\alpha,\alpha$ -diphenyl-1-piperidinebutanamide hydrochloride

**2.3 Currently Available Treatments:**

Two active pharmaceutical ingredients — loperamide and bismuth subsalicylate — form the basis for several approved over-the-counter treatments of diarrhea in the United States. Multiple loperamide formulations are approved for the over-the-counter treatment of diarrhea including liquid, caplets, and capsules. Banner desires approval of a new loperamide formulation — soft gelatin capsules — that is not currently approved for the treatment of diarrhea in the United States. See Table 1

**Table 1: Over-the-counter medications approved for the treatment of diarrhea in the United States**

<b>Drug</b>	<b>Formulations</b>	<b>Population</b>
<b>Loperamide (Imodium A-D®)</b>	oral caplets, oral solution, oral capsules, oral soft-gelatin capsules*	Adults and children over 6 years old
<b>Bismuth Subsalicylate (Kaopectate®, Pepto Bismol®)</b>	oral liquid, oral chewable tablets, oral caplets	Adults and children over 12 years old

\* Loperamide soft gelatin capsules are the subject of this NDA; they are not approved in the United States

Reference: Pharmacology Online

Three active pharmaceutical ingredients — loperamide, difenoxin, and diphenoxylate — form the basis for several prescription treatment of diarrhea in the United States. See Table 2.

**Table 2: Prescription medications approved for the treatment of diarrhea in the United States**

<b>Drug</b>	<b>NDA# for RLD</b>	<b>Formulations</b>	<b>Population</b>
<b>Loperamide (Imodium)</b>	NDA 17-694 (tablet) NDA (solution)	Oral tablets Oral solution	Adults and children over 2 years old
<b>Difenoxin hydrochloride and Atropine sulfate (Motofen®)</b>	NDA 17-744	Oral tablets	adults
<b>Diphenoxylate and Atropine (Lomotil®, Lonox®)</b>	NDA 12-462 (tablet) NDA 12-699 (solution)	Oral tablets Oral solution	Adults and children over 2 years old

RLD = reference listed drug

Reference: Pharmacology Online

#### **2.4 Highlights of Regulatory Experience in the United States:**

Below are the highlights of the regulatory experience of loperamide:

- In December 1976, loperamide (Imodium capsules, sponsored by Janssen) was initially approved as a **prescription** treatment for diarrhea under NDA 17-690;
- In 1984, another loperamide formulation (Imodium liquid sponsored by Janssen) was approved as a prescription treatment for diarrhea under NDA 19-037;
- In March 1988, loperamide (Imodium A-D liquid sponsored by McNeil Consumer Healthcare) was approved for the **over-the-counter** treatment of diarrhea;
- In November 1989, loperamide tablets (Imodium A-D, sponsored by McNeil) was approved for the over-the-counter treatment of diarrhea under NDA 19-860.
- In the 1990's, many OTC loperamide dosage formulations (including solutions, chewable tablets, and caplets) were approved by the FDA. Also, multiple generics were approved.

Currently many loperamide formulations are approved for the over-the-counter treatment of diarrhea in the United States. However, no prescription or OTC soft-gelatin capsule loperamide formulation is approved in the United States.

#### **2.5 Highlights of Safety Experience in the United States:**

Loperamide has been approved for almost 30 years in the United States. Furthermore, loperamide has been approved as an over-the-counter drug in the United States for about 17 years.

According to the data submitted under NDA 17-694 and reviewed previously by the Agency, loperamide is generally well tolerated and adverse drug events are usually self-limiting. The following adverse events have been reported: abdominal pain, abdominal distention, constipation, drowsiness, dizziness, xerostomia, fatigue, nausea, and vomiting. Paralytic ileus occurs rarely. Rare allergic events, including anaphylactoid reactions, bullous rash, and toxic epidermal necrolysis have been reported; in most cases the patients were on other medications that may have contributed to the allergic events.

## 2.6 Pre-submission Regulatory Activity:

On August 5, 2002, Banner submitted a Citizen's Petition to the Office of Generic Drugs (OGD) for their loperamide 1 mg and 2 mg soft gelatin capsules. The OGD denied the petition for their 2 mg loperamide drug product because the 2 mg dose could not conform to the dosing regimen of the RLD in pediatric patients between 6 and 12 years old. Loperamide caplets (the RLD) can be administered as half tablets to pediatric patients between 6 and 12 years old; whereas, the test loperamide soft gelatin capsules cannot be split in these pediatric patients.

On July 1, 2003, Banner requested a pre-IND meeting regarding their proposed new loperamide formulation (soft gelatin capsules). During the internal meeting, the Division of Gastrointestinal and Coagulation Drug Products (DGICDP) and the Division of Over-The-Counter Drug Products (DOTCDP) had the following comments:

- A 505(b)(2) application is a suitable approach for gaining approval of the proposed 1 mg and 2 mg loperamide doses;
- Imodium A-D caplets is the appropriate reference listed drug;
- If a biowaiver for the 1 mg loperamide dose is granted, then you only need to conduct a relative bioavailability study comparing the test and reference 2 mg loperamide doses;
- If the compositional proportionality is established between the 1 mg and 2 mg loperamide doses, an appropriate *in vivo* bioavailability study is conducted for the 2 mg loperamide dose, and similarity of the loperamide 1 mg and 2 mg doses is established; then you may request a biowaiver for the 1 mg dose;
- You do not need to conduct a comparative bioavailability study under fed conditions;
- Either an 8 mg or a 10 mg single-dose regimen may be used in the bioavailability study;
- If the test drug product is shown to be inferior compared to the reference listed drug (RLD), then additional efficacy data will be needed to support the application. If higher  $C_{max}$  and AUC values are shown for the test product relative to the RLD, then additional safety data may be needed in support of the application.

After Banner received the Agency's responses, Banner canceled the August 1, 2003 pre-IND meeting.

Banner did not request any additional meetings. Thus, End-of-phase 2 and Pre-NDA meetings were not conducted.

### **3.0 BIOEQUIVALENT STUDY:**

Study Title: Study R03-724 — “A relative bioavailability study of 2 mg loperamide hydrochloride soft gelatin capsules versus Imodium® A-D caplets under fasting conditions.”

Objectives: The objective of this study was to compare the relative bioavailability (rate and extent of absorption) of 2 mg loperamide soft gelatin capsules by the sponsor with that of Imodium® A-D, the RLD, following a single oral dose (4 pills of 2 mg of loperamide) in healthy volunteers administered under fasting conditions.

Methodology: This study was a randomized, single-center (in Fargo, ND) single-dose, 2-way crossover trial in healthy adult volunteers. A single 8 mg (4 pills of 2 mg) dose of loperamide caplets (Imodium® A-D), the RLD, by McNeil Consumer Healthcare was compared to a single 8 mg (4 pills of 2 mg) dose of the soft gelatin loperamide capsules (Test Product) by the sponsor. The randomization sequence was:

- Sequence 1 — Reference Product then 14 day washout period then Test Product
- Sequence 2 — Test Product then 14 day washout period then Reference Product

**MEDICAL REVIEWER’S COMMENTS:** The study had the same design as the design in two pivotal studies in ANDAs 74-194 and 75-232. The two pivotal studies were single dose (10 mg), 2-way crossover bioequivalent trials comparing Imodium® A-D, the RLD, to generic loperamide formulations in 30 healthy subjects.

**This protocol involved an approved dose of a new formulation of an approved drug. The approved drug has been available by prescription for almost 30 years and available OTC about 17 years and it has an acceptable safety profile. The loperamide prescription label states that an 8 mg loperamide dose once daily may be used for the treatment of chronic diarrhea. Therefore, the two 8 mg doses in this protocol were acceptable**

Eligibility Criteria: Table 3 displays the eligibility criteria of Study R03-724

**Table 3: Eligibility criteria of Study R03-724**

<p><b>Inclusion Criteria:</b> To be eligible to participate in the study, patients had to have met the following criteria:</p> <ul style="list-style-type: none"> <li>➤ Healthy men or women 18 years or older at the time of dosing</li> <li>➤ The weight range will not exceed 20% or will not go below 20% for height and body frame as per the “Desirable Weights for Adults” — the Metropolitan Height and Weight Table of 1983.</li> <li>➤ Females must be post-menopausal for one year; surgically sterile; or practicing an acceptable method of birth control for the duration of the study if of childbearing potential.</li> </ul>	<p><b>Exclusion Criteria:</b> If patients had the following conditions, they were not eligible to participate in the study:</p> <ul style="list-style-type: none"> <li>➤ A recent history of drug or alcohol addition or abuse</li> <li>➤ The presence of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic systems or psychiatric disease (as determined by the clinical investigators.)</li> <li>➤ Clinical laboratory test values (including CBC with differential, creatinine, BUN, glucose, total protein, hepatic panel, and urinalysis) outside the accepted reference range and when confirmed on re-examination deemed to be clinically significant.</li> <li>➤ A positive hepatitis B surface antigen or a reactive HIV antibody</li> <li>➤ A positive urine drug screen</li> <li>➤ A positive pregnancy screen in females</li> <li>➤ Breastfeeding</li> <li>➤ A history of allergic response to loperamide or related drugs</li> <li>➤ A history of clinically significant allergies including drug allergies</li> <li>➤ A clinically significant illness during the four weeks prior to dosing (as determined by the clinical investigators.)</li> <li>➤ The use of tobacco products</li> <li>➤ Taking a drug known to induce or inhibit hepatic drug metabolism in the 28 days prior to dosing</li> <li>➤ Donating greater than 150 mL of blood within 28 days prior to dosing.</li> <li>➤ Receiving any investigational drug within 28 days prior to dosing</li> <li>➤ Taking any systemic prescription medication in the 14 days prior to dosing</li> </ul>
---	---

Reference: Adapted from Study R03-724

**MEDICAL REVIEWER’S COMMENTS: The eligibility criteria were appropriate for this bioequivalent study.**

Events necessitating premature discontinuation: Over the course of the study, the investigator may have withdrawn any subject from the study in the case of unnecessary risk, adverse drug events, or noncompliance. At the discretion of the investigator, subjects may have been excluded or dropped from the study at any time if they:

- Consumed any prescription or nonprescription medication within 3 days of dosing and over the course of the study;
- Consumed grapefruit products, caffeine, or xanthine containing products at least 48 hours within dosing and during the periods when blood samples are collected; or
- Consumed alcohol within 48 hours of dosing or during blood sample collection.

**Schedule of Evaluations and Procedures:** See Table 4 for the summary of the schedule of evaluations and procedures. The protocol consisted of a screening period, a treatment period (including periods I and II), and a post-treatment period.

**TABLE 4: Summary of Evaluations and Procedures**

	SCREENING	PERIOD I	PERIOD II	STUDY EXIT
Consent Document	X			
Medical History	X			
Physical Examination	X			X
Electrocardiogram	X			
Vital Signs	X	X	X	X
Laboratory:				
CBC with differential	X			X
Chemistry	X			X
HIV Antibody Screen	X			
Hepatitis B Screen	X			
Urinalysis	X			
Urine Drug Screen	X			
Pregnancy Screen (females only)	X	X	X	X
Product Administered		X	X	
Blood Sample Collections for Drug Concentration (17) (0 to 72 hours)		X	X	

Reference: Study R03-724 — “A relative bioavailability study of 2 mg loperamide hydrochloride soft gelatin capsules versus Imodium® A-D caplets under fasting conditions.”

**Screening Period:** The screening process was completed 28 days within dosing. Screening included a history and a physical exam. Laboratory screening tests included an EKG, CBC with differential, creatinine, BUN, glucose, total protein, hepatic panel, HIV antibody, hepatitis B surface Antigen, urine drug screen, and urinalysis. At study check-in, the subjects were briefly evaluated to assess if they continue to meet the study inclusion/exclusion criteria. Furthermore, females had a blood pregnancy test.

**Treatment Period:** In the treatment period, the subjects received one formulation of loperamide followed by a 14 day wash out period and then received the second loperamide formulation. The subjects were confined approximately 10 hours prior to and until at least 24 hours after each dose. The subjects were given 240 ml of water with each dose and at two hours post-dose. Subjects fasted (except for the water allowed) approximately 10 hours prior to dose administration until at least 4 hours after dosing. A sitting blood pressure and heart rate were measured prior to dosing and (12 and 24 hours) after each dose. Subjects were questioned regarding possible adverse events and vital signs were performed throughout the treatment period. Frequent blood tests measuring loperamide levels were performed within one hour prior to dosing 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 (please see Table 5).

**Table 5: Blood collection times**

STUDY DAY	TIME	DOSE	BLOOD SAMPLE NUMBER	BLOOD COLLECTION TIME	QUERY FOR ADVERSE EVENTS	VITAL SIGNS	FLUID INTAKE	MEALS
Day -1.	2000 ( 8:00)	Report to Institute and Site Orientation						
Day 1	0645			Wake-Up				
	0700		1	-1:00 to 0:00	X	X		
	0800	X	N.A.	0:00			240 mL	
	0830		2	0:30				
	0900		3	1:00				
	1000		4	2:00			240 mL	
	1100		5	3:00				
	1200		6	4:00				
	1215							
	1230		7	4:30			480 mL	Lunch
	1300 ( 1:00)		8	5:00				
	1330 ( 1:30)		9	5:30				
	1400 ( 2:00)		10	6:00			240 mL	
	1600 ( 4:00)		11	8:00			240 mL	
	1830 ( 6:30)						480 mL	Dinner
	2000 ( 8:00)		12	12:00	X	X	240 mL	
	2230 (10:30)						240 mL	Snack
Day 2	0000		13	16:00				
	0700			Wake-Up				
	0800		14	**24:00	X	X		
	2000 ( 8:00)		15	36:00	X			
Day 3	0800		16	48:00	X			
Day 4	0800		17	72:00	X			

Reference: Study R03-724 – “A relative bioavailability study of 2 mg loperamide hydrochloride soft gelatin capsules versus Imodium® A-D caplets under fasting conditions.”

**Post-Treatment Period:** Study exit procedures were completed within 14 days after the last blood sample collection. The exit procedures included general observations, a physical examination, blood pressure, heart rate, and temperature evaluation. The exit blood tests included the following: CBC with differential, creatinine, BUN, glucose, total protein, and a hepatic panel. For female subjects, an additional pregnancy blood test was performed.

**MEDICAL REVIEWER’S COMMENTS:** The schedule of evaluations and procedures was satisfactory.

**Endpoints:** The three most important pre-specified endpoints in this study were the following pharmacokinetic parameters:

- #1)  $AUC_{0-t}$  (area under the concentration-time curve from zero to time t);
- #2)  $AUC_{0-\infty}$  (area under the concentration-time curve from zero to time infinity); and
- #3)  $C_{max}$  (peak drug concentration.)

Secondary endpoints included the following additional pharmacokinetic parameters:  $T_{max}$  (time to peak drug concentration),  $\lambda_z$  (terminal elimination rate constant), and  $t_{1/2}$  (termination half-life). Safety variables included vital signs, blood tests, and adverse drug events (AEs).

**Statistical Methods:** The pharmacokinetic parameters were evaluated statistically by an analysis of variance (ANOVA). Log transformed  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$ , estimates of the adjusted differences between treatment means and the standard error associated with these differences were used to

construct a 90% confidence interval for the ratio of the test to reference population means. To establish bioequivalence under fasting conditions, the 90% confidence interval for the ratio of the geometric means between the products should fall within the interval 80-125% for log transformed  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$ .

#### **4.0 PHARMACOKINETICS RESULTS:**

According to Dr. Tien-Mien Chen, the biopharmaceutics reviewer, 8 mg of loperamide soft gel capsules (test product) was bioequivalent to 8 mg of loperamide caplets (RLD) in Study R03-724. Please see his review for more details.

#### **5.0 SAFETY RESULTS:**

Out of the 30 subjects randomized in the bioequivalent study, 28 (93.3%) subjects completed the study and received both loperamide doses and 2 (6.7%) subjects (subject# 13 and subject# 17) discontinued the study treatment. Subject# 13 was a 38 year old white male (with no significant past medical history) who took the single-dose RLD in the first sequence and did not take the single-dose test dose in the second sequence for "personal reasons". Subject# 17 was a 45 year old white female (with a past history of a partial hysterectomy in 1996) who took the single-dose test drug in the first sequence. About 13 days after the test drug, she developed "an illness" and discontinued the study before receiving the RLD in the second sequence. About 17 days after the test drug, all of her post-test evaluations including physical examination and laboratory testing were normal.

**MEDICAL REVIEWER'S COMMENTS:** It appears that subject# 17's illness resolved. However, the case report form lacks detailed information regarding the specific nature of the illness. The illness should have been categorized as an AE. Its severity, its relationship to study drug, and therapeutic measures (if applicable) should have been recorded. Since this event occurred 13 days after the single test, more than 99% of the test loperamide dose was likely cleared from subject# 17's body. Therefore, it is unlikely that this "illness" was due to the test loperamide product.

In the bioequivalent study, there were no deaths and no serious adverse events among the 30 randomized, healthy subjects. Out of the 30 randomized subjects, four subjects each reported a single adverse event. Of the four adverse events, three were associated with the test product (loperamide soft-gelatin capsules) and one was associated with the RLD (Imodium A-D caplets). According to the investigators, only one AE was possibly associated with the test product and only one AE was possibly associated with the RLD.

All four AEs were described as mild, therefore, no AE was described as moderate or severe in this study. All four AEs resolved and all four AEs required no counter measures. Please see Table 6 for a list of all the AEs in Study R03-724

**MEDICAL REVIEWER'S COMMENTS:** This medical officer agrees with the investigator's categorization of the AEs. The AEs of subject# 22 and subject# 23 were possibly related to the study drug administered. The half-life of 8 mg of loperamide (for the test and the RLD) is long

(16-17 hours); therefore, both subjects had significant loperamide blood levels at the time of their AEs. Since both AE descriptions were nonspecific, the relationship to the study drugs cannot be determined.

Only one AE was possibly related to the test product (in subject# 22) and this AE was mild and the AE resolved without any treatment four hours later. Therefore, the safety of the test product (loperamide soft-gelatin capsules) and the RLD (Imodium A-D caplets) were very similar.

**Table 6: All the adverse events in Study R03-724**

AE #	Subject #	Study Drug	AE Description by Subject	Relationship to Study Drug*	AE Background from the Case Report Forms
1	22	Test	“stomach ache”	possible	59 year old white male (with history of well-controlled asthma and remote appendectomy) developed a “stomach ache” 19 hours after receiving the single-dose <b>test</b> drug. His mild symptoms resolved 4 hours later without treatment.
2	14	Test	“coughing”	unrelated	29 year old white female (with history of mild eczema and not taking any prescription or OTC medication) developed “coughing” 11 days after taking the single-dose <b>test</b> drug. Her mild symptoms resolved three days later without treatment.
3	23	RLD	“gassy”	possible	19 year old white male (with history of appendectomy about 15 months ago) developed a “gassy” feeling about 28 hours after taking the single-dose <b>RLD</b> . His mild symptoms resolved 6 hours later without treatment.
4	8	Test	“head cold”	unrelated	23 year old white male (with no significant past medical history and not taking any prescription or OTC medication) developed a “head cold” 10 days after taking the single-dose <b>test</b> drug. His mild symptoms resolved three days later without treatment.

\* Relationship to study drug according to the investigators

Test drug was Loperamide Soft-Gel Capsules (Banner) and the RLD was Imodium A-D (McNeil)

Reference: Adapted from Case Report Forms: Volume 7 - Pages 2679-93; Volume 7 - Pages 2779-95; Volume 8 - Pages 2909-23; Volume 8 - Pages 1919-38

For further safety evaluation included a safety update of loperamide, please see the medical officer review from the DOTCDP.

## 6.0 LABELING:

The sponsor has accepted all of the labeling changes suggested by the DOTCDP during this review cycle. This medical officer agrees with DOTCDP’s labeling recommendations for both the 1 mg and 2 mg loperamide doses. See Table 7 and Table 8 for the revised labeling for the 1 mg and 2 mg loperamide soft gelatin capsules, respectively.

3 Page(s) Withheld

       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

## 7.0 PEDIATRIC ISSUES:

Pursuant to the Pediatric Research Equity Act of 2003, Banner requested a partial waiver for the required safety and efficacy assessment of loperamide soft-gelatin capsules (1 mg and 2 mg) in the OTC treatment of diarrhea in pediatric patients ages birth to 2 years old. Banner states that since prescription loperamide is approved for the treatment of diarrhea in pediatric patients aged 2 to 18 years old, a full waiver is not required. Banner argues the following reasons to support its partial waiver request:

- #1) Their soft gelatin capsule formulation is not suitable for pediatric patients less than 2 years old because infants and young children cannot swallow their capsules and the dosing is not flexible;
- #2) Loperamide would not likely be used in this pediatric subpopulation because the standard of care for the treatment of diarrhea in young children is oral rehydration therapy or antibiotics.
- #3) Strong evidence suggests that loperamide is not safe in this pediatric subpopulation.

To support argument# 3, the sponsor cites case reports of the following AEs in infants who have received loperamide: severe constipation, ileus, apnea, coma, and death. Additionally, many pediatricians state that anti-diarrheal medications should be avoided in the initial treatment of diarrhea in neonates, infants, and young children because loperamide may prevent the clearance of viruses and bacteria from the lower gastrointestinal tract and thus prolong the diarrheal illness.

**MEDICAL REVIEWER'S COMMENTS:** This medical officer believes that the sponsor's partial waiver request for pediatric patients between 0 and 2 years old is valid. Loperamide is not part of the National Institutes of Health (NIH) "List of Drugs for Which Pediatric Studies Are Needed". This list prioritizes drugs that are most in need of study for use by pediatric patients to ensure their safety and efficacy [Federal Register of February 13, 2004 (70 FR 7243) and Federal Register of January 27, 2005 (70 FR 3937)].

**This medical officer believes that loperamide should not be used to self-treat pediatric patients from birth to 2 years old who have diarrhea. Currently, loperamide is not approved for OTC use in pediatric patients under 6 years old. This medical officer supports a partial waiver for the use of loperamide for the OTC treatment of diarrhea in pediatric patients between birth and 6 years old. Thus, this medical officer recommends that we grant their partial waiver request for pediatric patients, between birth and 2 years old.**

## 8.0 CONCLUSIONS:

From a clinical standpoint, loperamide soft-gelatin capsules appears bioequivalent to Imodium A-D caplets. In the 30 subject bioequivalent study, there were no deaths, no serious adverse events, and no significant AEs associated with the use of loperamide soft-gelatin capsules. Two patients withdrew from the study; however, their discontinuations were not related to study treatment. In the bioequivalent study, the safety of loperamide soft-gelatin capsules appeared similar to Imodium A-D caplets, the reference listed drug product. Additionally, loperamide has not demonstrated significant

safety signals as an approved drug product for the treatment of diarrhea in the United States in the past 30 years (including 17 years over-the-counter).

## 9.0 RECOMMENDATIONS:

From a clinical perspective, this medical officer recommends an **approval** action for the both loperamide soft gelatin capsule doses (1 mg and 2 mg) in the over-the-counter treatment of diarrhea. For the loperamide 2 mg dose, this medical officer recommends the following dosing regimen in adults and children 12 years and older: take 2 capsules after the first loose stool; 1 capsule after each subsequent loose stool; but no more than 4 capsules in 24 hours. For the loperamide 1 mg dose, this medical officer recommends the following dosing regimens:

<b>Age group</b>	<b>Loperamide 1 mg Dose</b>
<b>Adults and children 12 years old and over</b>	<b>4 capsules (4 mg) after the first loose stool; 2 capsules (2 mg) after each subsequent loose stool; but no more than 8 capsules (8 mg) in 24 hours</b>
<b>Children 9-11 years old</b>	<b>2 capsules (2 mg) after the first loose stool; 1 capsule (1 mg) after each subsequent loose stool; but no more than 6 capsules (6 mg) in 24 hours</b>
<b>Children 6-8 years old</b>	<b>2 capsules (2 mg) after the first loose stool; 1 capsule (1 mg) after each subsequent loose stool; but no more than 4 capsules (4 mg) in 24 hours</b>

Additionally, this medical officer recommends a partial waiver for the assessment of loperamide soft-gelatin capsules in the OTC treatment of diarrhea in pediatric patients from birth to two years old, under the Pediatric Research Equity Act of 2003.

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

/s/

-----  
Eric Brodsky  
7/22/05 04:34:51 PM  
MEDICAL OFFICER

Ruyi He  
7/22/05 05:04:45 PM  
MEDICAL OFFICER

I concur with Dr. Brodsky's evaluation, conclusions and recommendations.