

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 19-487/S-022

Name: Imodium A-D (Loperamide HCl) Liquid

Sponsor: McNeil Consumer & Specialty Pharmaceuticals

Approval Date: July 8, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-487/S-022

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-487/S-022

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-487/S-022

McNeil Consumer & Specialty Pharmaceuticals
Attention: Victoria Wagner-Weber
Associate Director, Regulatory Affairs
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Wagner-Weber:

Please refer to your supplemental new drug applications submitted March 5, 2004, received March 8, 2004, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for: Imodium® A-D (loperamide HCL) Liquid.

We also acknowledge receipt of your submissions dated June 9, June 30, July 1, and July 7, 2004.

This supplemental application proposes a reformulation of Imodium A-D liquid to an opaque, green liquid with a mint flavor.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text.

The final printed labeling (FPL) must be identical to the approved draft labeling (carton label principal display panel submitted March 5, 2004, and Drug Facts panel submitted July 1, 2004) and must be formatted in accordance with the requirements of 21 CFR 201.66.

We remind you to remove the phrase "NEW FORMULA" from the product labels after 180 days of OTC marketing.

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

NDA 19-487/S-022

Page 2

If you have any questions, call Laura Shay, Regulatory Project Manager, at (301) 827-2274.

Sincerely yours,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.

Deputy Director

Division of Over the Counter Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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

/s/

Brian Harvey
7/8/04 01:13:40 PM
Signed for Dr. Curtis Rosebraugh.


CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-487/S-022

LABELING

NOTES:

- 1) DRAWING SHOWN PRINT SIDE UP.
- 2) TOLERANCES UNLESS SPECIFIED +/- 1/64.
- 3) BASED ON NATIONAL LABEL DRAWING NO. 1-04-4

BVG. NO.		 <small>Consumer & Specialty Pharmaceuticals</small> <small>7000 Chippewa Hill Road, Fort Washington, PA 19034</small>		
LB-PS-1057				
DESIGN	SKH			
SCALE	NONE			
DATE	1-26-04			
INT.	NO.	DATE	REVISIONS	APPROVER


Drug Facts (continued)

Directions

- drink plenty of clear fluids to help prevent dehydration caused by diarrhea
- first right dose on chart. If possible, use weight to dose; otherwise use age.
- shake well before using
- only use attached measuring cup to dose product

adults and children 12 years and over	30 mL (6 tsp) after the first loose stool; 15 mL (3 tsp) after each subsequent loose stool; but no more than 60 mL (12 tsp) in 24 hours
children 9-11 years (60-95 lbs)	15 mL (3 tsp) after first loose stool; 7.5 mL (1 1/2 tsp) after each subsequent loose stool; but no more than 45 mL (9 tsp) in 24 hours
children 6-8 years (48-59 lbs)	15 mL (3 tsp) after first loose stool; 7.5 mL (1 1/2 tsp) after each subsequent loose stool; but no more than 30 mL (6 tsp) in 24 hours

NDC 50580-134-08



Imodium
Loperamide HCl A-D
Anti-Diarrheal

mint
flavor

8 FL OZ (240 mL) 1 mg Loperamide HCl per 15 mL

Drug Facts

Active Ingredient
(in each 5 mL)
Loperamide HCl 1 mg

Purpose
Anti-Diarrheal

Use
controls symptoms of diarrhea, including Traveler's Diarrhea

PAGE 4

COVER PAGE 1

Drug Facts (continued)

Warnings

Allergy alert: Do not use if you have ever had a rash or other allergic reaction to loperamide HCl

Do not use if you have bloody or black stool

Ask a doctor before use if you have

- fever
- mucus in the stool
- a history of liver disease

Ask a doctor or pharmacist before use if you are taking antibiotics

Drug Facts (continued)

When using this product

- lightheadedness, drowsiness or dizziness may occur.
- Be careful when driving or operating machinery.

Stop use and ask a doctor if


- symptoms get worse
- diarrhea lasts for more than 2 days
- you get abdominal swelling or bulging.

These may be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

PAGE 2

PAGE 3



3 0045-0134-08 0

Drug Facts (continued)

children under 6 years (up to 47 lbs) | ask a doctor

Other information

- each 30 mL (6 tsp) contains sodium 16 mg
- do not use if printed inner or outer neckband is broken or missing
- store between 20-25°C (68-77°F)
- see side panel for lot number and expiration date

Inactive ingredients

cellulose, citric acid, D&C yellow #10, FD&C blue #1, glycerin, flavor, propylene glycol, simethicone, sodium benzoate, sucralose, Vitamin dioxide, xanthan gum

Questions or comments?
call 1-800-862-5357 (English) or 1-888-456-6746 (Spanish)

© 2004 by McNeil Consumer & Specialty Pharmaceuticals 0 McNeil P.P.C., Inc. DIVISION OF MCNEIL-PPC, INC., FORT WASHINGTON, PA 19034 USA 128083

BASE PAGE 5

Labeling Format Information:

Fonts: Helvetica regular, bold, and bold oblique.			
Drug Facts:	8.5 pt	Leading:	6.5 pt
Header:	8 pt	Bullets:	5 pt
Subheader:	6 pt	Barlines:	2.5 pt
Body Text:	6 pt	Hairlines:	.5 pt
Drug Facts (continued):	8 pt		

Horizontal Scale: 80-85 % Average Kerning: -5

OUR DEPTH IS OUR STRENGTH

DESCRIPTION: **LB: BULK IMODIUM A-D 8 OZ**

FILE #: 3065156 VERSION: B-2

DATE: JUL 7 1 2004 CON1

PS IMAGE(S): **NEW ART**

TEAL	GREEN	LT BLUE	DK BLUE
YELLOW	BLACK		

D05M5470 McNeil DAG 07/23/04 REV 2

THIS DESIGN BLOCK MUST BE SAVED WITH FILE AND PRINTED ON THERMAL

NATIONAL PRINT BUYER INFORMATION BLOCK

NATIONAL PRINT BUYER:

PUT-UP NUMBER: _____

PART NUMBER: _____


DIE VINYL NUMBER: _____

NPA / PCN NUMBER: _____

FCC NUMBER: _____

PACKAGING LOCATION: _____

DOMESTIC COPY CLEARANCE APPROVAL BLOCK

 **Johnson & Johnson • MERCK**


ARTWORK APPROVAL INITIAL BLOCK


INITIALS: _____ DATE: _____

REGULATORY: _____

MEDICAL: _____


NOTES:

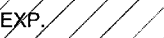
- 1) DRAWING SHOWN PRINT SIDE UP
- 2) ALL DIMENSIONS IN INCHES
- 3) TOLERANCE UNLESS SPECIFIED FRACTIONS $\pm 1/32$, ANGLES $\pm 1^\circ$
- 4)  LOT & EXP. DATE

				DWG. NO. LB-PS-1017		 Consumer & Specialty Pharmaceuticals 7050 Camp Hill Road, Fort Washington, PA 19034 TITLE: LABEL, PS 1 x 3 1/2
				DRAWN: SKH		
				SCALE: NONE		
				DATE: 3/14/03		
				APPROVED:		
SKH/JL	1	3/27/03	ADDED LOT & EXP. DATE AREA			
INIT.	NO.	DATE	REVISIONS			


Important: Read all product information before using. Keep the box for important information. Use: controls symptoms of diarrhea, including Traveler's Diarrhea

Warnings: Allergy alert: Do not use if you have ever had a rash or other allergic reaction to loperamide HCl. Do not use if you have bloody or black stool. **Directions:** • drink plenty of clear fluids to help prevent dehydration caused by diarrhea • find right dose on chart. If possible, use weight to dose; otherwise use age. • shake well before using • only use attached measuring cup

LOT: 

EXP: 

NDC 50580-134-01



Imodium
Loperamide HCl A-D
Anti-Diarrheal

Controls the symptoms of diarrhea

Mint flavor

1 mg loperamide HCl per 25 mL

1 FL OZ (30 mL)

to dose product. Adults and children 12 years and over: 30 mL (6 tsp) after the first loose stool; 15 mL (3 tsp) after each subsequent loose stool; but no more than 60 mL (12 tsp) in 24 hours. Children 9-11 years (60-95 lbs): 15 mL (3 tsp) after first loose stool; 7.5 mL (1 1/2 tsp) after each subsequent loose stool; but no more than 45 mL (9 tsp) in 24 hours. Children 6-8 years (40-55 lbs): 15 mL (3 tsp) after first loose stool; 7.5 mL (1 1/2 tsp) after each subsequent loose stool; but no more than 30 mL (6 tsp) in 24 hours. Children under 6 years (up to 47 lbs): ask a doctor. **Other information:** • each 30 mL (6 tsp) contains: sodium 10 mg • do not use if printed inner or outer neckband is broken or missing • store between 20-25°C (68-77°F)

Dist. by: MCNEIL-PPC, INC. © MCNEIL-PPC, Inc. '04
FORT WASHINGTON, PA 19034 USA www.imodium.com 128091

200 % OF ACTUAL SIZE



Labeling Format Information:

Fonts: Helvetica condensed black oblique, condensed black, condensed bold.

Drug Facts:	NA pt	Leading:	4.9 pt
Header:	4.5 pt	Bullets:	4.5 pt
Subheader:	4.5 pt	Barlines:	NA pt
Body Text:	4.5 pt	Hairlines:	.5 pt
Drug Facts (continued):	NA pt		

Horizontal Scale: 75-77 % Average Kerning: 0







OUR DEPTHS OF KNOWLEDGE

DESCRIPTION: LBL IMODIUM A-D 1 OZ

FILE #: 3085155 VERSION: D1

DATE: JULY 2, 2004 CONT.:

PS IMAGE(S): NEW ART

			
TEAL	GREEN	LT BLUE	DK BLUE
			
YELLOW	BLACK		

THIS DESIGN BLOCK MUST BE SAVED WITH FILE AND PRINTED ON THERMAL.

NATIONAL PRINT BUYER INFORMATION BLOCK

NATIONAL PRINT BUYER:

PUT-UP NUMBER:

PART NUMBER:

DIE VINYL NUMBER:

NPA / PCN NUMBER:

FCC NUMBER:

PACKAGING LOCATION:

DOMESTIC COPY CLEARANCE APPROVAL BLOCK



McNeil Johnson & Johnson • MERCK


ARTWORK APPROVAL INITIAL BLOCK

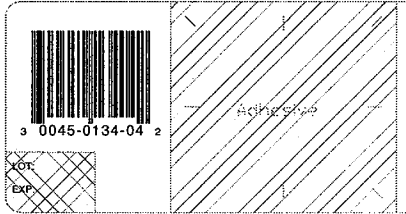
INITIALS DATE

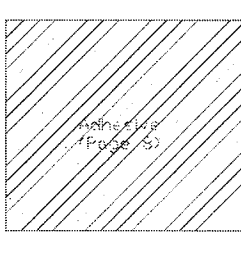
REGULATORY

MEDICAL

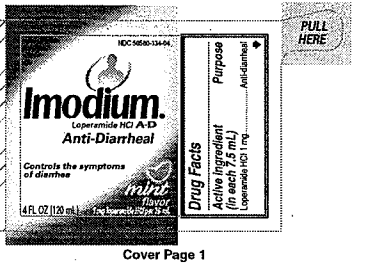
 Adhesive
 Lot & Exp. Date

			DWG. NO. LB-PS-1019	 Consumer & Specialty Pharmaceuticals 7050 Camp Hill Road, Fort Washington, PA 19034 TITLE: BOOKLET IMODIUM 4 OZ.
			DRAWN SKH	
			SCALE NONE	
			DATE	
			APPROVED	
INIT.	NO.	DATE	REVISIONS	

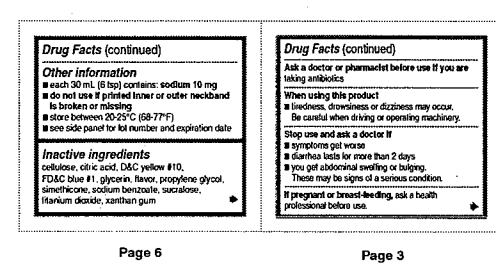




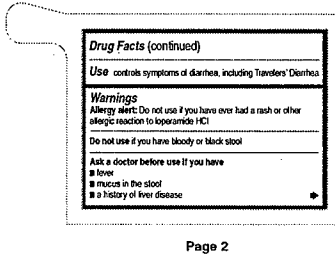
Cover Page 1



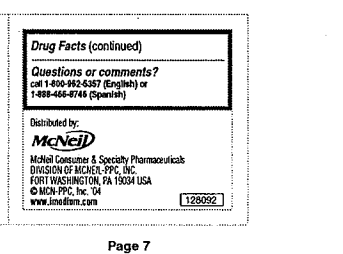
Page 6



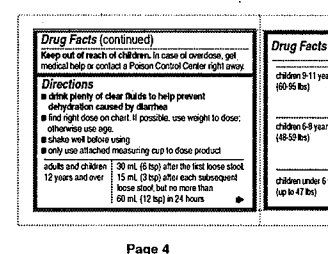
Page 3



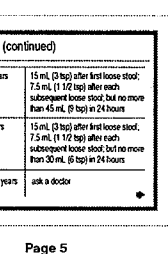
Page 2



Page 7



Page 4




Page 5

Labeling Format Information:





Fonts: Helvetica regular, bold, and bold oblique.

Drug Facts:	10 pt	Leading:	6.5 pt
Header:	8 pt	Bullets:	5 pt
Subheader:	6 pt	Barlines:	2.5 pt
Body Text:	6 pt	Hairlines:	.5 pt
Drug Facts (continued):	8 pt		

Horizontal Scale: 72-80 % Average Kerning: -10

<p style="text-align: center;">OUR DEPTH IS OUR STRENGTH</p> <p>DESCRIPTION: <u>LB, BKLT IMODIUM A-D 4 OZ</u></p> <p>FILE #: <u>3005166</u> VERSION: <u>A-2</u></p> <p>DATE: <u>JULY 1, 2004</u> COI: _____</p> <p>PS IMAGE(S) <u>NEW ART</u></p> <table border="1" style="width: 100%; text-align: center;"> <tr> <td>TEAL</td> <td>GREEN</td> <td>LT BLUE</td> <td>DK BLUE</td> </tr> <tr> <td>YELLOW</td> <td>BLACK</td> <td></td> <td></td> </tr> </table> <p style="font-size: small;">DOMESTIC MCM 040 6/17/07 REV 2 THIS DESIGN BLOCK MUST BE SAVED WITH FILE AND PRINTED ON THERMAL.</p>	TEAL	GREEN	LT BLUE	DK BLUE	YELLOW	BLACK			<p style="text-align: center;">INFORMATION BLOCK</p> <p style="text-align: center;">NATIONAL PRINT BUYER:</p> <p>PUT-UP NUMBER: _____</p> <p>PART NUMBER: _____</p> <p>DIE VINYL NUMBER: _____</p> <p>NPA / PCN NUMBER: _____</p> <p>FCC NUMBER: _____</p> <p>PACKAGING LOCATION: _____</p>	<p style="text-align: center;">DOMESTIC COPY CLEARANCE APPROVAL BLOCK</p> <p style="text-align: center;"> Johnson & Johnson • MERCK</p> <p style="text-align: center;">ARTWORK APPROVAL INITIAL BLOCK</p> <p>INITIALS: _____ DATE: _____</p> <p>REGULATORY: _____</p> <p>MEDICAL: _____</p>
TEAL	GREEN	LT BLUE	DK BLUE							
YELLOW	BLACK									

NOTES:

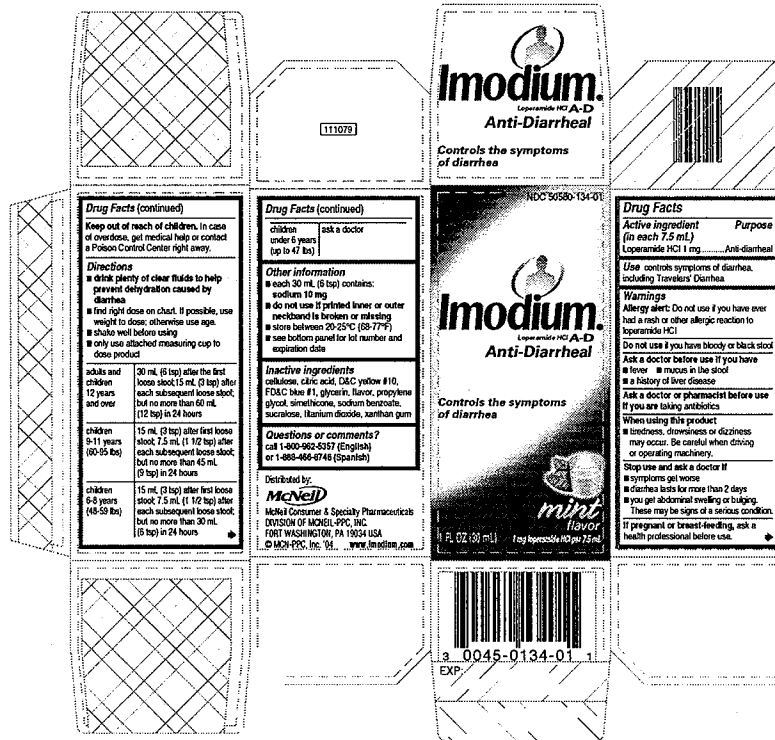
- 1) DRAWING SHOWN PRINT SIDE UP
- 2) ALL DIMENSIONS IN INCHES
- 3) TOLERANCES UNLESS SPECIFIED: FRACTIONS ±1/32 ANGLES ±1°
- 4) --- NO PRINT
- 5)  KNOCK OUT AREA
- 6)  VISIONS BARCODE AREA.
- 7)  EXP DATE AREA
- 8)  LOT AREA

DW/SH	14	3/25/04	REMOVED HOOKOUT AREAS / UPDATED NOTES.
ARS/TH	13	4/12/00	REVERSE BACK TO REV 10 LEV.
ARS/TH	12	4/10/00	REMOVED MANUF. AREA
ARS/HX	11	2/21/00	SPLIT LDT, EXP, MANUF
ARS/JS	10	12/1/99	ADDED NO VARNISH TO HIN FLAP
ARS/CH	9	8/12/99	SPLIT LDT & EXP AREA
ARS	8	6/25/97	ADDED DIV INFO
EMP	7	7-6-93	ADDED VISION BARCODE AREA
EMP	6	7-23-92	ADDED LDT/EXP. DATE AREA
EMP	5	1-2-92	REDEAVN DN NEW FORMAT
WBC	4	9-28-89	FLAP ANGLE AND RADII CORRECTED
TMV	3	6-13-89	DIE VINYL DIMENSIONS CORRECTED
WBC	2	6-6-88	DEPTH DIMENSION CORRECTED
WBC	1	3-21-88	NOTE ADDED: PRINT SIDE UP
INIT.	NOL	DATE	REVISIONS

DWG. NO.	FC-C-252
DRAWN	CGD/WBC
PLOT SCALE	NONE
DATE	10-26-87

McNEIL
 CONSUMER PRODUCTS CO.
 CAMP HILL ROAD, FORT WASHINGTON, PA. 19034

TITLE:
 CARTON, SEAL ENB
 1.50 L X 1.50 W
 X 3.06 D



Labeling Format Information:

Fonts: Helvetica regular, bold, and bold oblique.

Drug Facts:	8.5 pt	Leading:	6.5 pt
Header:	7 pt	Bullets:	5 pt
Subheader:	6 pt	Barlines:	2.5 pt
Body Text:	6 pt	Hairlines:	.5 pt
Drug Facts (continued):	7 pt		

Horizontal Scale: 78-80 % Average Kerning: -15

INFORMATION BLOCK

OUR DEPTH IS OUR STRENGTH	
DESCRIPTION	CTN IMODIUM A-D 1 OZ
FILE #	0005184
VERSION	A-1
DATE	JULY 30, 2004
CON	
PS IMAGE(S)	NEW ART

DOMESTIC MCM (GND) 12/1/03 REV 7
 THIS DESIGN BLOCK MUST BE SAVED WITH FILE AND PRINTED ON THERMAL.

NATIONAL PRINT BUYER INFORMATION BLOCK

NATIONAL PRINT BUYER:	
PUT-UP NUMBER:	
PART NUMBER:	
DIE VINYL NUMBER:	
NPA / PCN NUMBER:	
PCO NUMBER:	
PACKAGING LOCATION:	

DOMESTIC COPY CLEARANCE APPROVAL BLOCK

McNeil Johnson & Johnson • MERCK	
ARTWORK APPROVAL INITIAL BLOCK	
INITIALS	DATE
REGULATORY	
MEDICAL	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-487/S-022

LABELING REVIEWS

Division of OTC Drug Products Labeling Review for an NDA Supplement

NDA 19-487 / SCF-022

Submission Date: March 5, 2004
Received Date: March 8, 2004
Drug product: IMODIUM A-D Liquid
Active ingredient: Loperamide HCl
Pharmacological category: anti-diarrheal
Sponsor/Contact: Cynthia Gulian
Assistant Director, CMC Regulatory Affairs
McNeil Consumer & Specialty Pharmaceuticals
7050 Camp Hill Road
Fort Washington, PA 19034
(215)273-8464
Labeling submitted: 1 oz carton label, 1 oz bottle label,
4 oz booklet label,
8 oz booklet label
Reviewer: Reynold Tan
Review date: June 25, 2004
Project manager: Laura Shay

Background: The sponsor submitted this supplemental new drug application (NDA 19-487 / SCF-022) on March 5, 2004 to provide for a reformulation to a mint flavor liquid of the Imodium A-D Liquid product. This application included draft labeling for the reformulated product. For the 1 oz size product, the sponsor submitted the carton and bottle labels. For the 4 oz and 8 oz size products; the sponsor submitted the booklet-style labels, which affix to the bottles.

Reviewer's Comments:

The following differences were noted between the submitted labels and previously approved labels:

(principal display panels):

1) The phrase "NEW FORMULA" appears in red upon a yellow banner. (For the 1 oz size, this NEW FORMULA banner also appears on the end flap of the carton label.)

Comment: This change is acceptable. The phrase "NEW FORMULA" must be removed after 180 days of OTC marketing.

2) The statement "contains 0.5% Alcohol" is removed.

Comment: This change is acceptable.

3) The description "Mint Flavor Liquid" replaces "Cherry Mint Flavor Liquid."

Comment: This change is acceptable.

4) The strength of the drug, described as "1 mg loperamide HCl per 7.5 mL," replaces the previous description, "Each tsp (5 mL) contains 1 mg loperamide HCl."

Comment: This change is acceptable

5) (For the 4 oz and 8 oz size products only) A peel back tab which states, "To read all Warnings and Directions before purchase PEEL BACK HERE," is added.

Comment: This change is acceptable.

(Drug Facts labeling): *Unless otherwise noted, the reviewer's comments refer to the 1, 4, and 8 oz size products.*

1) Under "Active ingredient," the amount of drug is stated as "(in each 7.5 mL) Loperamide HCl 1 mg." For the original Imodium A-D Liquid formulation, the amount of drug is stated as "(in each teaspoonful = 5 mL) Loperamide HCl 1 mg."

Comment: The "Directions" section instructs the consumer to use only the attached measuring cup to dose the product. The unit dose marked on this measuring cup should reflect both the units of dosage stated in the "Directions" and "Active ingredient" sections. The measuring cup was not submitted for review. This cup should be marked at 7.5 mL (1½ tsp), 15 mL (3 tsp), and 30 mL (6 tsp) to correspond to the dosages recommended under "Directions."

2) *Comment:* The "Directions" section for the 1 oz product only gives recommended doses in teaspoons, whereas the amount of drug in the "Active ingredient" section is given in milliliters ("in each 7.5 mL"). Under "Active ingredient," the amount of drug must be stated in terms of the dosage unit provided under "Directions" (see 21 CFR 201.66(c)(2)). Therefore, the amount of drug under "Active ingredient" must also be given in teaspoons. Note that the "Active ingredient" and "Directions" sections for the 1 oz product would conform to the regulation, 21 CFR 201.66(c)(2), if the recommended dosages in the "Directions" section for the 1 oz product appeared in both milliliters and teaspoons, as they do for the 4 oz and 8 oz products.

3) Under "Directions," two additional bulleted statements are added: "shake well before using" and "only use attached measuring cup to dose product."

Comment: This change is acceptable.

4) Under "Directions," recommended doses are adjusted to account for the lower concentration of loperamide HCl in the reformulated product compared to the original product.

Comment: This change is acceptable. However, for the 1 oz product, the recommended doses should be provided in both units of milliliters and teaspoons. (see above, *Comment 2* under "(Drug Facts labeling)").

5) Under "Other information," the tamper-evident statement "do not use if printed inner or outer neckband is broken or missing" replaces "do not use if carton is opened or if printed plastic neck wrap is broken or missing."

Comment: This change is acceptable.

6) Under "Other information," the statement "see bottom panel for expiration date and lot number" is removed.

Comment: This change is acceptable.

7) *Comment:* The reformulated product contains — mg sodium benzoate per 7.5 mL. At this concentration, the recommended 30 mL (6 tsp) dose for adults or children 12 years and over contains more than 5 mg of sodium. If the sodium content of a single recommended dose of an OTC drug product intended for oral ingestion is 5 mg or more, the labeling of the product must contain the sodium content per dosage unit (see 21 CFR 201.64(a)). The sodium content information should appear immediately following the "Other information" heading as follows (see 21 CFR 201.64(b) and 201.66(c)(7)(i)):

- each 30 mL (6 tsp) contains: **sodium 10 mg**

8) Under "Inactive ingredients," the list of ingredients reflects the reformulation of the product.

Comment: This change is acceptable.

9) *Comment:* The labeling conforms to the format requirements in 21 CFR 201.66(d). Type sizes for the title, headings, and subheadings conform to the format requirements in 21 CFR 201.66(d)(10).

Reviewer's recommendations: The following comments can be conveyed to the sponsor:

1) The sponsor must verify that the measuring cup used to dose the product is marked at the 7.5 mL (1½ tsp), 15 mL (3 tsp), and 30 mL (6 tsp) marks, thereby providing both units of milliliters and teaspoons for the recommended doses.

2) For the dosing table that appears in the "Directions" section of the 1 oz size product, the recommended dosages must appear in both milliliters and teaspoons, as they do for the 4 oz and 8 oz products.

3) Immediately following the "Other information" heading, the sponsor must include the sodium content information as follows (see 21 CFR 201.64(b) and 201.66(c)(7)(i)):

- each 30 mL (6 tsp) contains: **sodium 10 mg**

4) The sponsor must remove the phrase "NEW FORMULA" from the product labels after 180 days of OTC marketing.

5) The sponsor is reminded of their submission on December 15, 2003 (NDA 19-487/SLR-021) proposing added warnings alerting consumers to the possibility of the adverse effects of toxic megacolon and sedation that may be associated with the use of loperamide HCl. The sponsor

should include these warnings using the language recommended by FDA in the June 16, 2004 approval letter.

The sponsor must incorporate these changes in labeling before this supplement is approved.

Reynold Tan, Ph.D.
IDS/Biologist, HFD-560

Helen Cothran, B.S.
Team Leader, HFD-560

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Helen Cothran
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Division of OTC Drug Products Labeling Review for an NDA Supplement

NDA 19-487 / SCF-022 / July 1, 2004 submission

Submission Date: July 1, 2004
Received Date: July 1, 2004
Drug product: IMODIUM A-D Liquid
Active ingredient: Loperamide HCl
Pharmacological category: anti-diarrheal
Sponsor/Contact: Victoria Wagner-Weber
Associate Director, Regulatory Affairs
McNeil Consumer & Specialty Pharmaceuticals
7050 Camp Hill Road
Fort Washington, PA 19034
(215)273-8278
Labeling submitted: Drug Facts labeling (WORD version) label
Reviewer: Reynold Tan
Review date: July 6, 2004
Project manager: Laura Shay

Background: The sponsor sent a fax communication on July 1, 2004 which included the Drug Facts labeling in Microsoft Word format for the reformulated mint-flavor Imodium A-D Liquid (NDA 19-487 / SCF-022). This new Drug Facts labeling was submitted in response to FDA's June 28, 2004 fax containing labeling recommendations for this product. These recommendations included: 1) Provide the recommended dosages in both milliliters and teaspoons in the dosing table under "**Directions**" for the 1 oz size product 2) include the sodium content information in "**Other information**" according to 21 CFR 201.64(b) and 201.66(c)(7)(i), and 3) add the proposed warnings alerting consumers to the adverse effects of toxic megacolon and sedation that may be associated with the use of loperamide HCl. The sponsor also sent representative containers for the 1 oz, 4 oz, and 8 oz packages on June 28, 2004 and stated that final printed labeling would be submitted for all three sizes within 30 days of final approval of SCF-022.

Reviewer's Comments:

1) The phrase "NEW FORMULA" appears in red upon a yellow banner. (For the 1 oz size, this NEW FORMULA banner also appears on the end flap of the carton label.)

Comment: This change is acceptable. However, the phrase "NEW FORMULA" must be removed after 180 days of OTC marketing.

2) The dosing cup for the 1 oz size product is marked in units of milliliters only, whereas the dosing cups for the 4 oz and 8 oz size products are marked in units of both milliliters and

teaspoons. The sponsor revised the dosing table under “Directions” for the 1 oz size product to provide doses in both units of milliliters and teaspoons, consistent with the “Directions” sections for the 4 oz and 8 oz packages.

Comment: The markings on the dosing cups are acceptable. While the dosing cup for the 1 oz size product provides markings in milliliter units only, the revised dosing table under “Directions” now provides doses in both units of milliliters and teaspoons.

3) The first bulleted statement in the “Other information” section reads:
“each 30 mL (6 tsp) contains: **sodium 10 mg**”.

Comment: This change is acceptable.

4) To alert consumers to the possibility of sedative effects associated with the use of loperamide HCl, the sponsor added a warning statement. This warning statement reads:

“When using this product

- tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery.”

Comment: This change is acceptable.

5) To alert consumers to the possibility of the adverse effects of toxic megacolon that may be associated with the use of loperamide HCl, the sponsor added a warning statement. This warning statement reads:

“Stop use and ask a doctor if

- you get abdominal swelling or bulging. These may be signs of a serious condition.”

Comment: This change is acceptable.

Reviewer’s recommendation: The following comment can be conveyed to the sponsor:

1) The sponsor must remove the phrase “NEW FORMULA” from the product labels after 180 days of OTC marketing.

Reynold Tan, Ph.D.
IDS/Biologist, HFD-560

Helen Cothran, B.S.
Team Leader, HFD-560

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Helen Cothran
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Division of OTC Drug Products Labeling Review for an NDA Supplement

NDA 19-487 / SLR-021(FA) / SCF-022(FA)

Submission Date: October 5, 2004

Received Date: October 15, 2004

Drug product: IMODIUM A-D Liquid, 1 mg/ 7.5 mL (reformulated)

Active ingredient: loperamide HCl

Pharmacological category: anti-diarrheal

Sponsor/Contact: Victoria Wagner-Weber
Director, Marketed Products
McNeil Consumer & Specialty Pharmaceuticals
7050 Camp Hill Road
Fort Washington, PA 19034
(215) 273-8278

Labeling submitted: 1 oz (30 mL) carton label, 1 oz bottle label,
4 oz (120 mL) booklet label,
8 oz (240 mL) booklet label

Reviewer: Reynold Tan

Review date: November 9, 2004

Project manager: Laura Shay

Background: In a supplemental new drug application (NDA 19-487 / SLR-021) submitted on December 15, 2003, the sponsor proposed adding label warnings alerting consumers to the possibility of the adverse effects of toxic megacolon and sedation that may be associated with the use of loperamide HCl. FDA recommended warning language in the June 16, 2004 approval letter for this application. The sponsor submitted another supplemental new drug application (NDA 19-487 / SCF-022) on March 5, 2004 to provide for a reformulation to a mint flavor liquid of the Imodium A-D Liquid product. This submission (NDA 19-487 / SLR-021(FA) / SCF-022(FA)) includes the final printed labeling that incorporates several labeling changes recommended by FDA following the review of submitted draft labeling.

Reviewer's Comments:

The following changes are noted between the sponsor's draft labeling submitted on March 5, 2004 and the final printed labeling in this submission:

1) The sponsor adds a new section under the subheading "**When using this product.**" The warning under this subheading reads "tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery."

Comment: This change is acceptable.

2) The sponsor adds a third bulleted statement under the subheading “**Stop use and ask a doctor if**” that reads “you get abdominal swelling or bulging. These may be signs of a serious condition.”

Comment: This change is acceptable.

3) The sponsor provides doses in both units of milliliters and teaspoons in the “**Directions**” sections of labels.

Comment: This change is acceptable.

4) The sponsor adds the bulleted statement “each 30 mL (6 tsp) contains: **sodium 10 mg**” as the first bulleted statement under “**Other information**”.

Comment: This change is acceptable.

5) *Comment:* In all of the labeling, position the tradename “Imodium A-D” and the statement of identity (SOI) “Loperamide HCl/Anti-Diarrheal” such that the letters “A-D” do not appear to be part of the SOI.

Reviewer’s recommendations: The following comments can be conveyed to the sponsor:

The final printed labels submitted for the 1 oz (30 mL) carton label, 1 oz bottle label, 4 oz (120 mL) booklet label, and the 8 oz (240mL) booklet label are acceptable. An ACKNOWLEDGED AND RETAINED letter can be issued to the sponsor. However, at the next printing for all labeling, position the tradename “Imodium A-D” and the statement of identity (SOI) “Loperamide HCl/Anti-Diarrheal” such that the letters “A-D” do not appear to be part of the SOI. Submit this change in the next annual report.

Reynold Tan, Ph.D.
IDS/Biologist, HFD-560

Helen Cothran, B.S.
Team Leader, HFD-560

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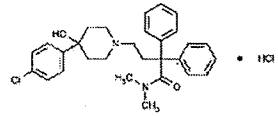
Reynold Tan
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Helen Cothran
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-487/S-022

CHEMISTRY REVIEW

Chemistry Review # 1	1. Division HFD-560	2. NDA Number 19-487
3. Name and Address of Applicant McNeil Consumer & Specialty Pharmaceuticals Attention: Lynn Pawelski, Director, Regulatory Affairs 750 Camp Hill Road Fort Washington, PA 19034 Phone: 215-273-7731		4. Supplement Number: SCF-022 Letter Date: 3/05/04 Stamp Date: 3/08/04 PDUFA Due Date: 7/08/04
5. Name of Drug Immodium ® A-D Liquid	6. Nonproprietary Name Loperamide HCl, USP	
7. Supplement Provides for: Changes in formulation, manufacturing process, drug product manufacturing and testing sites, container resin, label adhesive, and regulatory and alternative analytical procedures		8. Amendment(s) BC, dated 6/30/04 BC, dated 7/07/07 (fax)
9. Pharmacological Category Controls the symptoms of diarrhea, including Traveler's Diarrhea	10. How Dispensed OTC	11. Related Documents N/A
12. Dosage Form Solution	13. Potency(ies) 1 mg/7.5 mL	
14. Chemical Name and Structure see USAN 4-(p-Chlorophenyl)-4-hydroxy-N,N-dimethyl- α , α -diphenyl-1-piperidinebutyramide monohydrochloride, C ₂₉ H ₃₃ ClN ₂ O ₂ · HCl, Mol. wt. 513.50		
15. Comment <p style="text-align: center;">Prior Approval Supplement</p> <p>This supplement provides for changes in formulation, manufacturing process, drug product manufacturing and testing sites, container resin, label adhesive, and regulatory and alternative analytical procedures.</p> <p>The proposed resins and label adhesive were stated to comply with 21 CFR § 177.1520 and § 175.105 respectively for suitability. The supplement included test results of Physicochemical Tests-Plastics <USP 661> and Containers-Permeation Test <USP 671> for compatibility of the proposed container material. The supplement also included up to 12 months of long-term (25°C/60%RH) and 6 months accelerated (40°C) stability data on one production scale batch each in 1 oz, 4 oz and 8 oz bottles in support of the proposed changes. The submitted stability data did not indicate any adverse effect on the drug product because of the proposed changes.</p>		
16. Conclusions and Recommendations This supplement is recommended for approval. This supplement contains labeling. Action letter will be issued by HFD-560.		
17. Name Rao Puttagunta, Ph.D., Reviewer		Date 7/01/04
18. Concurrence John Smith, Ph.D., Chemistry Team Leader		

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John Smith
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CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-487/S-022

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS
REVIEW

Office of Clinical Pharmacology and Biopharmaceutics Review

NDA #	19-487 (SCF-022)
Submission Date (s)	March 5 th , 2004, June 9 th , 2004, July 1 st , 2004
Brand Name	Imodium [®] A-D Liquid
Generic Name	Loperamide Hydrochloride
Reviewer	Abimbola Adebawale Ph.D.
Team Leader	Dennis Bashaw Pharm.D.
OCPB Division	DPE-III
OND division	HFD-560
Sponsor	McNeil Consumer and Specialty Pharmaceuticals, Fort Washington, PA 19034
Submission Type; Code	Supplemental New Drug Application
Formulation; Strength(s)	Oral Solution; 1 mg/7.5 mL
Indication	Controls symptoms of diarrhea, including Traveler's Diarrhea

1 Executive Summary

In this sNDA, the applicant is seeking approval for a reformulation of the currently marketed Imodium[®] (loperamide hydrochloride) A-D liquid, to improve the flavor and aesthetic qualities of the product. Reformulated Imodium[®] A-D liquid is a green, opaque liquid with a mint flavor, while the currently marketed product is a clear, colorless, cherry flavored liquid. The reformulated Loperamide Liquid (1 mg/7.5 mL) is also less concentrated than the currently marketed Imodium A-D liquid, (1 mg/5 mL).

In this submission the applicant included a bioequivalence study (No. 15-001) to link the reformulated product and the currently marketed product, to support these changes. A review of the study is discussed in this document.

1.1 Recommendation

The results of the bioequivalence study demonstrated that the reformulated Imodium A-D liquid is bioequivalent to the currently marketed Imodium A-D liquid. Therefore the data provided has met the requirements of 21CFR 320 and, is acceptable from the clinical pharmacology and biopharmaceutics perspective.

1.2 Phase IV Commitments: No Phase IV commitments are requested.

Abimbola Adebawale, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Dennis Bashaw, Pharm.D.
Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

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3 Summary of CPB Findings

Loperamide was approved by the FDA in 1976 for the control of the symptoms of diarrhea. It is currently available OTC as single-ingredient caplets (2 mg) and clear liquid (1 mg/5mL). It is also available in combination with simethicone as chewable and conventional tablets. The current application is for a reformulation of the currently marketed liquid.

The bioequivalence study included in this submission indicated that the reformulated liquid is bioequivalent to the currently marketed liquid as demonstrated by the 90% CI of AUC and Cmax meeting the Agency criteria of 80-125 %.

