CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBERS:

NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

Names:

NDA 19-487 Imodium (Loperamide HCl) A-D Liquid
NDA 19-860 Imodium (Loperamide HCl) Chewable Tablets
NDA 20-606 Imodium Advanced (Loperamide HCl/ Simethicone) Chewable Tablets
NDA 21-140 Imodium Advanced (Loperamide HCl/ Simethicone) Caplets

Sponsor:

McNeil Consumer & Specialty Pharmaceuticals Products, Inc.

Approval Date: June 16, 2004

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APPLICATION NUMBERS:

NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS:

NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

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 December 15, 2003, received December 16, 2003, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for: Imodium® A-D (loperamide HCL) Liquid, Imodium (loperamide HCL/simethicone) Caplets, Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets, Imodium Advanced (loperamide HCL/simethicone) Caplets.

We also acknowledge receipt of your submissions dated March 29, 2004, and June 11, 2004.

These supplemental applications propose revised labeling under the "Stop use and ask a doctor if" and "Other information" sections.

We have completed our review of these applications, as amended. These applications are 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 submitted June 11, 2004) and must be formatted in accordance with the requirements of 21 CFR 201.66. We noted that the subheading "**When using this product**" does not appear in bold type in the approved draft labeling. We remind you to use bold type for all headings and subheadings (21 CFR 201.66 (d)(3)) .

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).

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/

Curtis Rosebraugh
6/16/04 10:20:43 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS:

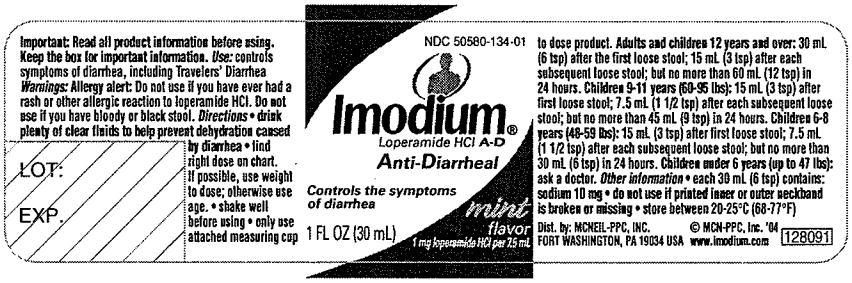
NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

LABELING

NOTES:

1) DRAWING SHOWN PRINT SIDE UP
2) ALL DIMENSIONS IN INCHES
3) TOLERANCE UNLESS SPECIFIED
   FRACTIONS ±1/32, ANGLES ±1°
4) ▨ LOT & EXP. DATE

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



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

DESCRIPTION LSL PRODRUM A-D 1 OZ.
FILE # 2005158 VERSION D.5
DATE JULY 2, 2001 CON...
PS IMAGE(S) NEW ART

TEAL	GREEN	LT BLUE	DK BLUE
YELLOW	BLACK		

DOMESTIC MANUFACTURING SITE?
THIS DESIGN BLOCK MUST BE SAVED WITH FILE AND PRINTED ON THERMAL

FINAL PRINT BUYER INFORMATION BLOCK

NATIONAL PRINT BUYER:
PUT-UP NUMBER:
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ARTWORK APPROVAL INITIAL BLOCK

	INITIALS	DATE
REGULATORY		
MEDICAL		

NOTES:

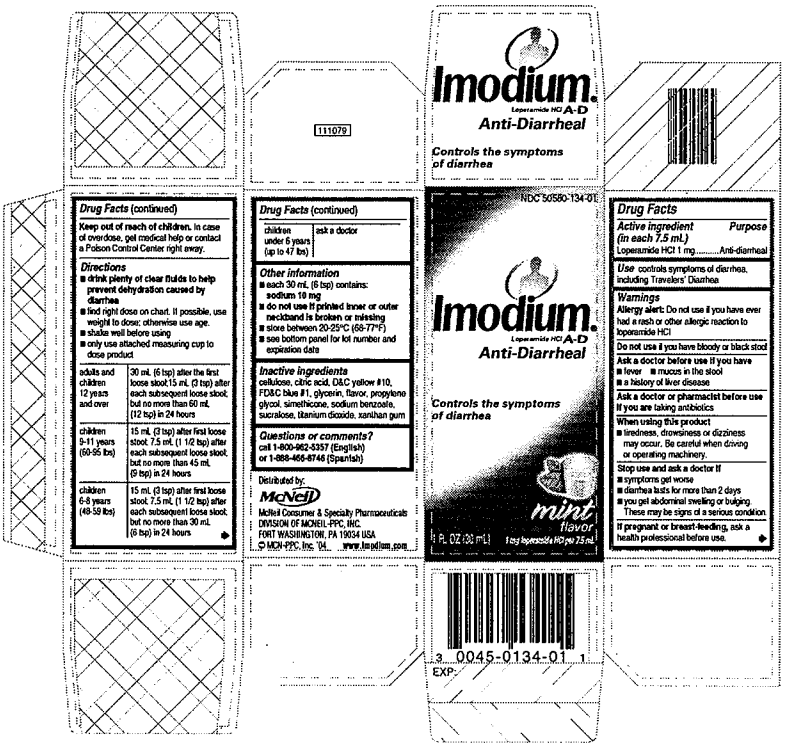
1) DRAWING SHOWN PRINT SIDE UP
2) ALL DIMENSIONS IN INCHES
3) TOLERANCES UNLESS SPECIFIED:
   FRACTIONS ±1/32
   ANGLES ±1°
4) --- NO PRINT
5) KNOCK OUT AREA
6) VISIONS BARCODE AREA.
7) EXP DATE AREA
8) LOT AREA

INIT.	NO.	DATE	REVISIONS
DM/SH	14	3/25/04	REMOVED KNOCKOUT AREAS / UPDATED NOTES.
ARS/TM	13	4/12/00	REVERSE BACK TO REV 10 LEV.
ARS/TM	12	4/10/00	REMOVED MANUF. AREA
ARS/HX	11	2/21/00	SPLIT LOT, EXP, MANUF
ARS/JG	10	12/1/99	ADDED NO VARNISH TO MIN FLAP
ARS/CM	9	8/12/98	SPLIT LOT & EXP AREA
ARS	8	6/25/97	ADDED DV INFO
EMP	7	7-6-93	ADDED VISION BARCODE AREA
EMP	6	7-23-92	ADDED LOT/EXP. DATE AREA
EMP	5	1-2-92	REDRAWN ON NEW FORMAT
WBC	4	8-28-89	FLAP ANGLE AND RADII CORRECTED
TMW	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

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 END
1.50 L X 1.50 W
X 3.06 D



Labeling Format Information:

Fonts: Helvetica regular, bold, and bold oblique.

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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

DESCRIPTION CTN IMODIUM A-D 1 OZ
FILE # 3905194 **VERSION** A-1
DATE JULY 30, 2004 **CON**
PS IMAGE(S) NEW ART

TEAL	GREEN	LT BLUE	DK BLUE
YELLOW	BLACK		

DOMESTIC MLN GAD 671763 REV 2

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

NATIONAL PRINT BUYER INFORMATION BLOCK

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ARTWORK APPROVAL INITIAL BLOCK

	INITIALS	DATE
REGULATORY		
MEDICAL		

Adhesive

Lot & Exp. Date

INIT.	NO.	DATE	REVISIONS

DWG. NO. LB-PS-1019

DRAWN SKH

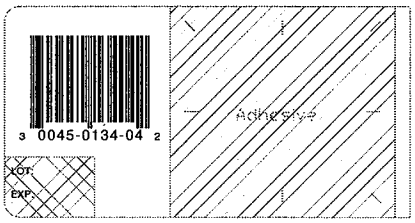
SCALE NONE

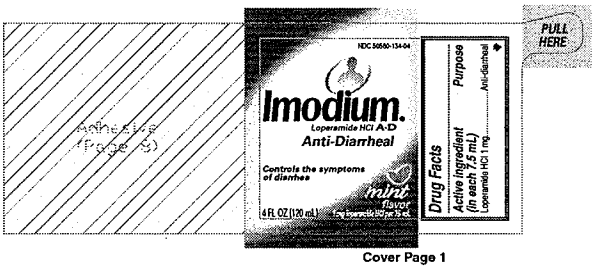
DATE

APPROVED

McNeil
Consumer & Specialty Pharmaceuticals
7050 Camp Hill Road, Fort Washington, PA 19034

TITLE:
BOOKLET
IMODIUM 4 OZ.





Cover Page 1

Drug Facts (continued)

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)
- 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, titanium dioxide, xanthan gum

Page 6

Drug Facts (continued)

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

When using this product
- tiredness, 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.

Page 3

Drug Facts (continued)

Use controls symptoms of diarrhea, including Travelers' 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

Ask a doctor before use if you have
- fever
- mucus in the stool
- a history of liver disease

Page 2

Drug Facts (continued)

Questions or comments?
call 1-800-962-5357 (English) or 1-888-466-8746 (Spanish)

Distributed by:
McNeil
McNeil Consumer & Specialty Pharmaceuticals
DIVISION OF MCNEIL-PPC, INC
FORT WASHINGTON, PA 19034 USA
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www.imodium.com

128092

Page 7

Drug Facts (continued)

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away

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 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

Page 4

Drug Facts (continued)

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

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

DESCRIPTION LBL BKLT IMODIUM A-D 4 OZ

FILE # 3005156 **VERSION** A-2

DATE JULY 1, 2004 **COI**

PS IMAGE(S) NEW ART

TEAL	GREEN	LT BLUE	DK BLUE
YELLOW	BLACK		

DOMESTIC McN GAG 011705 REV 2

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

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ARTWORK APPROVAL INITIAL BLOCK

	INITIALS	DATE
REGULATORY		
MEDICAL		

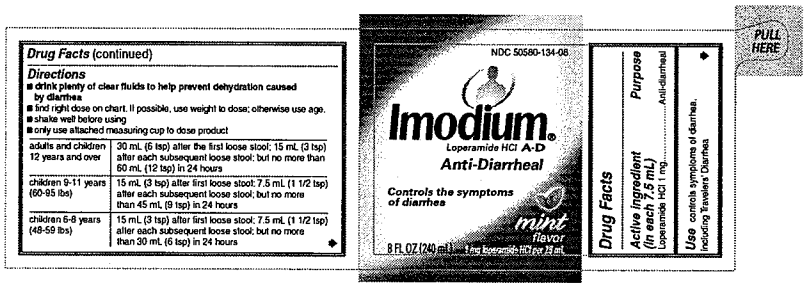
NOTES:
1) DRAWING SHOWN PRINT SIDE UP.
2) TOLERANCES UNLESS SPECIFIED +/- 1/64.
3) BASED ON NATIONAL LABEL DRAWING NO. 1-04-4

INIT.	NO.	DATE	REVISIONS

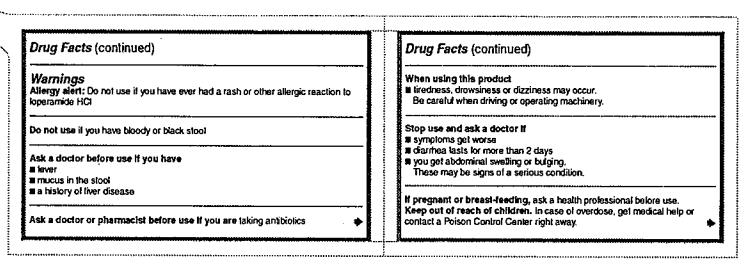
DWG NO. LB-PS-1057
DRAWN SKH
SCALE NONE
DATE 1-26-04
APPROVED

McNeil Consumer & Specialty Pharmaceuticals
7050 Camp Hill Road, Fort Washington, PA 19034

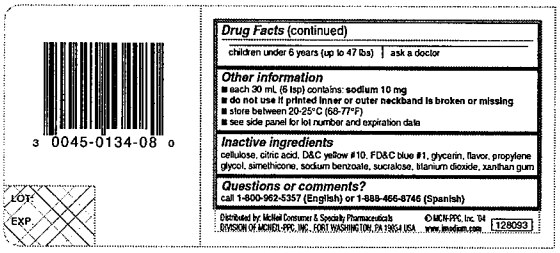
TITLE: LABEL
IMODIUM 8OZ. BOTTLE



PAGE 4 COVER PAGE 1



PAGE 2 PAGE 3



BASE PAGE 5

Labeling Format Information:

Fonts: Helvetica regular, bold, and bold oblique.

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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

DESCRIPTION LBL BKLT IMODIUM A-D 8 OZ
FILE # 3005156 **VERSION** S-2
DATE JULY 1, 2004 **CONTACT**
PS IMAGE(S) NEW ART

TEAL	GREEN	LT BLUE	DK BLUE
YELLOW	BLACK		

DOMESTIC McN GAG 6/17/03 REV 2

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	INITIALS	DATE
REGULATORY		
MEDICAL		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS:

NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

LABELING REVIEWS

OTC Drug Clinical Review
FOR NDA (LABELING)

Division of Over-The-Counter Drug Products • HFD-560
Center for Drug Evaluation and Research • Food and Drug Administration
Rockville • MD 20857

OTC Labeling Changes for all Imodium NDAs

NDA 19-487/SLR-021 (Imodium A-D Liquid)
NDA 19-860/SLR-020 (Imodium Caplets)
NDA 20-606/SLR-009 (Imodium Advanced Chewable Tablets)
NDA 21-140/SLR-003 (Imodium Advanced Caplets)

SUBMISSION	**OTC labeling supplement**
CLINICAL INDICATION	**Anti-diarrhea**
ADMINISTRATION	**Oral**
SPONSOR	**McNeil Consumer & Specialty 7050 Camp Hill Rd Fort Washington, PA 19034**
SUBMISSION DATE	**December 15, 2003**
RESUBMISSION PER REQUEST	**March 29, 2004**
REVIEW COMPLETE DATE	**May 17, 2004**

REVIEWER Jin Chen, *MD, PhD, MPH*

BACKGROUND

The sponsor submitted a labeling supplement (additional warnings) for the label of four currently-marketed Imodium OTC products: Imodium A-D liquid (NDA 19-487, a single ingredient – loperamide), Imodium caplet (NDA 19-860, a single ingredient – loperamide), Imodium advanced Chewable Tablet (NDA 20-606, loperamide and simethicone) and Imodium Advanced Caplet (NDA 21-140, loperamide and simethicone).

Loperamide, an opioid analogue, relieves diarrheal symptoms through slowing intestinal motility (thus affecting water and electrolyte movement through the bowel) and reducing GI secretion too. Simethicone acts in the stomach and intestines by altering the surface tension of gas bubbles enabling them to coalesce, thereby freeing and eliminating the gas more easily by belching or passing flatus.

Loperamide is 40% absorbed from the GI following oral administration and 97% plasma protein-bound (Clinical Pharmacology Online, http://cpip.gsm.com/). It apparently does not easily cross the blood brain barrier, and is thus less likely to elicit CNS effects of an opioid. Overdose, however, can result in CNS depression and paralytic ileus. Children may be more sensitive than adults to the CNS-depressant effects of loperamide. In patients with active inflammatory disease of the colon, loperamide should be used with great caution, if at all, to prevent development of toxic megacolon (*Goodman & Gilman's The Pharmacological Basis of Therapeutics - 10th Ed. 2001*).

REVIEW

In the original submission (dated December 15, 2003), the sponsor provided only side-by-side comparison of current OTC labels of the four Imodium products with the revised labels. As per the Agency's request, the sponsor submitted a brief summary of post-marketing AE reports to support the rationale for the labeling revisions on March 29, 2004. The sponsor proposed the following 2 labeling revisions to all currently-marketed OTC Imodium products:

1. **Add "*you* ——————— *abdominal swelling or bulging*" under "*Stop use and ask a doctor if*"**

The "*abdominal swelling or bulging*" or "abdominal distention" is a clinical symptom of toxic megacolon and paralytic ileus, a potentially serious adverse event which may occur in patients with infectious diarrhea (bacteria or virus) and using loperamide. The Rx Imodium labeling was revised to address this concern (Imodium capsule, NDA 17-694/SLR-047), as per the sponsor's letter dated on November 21, 2003 (included in the Dec-15-2003 submission) and the labeling review (by HFD-180 on February 16, 1999). The Rx Imodium is not currently marketed in US but the NDA is still active.

To support the OTC labeling revision in current submissions, the sponsor performed a literature search on the Drug safety Surveillance (DSS) database (*the sponsor's in-house database*) with following terms: "megacolon required", megacolon congenital", intestinal perforation", "intestinal necrosis" or "ileus paralytic". The search covered both spontaneous reports (*approach was not specified in the submission*) and literature sources in all countries through May 31, 2002 (*the starting year was not specified in the submission*). The sponsor stated that the reporting rate for megacolon, including toxic megacolon in the setting of colitis and in patients with AIDS, is < 1/10,000. There were 5 loperamide-related deaths (Table 1), but the rate of loperamide-related events is not analyzed.

Table 1. **Megacolon and Relevance to Loperamide**

Megacolon	Number of Case	Remark
Total	43	
Confirmed ("True")	27	
Gender	20M/6F	1 unknown
Megacolon Acquired*	26	
Paralytic ileus	1	
Literature reports	19	11 = single series, 3 = secondary reports, 5 = individual source
Spontaneous report	7	
Regulatory agency	1	
Bacterial/viral infection	15	
Inflammatory bowel Syndrome	2	
Loperamide-related fatalities	5	

Data are extracted from the sponsor's brief summary. Exposure information (denominator) is not provided. The sponsor did not state if the "loperamide-related fatalities" in the submission was associated with megacolon only but not others.

* "required" was used in the sponsor's submission; it could be mis-spelling.

[Reviewer's Comments]

a. The case report suggests that megacolon may be associated with using loperamide in some patients.

b. The loperamide-related megacolon reports may have been under-reported due to the following uncertainties:

1) Nature of the DSS database was not specified, such as source, coverage, contents (published or unpublished, spontaneous reporting, etc), coverage period.

2) The megacolon rate in general population was <1/10,000, however, the rate related to loperamide treatment is unknown.

3) The reporting period and exposure information associated with the megacolon events are unknown.

2. Add "*tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery*" under "*Other information*"

The sponsor first proposed to include sedative effects of loperamide products in a labeling supplement submission of Rx Imodium Capsule (NDA 17-694/SLR-047) submitted in 1998, as discussed in the clinical review completed by HFD-180 on Feb 16, 1999. There were no supportive data provided in the Rx labeling supplement submission, as indicated in the clinical review. The "*tiredness, drowsiness or dizziness*" was added to the Rx labeling, as shown in 2000 PDR, page 1679. It is unknown what justification was used to update the Rx labeling. The Rx Imodium is no longer marketed in US.

To support this proposed OTC labeling revision, in the current submission, the sponsor provided a brief summary of literature based on searching the DSS database on loperamide-related sedative events in all formulations containing loperamide (Rx and OTC). There were 65 cases of drowsiness and 50 case of dizziness reported for all formulations of loperamide (Table 2).

***Table 2.* Loperamide-associated sedation case reports**

Sedation	Number of Case
Drowsiness	65
Overdose, Loperamide/Sedative agent, Medication error, Associated with other AEs (such as allergic)	30
Loperamide-related ("on-label use?"*)	35
Loperamide HCl	19
Loperamide/simethicone	8
Imodium A-D	7
Loperamide oxide	1
Dizziness	50
Loperamide HCl	10
Other formulations	40

Data are extracted from the sponsor's brief summary in the submission. Exposure information (denominator) was not estimated. * The sponsor did not

specify the remaining 35 cases (of 65); presumably they were "on-label use" of loperamide products.

[Reviewer's comments]

a. The case reports suggest that loperamide may cause sedative effects, although the incidence and pharmacological association (CNS suppression and/or complications of diarrheal illness) are unknown. Consumers should be warned appropriately in the label.

b. This information should be added under "Warnings" instead of "Other information."

c. The sponsor did not comment on if there are any driving or machinery operation accidents related to loperamide medication.

d. The reporting period and exposure information associated with the sedative events are unknown.

CONCLUSION

The proposed revision to the OTC labels of Imodium products is acceptable.

RECOMMENDATION

The label should be modified as proposed by the sponsor, but the sedation warning should be added under the "Warnings" section instead of under the "Other information".

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

/s/

Jin Chen
5/17/04 03:45:59 PM
MEDICAL OFFICER

Andrea Segal
5/17/04 04:09:59 PM
MEDICAL OFFICER

Review of Labeling Supplements

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATE: 12/15/03	**RECEIVED DATE:** 12/16/03
NDA/REPORT#s	19-487/SLR-021, 19-860/SLR-020, 20-606/SLR-009, and 21-140/SLR-003
Drug Products	Imodium A-D Liquid, Imodium Caplets, Imodium Advanced Chewable Tablets, and Imodium Advanced Caplets
Sponsor/Contact	McNeil Consumer & Specialty Pharmaceuticals Attn: Victoria Wagner-Weber, Assoc. Dir., Regulatory Affairs 7050 Camp Hill Road Fort Washington, PA 19034 215-273-8278
Active Ingredient	Loperamide HCl (Imodium A-D Liquid, Imodium Caplets) Loperamide HCl/Simethicone (Imodium Advanced Chewable Tablets, Imodium Advanced Caplets)
Pharmacological Category	Anti-diarrheal (Imodium A-D Liquid, Imodium Caplets), Anti-diarrheal/Anti-gas (Imodium Advanced Chewable Tablets, Imodium Advanced Caplets)
Review Date	May 26, 2004
Reviewer	Reynold Tan

Background:

The sponsor submitted supplemental new drug applications (NDAs 19-487/SLR-021, 19-860/SLR-020, 20-606/SLR-009, and 21-140/SLR-003) on December 15, 2003 (received December 16, 2003) proposing changes in labeling for Imodium A-D Liquid, Imodium Caplets, Imodium Advanced Chewable Tablets, and Imodium Advanced Caplets, respectively. The sponsor further submitted a brief summary of adverse events reports at FDA's request and performed a literature search on its in-house Drug Safety Surveillance (DSS) database to support their proposed changes on March 29, 2004 ("BM", minor amendments, to the four supplemental applications listed above). These changes address a concern over the association of loperamide use with the potentially serious adverse events of toxic megacolon and paralytic ileus. Additionally, case reports suggest loperamide may cause sedative effects. See HFD-560 (Dr. Jin Chen's) clinical review of these labeling supplements dated May 17, 2004. Previously, the sponsor had notified FDA of its intention to revise the labeling for Rx Imodium Capsules to address these concerns (NDA 17-694/SLR-047) in a letter dated November 21, 2003.

Reviewer's comments:

In the supplemental new drug applications (NDAs 19-487/SLR-021, 19-860/SLR-020, 20-606/SLR-009, and 21-140/SLR-003), the sponsor provides side-by-side comparisons of the current and proposed Drug Facts labeling for each of the four Imodium products (Imodium A-D Liquid, Imodium Caplets, Imodium Advanced Chewable Tablets, and Imodium Advanced Caplets, respectively). These comparisons appear in table format with a Description/Reason for Change column describing each of the proposed changes.

Four changes are proposed for each of the four Imodium products:

1.) Under the "Stop use and ask a doctor if" subheading, "you ——————— abdominal swelling or bulging" is added as the third bulleted statement.
Comment: Abdominal swelling or bulging is a symptom of toxic megacolon and paralytic ileus. Consumers should be informed that this symptom may be indicative of a serious condition. The warning should be added as the third bulleted statement to read:

Stop use and ask a doctor if
■you get abdominal swelling or bulging. These may be signs of a serious condition.

2.) Under the "Other information" heading, "tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery." is added as the first bulleted statement.
Comment: This information properly belongs under the "When using this product" subheading in the "Warnings" section (see 21 CFR 201.66(c)(5)(vi)). The warning should read:

When using this product
■tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery.

This warning should appear after the "Ask a doctor or pharmacist before use if you are taking antibiotics" warning.

3.) Under the "Questions or comments?" heading, the telephone assistance numbers appear as "Call 1-800-962-5357 (English) or 1-888-466-8746 (Spanish)."
Comment: This change is acceptable.

4.) The manufacturer's name is changed from McNeil Consumer Healthcare to McNeil Consumer & Specialty Pharmaceuticals.
Comment: This change is acceptable.

One change is proposed for the Imodium A-D Liquid product only:

1) Under the "Directions" heading, "shake well before using" and "only use attached measuring cup to dose product" are added as bulleted statements.
Comment: These changes are acceptable.

Reviewer's recommendations:

The following comments can be conveyed to the sponsor:

1.) To inform the consumer that abdominal swelling or bulging could be signs of a serious condition, the third bulleted statement under the "Stop use and ask a doctor if" subheading should read:
Stop use and ask a doctor if
■you get abdominal swelling or bulging. These may be signs of a serious condition.

2.) The statement, "tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery.", which appears under the "Other information" heading, properly belongs under the "When using this product" subheading in the "Warnings" section (see 21 CFR 201.66(c)(5)(vi)). The warning should read:
When using this product
■tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery.

This warning should appear after the "Ask a doctor or pharmacist before use if you are taking antibiotics" warning.

3) "Call 1-800-962-5357 (English) or 1-888-466-8746 (Spanish)", appearing under the "Questions or comments?" heading, is acceptable.

4) The change from "McNeil Consumer Healthcare" to "McNeil Consumer & Specialty Pharmaceuticals" is acceptable.

5) Adding "shake well before using" and "only use attached measuring cup to dose product" as bulleted statements under the "Directions" heading for the Imodium A-D Liquid product is acceptable.

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

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

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/s/

Reynold Tan
5/26/04 01:59:57 PM
INTERDISCIPLINARY

Helen Cothran
5/26/04 04:21:48 PM
INTERDISCIPLINARY

Division of Over-the-Counter Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Numbers: NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

Name of Drugs: Imodium® A-D (loperamide HCL) Liquid
Imodium (loperamide HCL/simethicone) Caplets
Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets
Imodium Advanced (loperamide HCL/simethicone) Caplets

Applicant: McNeil Consumer & Specialty Pharmaceuticals

Material Reviewed:

Submission Date: June 11, 2004

Receipt Date: June 15, 2004

Background and Summary

McNeil Consumer & Specialty Pharmaceuticals submitted supplemental new drug applications on December 15, 2003, received December 16, 2003, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following products: Imodium® A-D (loperamide HCL) Liquid, Imodium (loperamide HCL/simethicone) Caplets, Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets, Imodium Advanced (loperamide HCL/simethicone) Caplets. These supplemental applications propose revised labeling under the "Stop use and ask a doctor if" and "Other information" sections. The following comments and recommendations were sent to the company on June 3, 2004:

1.) In order to inform the consumer that abdominal swelling or bulging could be signs of a serious condition, the third bulleted statement under the "**Stop use and ask a doctor if**" subheading should read:

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

2) Move the statement, "tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery.", from under ***Other information*** and place it under a new subheading entitled "**When using this product**" under ***Warnings*** (see 21 CFR 201.66(c)(5)(vi)). This new subheading should follow the "**Ask a doctor or pharmacist before use if you are** taking antibiotics" subheading.

The sponsor responded to these recommendations and comments in amendments dated June 11, 2004.

Review

In the June 11, 2004, amendments, all of the above recommended changes were incorporated into the draft labeling. These changes are acceptable with the exception of the omission of bolding for the subheading "**When using this product**" (21 CFR 201.66 (d)(3)).

- There were no other changes to the proposed labeling.

Conclusions

The draft label submitted June 11, 2004, is acceptable. The requirement to have all headings and subheadings in bold type will be conveyed to the sponsor.

Laura Shay
{See appended electronic signature page}
Regulatory Project Manger
Division of Over the Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Supervisory Comment/Concurrence:

Dave Hilfiker
{See appended electronic signature page}
Chief, Project Management
Division of Over the Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Laura Shay
6/16/04 09:43:26 AM
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David Hilfiker
6/17/04 01:54:32 PM
CSO

Laura Shay
6/18/04 01:13:53 PM
UNKNOWN

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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/s/

Reynold Tan
11/9/04 04:37:31 PM
INTERDISCIPLINARY

Helen Cothran
11/10/04 01:47:28 PM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBERS:

NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PRIOR APPROVAL SUPPLEMENT

NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

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

Dear Ms Wagner-Weber:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Imodium® A-D (loperamide HCL) Liquid
NDA Number:	19-487
Supplement number:	021
Name of Drug Product:	Imodium (loperamide HCL/simethicone) Caplets
NDA Number:	19-860
Supplement number:	020
Name of Drug Product:	Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets
NDA Number:	20-606
Supplement number:	009
Name of Drug Product:	Imodium Advanced (loperamide HCL/simethicone) Caplets
NDA Number:	21-140
Supplement number:	003

Date of supplements: December 15, 2003

Date of receipt: December 16, 2003

These supplemental applications propose revised labeling under the "Stop and ask a doctor if" section.

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on February 14, 2004, in accordance with 21 CFR 314.101(a). If the applications are filed, the goal date will be June 16, 2004.

All communications concerning these supplements should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Over the Counter Drug Products, HFD-560
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over the Counter Drug Products, HFD-560
Attention: Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

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

Sincerely yours,

{See appended electronic signature page}

David Hilfiker
Chief, Project Management Staff
Division of Over the Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

David Hilfiker
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

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 December 15, 2003, received December 16, 2003, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for: Imodium® A-D (loperamide HCL) Liquid, Imodium (loperamide HCL/simethicone) Caplets, Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets, Imodium Advanced (loperamide HCL/simethicone) Caplets

We have reviewed the referenced material and have the following request in order for us to proceed with our review.

Please provide us in table format a brief summary of the clinical data that supports your proposed labeling changes.

In order to ensure a timely action for this new drug application, we request that you respond to the issues listed below as soon as possible.

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.
Deputy Division Director
Division of Over the Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-487/S-021
NDA 19-860/S-020
NDA 20-606/S-009
NDA 21-140/S-003

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

Dear Ms. Wagner-Weber:

We have received your supplemental drug applications submitted December 15, 2003, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following: Imodium® A-D (loperamide HCL) Liquid (NDA 19-487/S-021), Imodium (loperamide HCL) Caplets (NDA 19-860/S-020), Imodium Advanced (loperamide HCL/simethicone) Chewable Tablets (NDA 20-606/S-009), and Imodium Advanced (loperamide HCL/simethicone) Caplets (NDA 21-140/S-003).

These supplemental applications propose revised labeling under the "Stop use and ask a doctor if" and "Other information" sections.

We have reviewed these supplemental applications and have the following comments and recommendations.

1.) In order to inform the consumer that abdominal swelling or bulging could be signs of a serious condition, the third bulleted statement under the "**Stop use and ask a doctor if**" subheading should read:

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

2.) Move the statement, "tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery.", from under ***Other information*** and place it under a new subheading entitled "**When using this product**" under ***Warnings*** (see 21 CFR 201.66(c)(5)(vi)). This new subheading should follow the "**Ask a doctor or pharmacist before use if you are** taking antibiotics" subheading.

In order to ensure a timely action for this supplemental new drug application, we request that you respond to the issue listed above as soon as possible. If you have any questions, you may call Laura Shay, Regulatory Project Manager, at (301) 827-2274.

Sincerely,
{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

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/s/

Curtis Rosebraugh
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-487/S-021

McNeil Consumer & Specialty Pharmaceuticals
Attention: Victoria Wagner-Weber
Director, Regulatory Development
7050 Camp Hill Road
Fort Washington, PA 19034-2299

Dear Ms. Wagner-Weber:

We acknowledge receipt of your October 5, 2004 submission containing final printed labeling in response to our June 16, 2004, letter approving your supplemental new drug application for Imodium A-D (loperamide HCl) Liquid.

We have reviewed the labeling that you submitted in accordance with our June 16, 2004, letter and we find it acceptable.

At next printing make the following changes and submit these changes in the next annual report:

1. Position the tradename "Imodium A-D" and the statement of identity (SOI) "Loperamide HCl/Anti-Diarrheal" so that the letters "A-D" do not appear to be part of the SOI.

2. Replace the hairline that divides the ***Directions*** section from the **Keep out of reach of children** section with a barline.

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

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D.
Deputy Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
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