

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 19-487/S-023

Name: Imodium A-D (Loperamide HCl) Liquid

Sponsor: McNeil Consumer & Specialty Pharmaceuticals

Approval Date: June 8, 2005

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**APPLICATION NUMBER:
NDA 19-487/S-023**

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APPLICATION NUMBER:
NDA 19-487/S-023

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-487/S-023

McNeil Consumer & Specialty Products
Attention: Carolyn Zlogar
Manager, CMC Regulatory
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Zlogar:

Please refer to your supplemental new drug application dated December 22, 2004, received December 23, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imodium A-D (loperamide HCL) Liquid.

This supplemental new drug application proposes a new 12 oz bottle package size and the addition of a (b) (4) production batch.

We have completed our review of this application. 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 submitted labeling (immediate container label submitted on December 22, 2004), and must be formatted in accordance with the requirements of 21 CFR 201.66.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 19-487/S-023.**" Approval of this submission by FDA is not required before the labeling is used.

We also recommend the following labeling changes. These changes are not a condition of approval. You may incorporate these changes in the labeling at the next time of printing and submit the revised labeling in the following annual report.

- 1) Vertically align the bulleted statements in the, "**Stop use and ask a doctor if**" and "**Directions**" sections according to 21 CFR 201.66(d)(4), so that the bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading are vertically aligned with the bulleted statements appearing on the previous line.
- 2) Move the statement "**Keep out of reach of children**" to a new line, in alignment with the other left justified Drug Facts headings to conform with 21 CFR 201.66(b)(7) and (d)(1).

If you issue a letter communicating important information about this drug product (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 LCDR Keith Olin, Regulatory Project Manager, at (301) 827-2293.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Acting Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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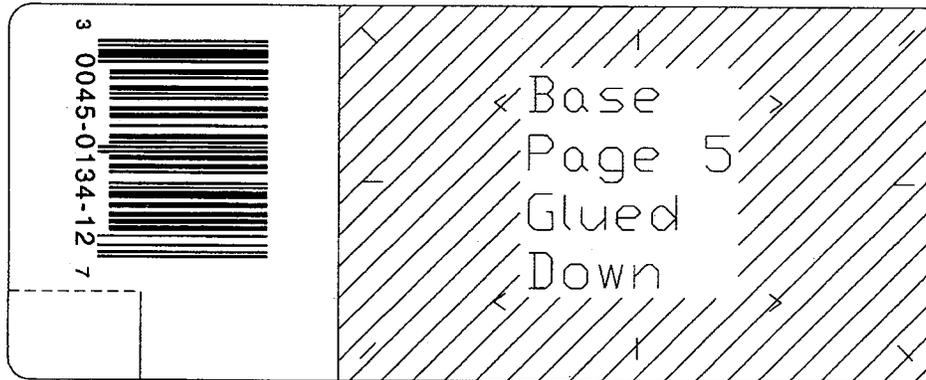
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Curtis Rosebraugh
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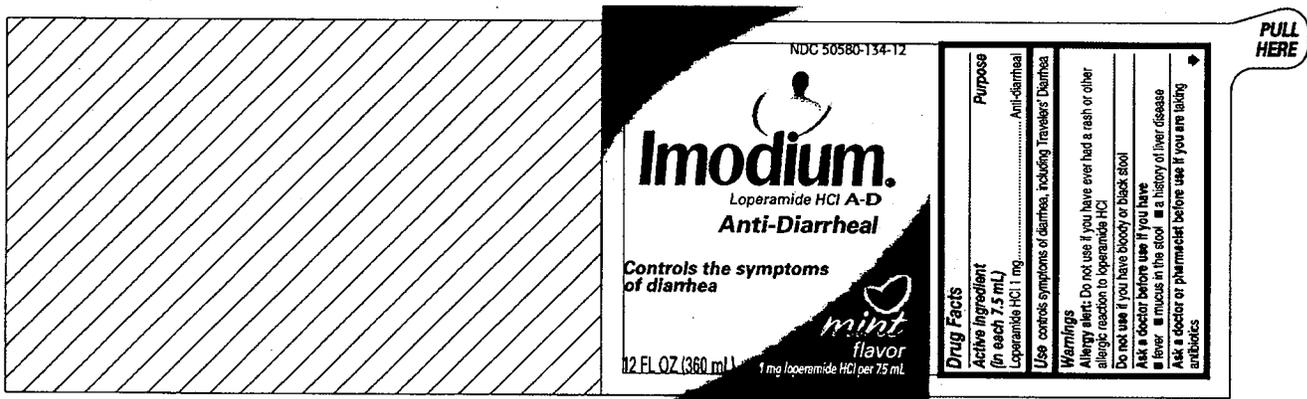
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LABELING



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COVER Page 1

Drug Facts (continued)

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 bloating. 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.

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
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

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Drug Facts (continued)

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)
- 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

Questions or comments?

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

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APPLICATION NUMBER:
NDA 19-487/S-023

LABELING REVIEW

Division of OTC Drug Products Labeling Review for an NDA Supplement

NDA 19-487 / SCP-023

Submission Date: December 22, 2004
Received Date: December 23, 2004
Drug product: IMODIUM A-D Liquid
Active ingredient: Loperamide HCl
Pharmacological category: anti-diarrheal
Sponsor/Contact: Carolyn Zlogar
Manager, CMC Regulatory Affairs
McNeil Consumer & Specialty Pharmaceuticals
7050 Camp Hill Road
Fort Washington, PA 19034
(215)273-8476
Labeling submitted: 12 oz bottle label
Reviewer: Reynold Tan
Review date: June 1, 2005
Project manager: Keith Olin

Background: In this CBE-30 supplement, the sponsor requested approval of a new bottle size for Imodium A-D Liquid. The sponsor provided a representative label for the proposed 12 oz bottle package, noting that the proposed label is consistent with the labels for the 4 and 8 oz bottles approved on 7/8/04 (NDA 19-487/ S-022).

Concerning that supplement (S-022), FDA requested that the sponsor reposition the tradename "Imodium A-D" such that the "A-D" does not appear to be part of the statement of identity "Loperamide HCl/ Anti-Diarrheal." Also, FDA requested that the hairline dividing the "Directions" section from the preceding "Keep out of reach of children" warning be replaced with a barline. In this supplement, the sponsor states that these two changes will be reflected in a subsequent annual report.

Reviewer's Comments:

1) A barline correctly separates the "Directions" section from the preceding "Keep out of reach of children" warning in the "Warnings" section.

Comment: This change had been recommended and is acceptable.

2) The bullets in the "Stop use and ask a doctor if" and "Directions" sections do not conform to format requirements in 21 CFR 201.66(d)(4).

Comment: According to 21 CFR 201.66(d)(4), "additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned

with the bulleted statements appearing on the previous line.” The bullets in the “**Stop use and ask a doctor if**” and “**Directions**” sections should be aligned according to this regulation.

3) The text of the “**If pregnant or breast-feeding**” and “**Keep out of reach of children**” warnings wraps over two successive lines.

Comment: The statements “**If pregnant or breast-feeding**” and “**Keep out of reach of children**” are defined as headings, according to 21 CFR 201.66(b)(7). All headings must be left justified, according to 21 CFR 201.66(d)(1). Therefore, the statement “**Keep out of reach of children**” should appear on a new line.

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

1) Align the bullets in the “**Stop use and ask a doctor if**” and “**Directions**” sections according to 21 CFR 201.66(d)(4), which states that additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line.

2) To conform with 21 CFR 201.66(b)(7) and (d)(1), move the statement “**Keep out of reach of children**” to a new line, in alignment with the other left justified Drug Facts headings.

The sponsor should make these changes in the labeling at the next printing and submit the revised labeling 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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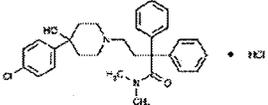
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Helen Cothran
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INTERDISCIPLINARY

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APPLICATION NUMBER:
NDA 19-487/S-023

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: Carolyn Zlogar, Manager, CMC Regulatory Affairs 7050 Camp Hill Road Fort Washington, PA 19034 Phone: 215-273-8476		4. Supplement Number: SCP-023 Letter Date: 12/22/04 Stamp Date: 12/23/04 Due Date: 6/23/05
5. Name of Drug IMODIUM A-D Liquid	6. Nonproprietary Name Loperamide HCl	
7. Supplement Provides for: A new container size (12 oz) of polypropylene bottles and addition of _____ production batch _____ size for the drug product.		8. Amendment(s) N/A
9. Pharmacological Category Controls the symptoms of diarrhea, including Traveler's Diarrhea	10. How Dispensed OTC	11. Related Documents N/A
12. Dosage Form Oral Liquid	13. Potency(ies) 1 mg/7.5mL	
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 Changes Being Effected in 30 days This supplement provides for a new container size (12 oz) of polypropylene (PP) bottles and addition of _____ production batch _____ size for the drug product. The PP resin _____ used in the proposed bottle size was stated to be the same resin that is currently used in the bottles for the applicant's Infants' Motrin® Drops (NDA 20-603). The closure materials were stated to be the same as those used for the currently approved container sizes (NDA 19-487/S-022). The Manufacturing process, equipment, and parameters were stated to be similar to those used for the current _____ batch size. The updated batch formula for the proposed batch size was provided along with the master and executed batch records. The supplement included test results of Physicochemical Tests-Plastics <USP 661> and Containers-Permeation Test <USP 671>. The submitted data conforms to the USP requirements. The supplement included three months of stability data at long-term (25°C/60%RH), accelerated (40°C), and cycle (-20°C to +25°C) conditions on one production scale batch in support of the proposed change. The submitted stability data did not indicate any adverse effect on the drug product because of the proposed change.		
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	Signature	Date 5/23/05
18. Concurrence John Smith, Ph.D., Chemistry Team Leader		

Review Notes**Stability Data Summary**

No. of Batches /Size	Storage Conditions	Available Data
1/Production	25°C/60%RH 40°C Cycle (-20°C to +25°C)	3 months 3 months Three cycles at -20°C for 4 days, then at +25°C/60%RH for 3 days

Evaluation: Submitted stability data on one production batch of drug product packaged in the proposed 12 oz size bottles conforms to established acceptance criteria, and the data on assay did not show any trends except for random variation and the degradant. _____ was not detectable. The submitted data did not indicate any adverse effect on the drug product because of the proposed change. **Adequate.**

Stability Commitment: The applicant commits to place the first commercial production batch and annual batches thereafter, packaged in 12 oz PP bottles made with the proposed resin, on long-term stability according to the approved stability protocol. **Adequate.**

Expiration Period: The applicant proposed to retain the current expiration dating period of 24 months. **Acceptable.**

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/s/

Rao Puttagunta
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CHEMIST

John Smith
5/24/05 01:35:01 PM
CHEMIST

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APPLICATION NUMBER:

NDA 19-487/S-023

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-487/S-023

CBE-30 SUPPLEMENT

McNeil Consumer & Specialty Products
Attention: Carolyn Zlogar
Manager, CMC Regulatory
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Zlogar:

We have received your supplemental drug application 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: 023

Date of supplement: December 22, 2004

Date of receipt: December 23, 2004

This supplemental application, submitted as a "Supplement - Changes Being Effected in 30 days," proposes a new 12 oz bottle package size and the addition of a — production batch.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 23, 2005.

**APPEARS THIS WAY
ON ORIGINAL**

All communications concerning this supplement 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}

Leah Christl, Ph.D.
Acting 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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Leah Christl
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