CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-140

ADMINISTRATIVE DOCUMENTS

14.0 Patent Certification

To the best of the applicant's knowledge this product, method of use and process is not covered by any other enforceable patent.

Name	Joseph F. Leightner
Title	Patent Attorney Registration Number 34, 209
Date	October 25, 1999

13.0 Patent Information

1. General

a. Patent Number and Expiration Date
5,248,505 Expiration September 28, 2010

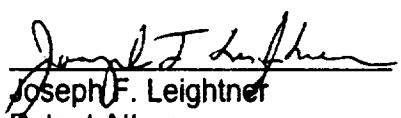
b. Type of Patent
Method of use

c. Name of Patent Owner
McNeil-PPC, Inc.

d. US Agent
McNeil-PPC, Inc.

1. Declaration (for formulation, composition, or method of use patents)

The undersigned declares that Patent No. 5,248,505 covers the formulation, composition, and/or method of use of IMODIUM® Advanced Caplet. This product is submitted for approval in this new drug application under section 505 of the Federal Food, Drug and Cosmetic Act.

Name 
Joseph F. Leightner

Title Patent Attorney
Registration Number 34,209

Date October 25, 1999

13.0 Patent Information

2. General

a. Patent Number and Expiration Date
5,612,054 Expiration September 28, 2010

b. Type of Patent
Formulation

c. Name of Patent Owner
McNeil-PPC, Inc.

d. US Agent
McNeil-PPC, Inc

2. Declaration (for formulation, composition, or method of use patents)

The undersigned declares that Patent No. 5,612,054 covers the formulation, composition, and/or method of use of IMODIUM® Advanced Caplet. This product is submitted for approval in this new drug application under section 505 of the Federal Food, Drug and Cosmetic Act.

Name 
Joseph F. Leightner
Title Patent Attorney
Registration Number 34,209
Date October 25, 1999

Reprinted from ... on 12/1/00 (Signature last page)

EXCLUSIVITY SUMMARY for NDA # 21-140 SUPPL # _____
Trade Name Imodium Advanced Caplet
Generic Name Loperamide/Simethicone
Applicant Name McNeil Consumer Healthcare HFD- 180
Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /__X_/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are

there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Kati Johnson 11/24/00
Signature of Preparer Date
Title: Chief, Project Management Staff, HFD-180

Lilia Talarico 11/24/00
Signature of Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

16.0 Debarment Certification

McNeil Consumer Healthcare hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	021140	**Trade Name:**	IMODIUM ADVANCED(LOPERAMIDE HCL/SIMETHIC
Supplement Number:	000	**Generic Name:**	LOPERAMIDE HCL/SIMETHICONE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	CONTROLS SYMPTOMS OF DIARRHEA PLUS BLOATING/PRESSURE/ AND CRAMPS COMMONLY REFERRED TO AS GAS
Action Date:	11/1/99		

Indication # 1 provides for the use of Imodium Advanced (loperamide HCl and simethicone) Caplet in controlling symptoms of diarrhea plus bloating, pressure, and cramps commonly referred to as gas.

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any): Per the DOTCCDP (HFD-560), pediatric waiver has been granted for children under 6 years of age

	Lower Range	Upper Range	Status	Date
6 years	Adult	Waived	12/1/00	

Comments: This application is approved for persons 6 years of age and older. There is already an approved chewable tablet formulation under NDA 20-606 that could be used in patients under 6 years of age. Therefore a waiver was granted.

This page was last edited on 12/1/00

Signature /S/ Date 12/1/00

Memorandum to File

NDA 21-140
Drug Product: Imodium Advanced Caplets
Date: 11/28/00
Subject: Division Response to Labeling Comments from HFD-180 (Clinical Pharmacology and Biopharmaceutics Review and CMC)

1. The Statement "Children under 6 years (up to 47 lbs): ask a doctor" is the standard OTC text used for Drug Facts labeling requirements under 21 CFR 201.66.

2. The sponsor was contacted regarding whether the age or weight would be the primary criteria when selecting a dose. The sponsor's response is that the label should reflect that the consumer should use weight to dose, and if weight was not available, the consumer should then use age. (See Memorandum of Telecon dated 8/2/2000).

3. The caplet is scored, but the ability of caplet to be easily broken into two equal parts should be evaluated by CMC.

4. In response to statement by CMC that reads "The drug product should not be marketed with unapproved container/closure system" is not an issue that our Division should be addressing. The adequacy of the container/closure system should be addressed by CMC.

/S/ 11/28/00
Gloria Chang, R.Ph.
Interdisciplinary Scientist, HFD-560

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

Attachment

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 14, 2000 DFS 11/14/00 Liang Zh

FROM: Liang Zhou, Ph.D., Chemistry Team Leader, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 21-140 Imodium Advanced Caplet

TO: NDA 21-140

The purpose of this Memo as my recommendation which overrides the chemistry reviewer's conclusions /recommendation reached in chemistry review #2 dated November 14, 2000.

Mr. Adams indicated in his chemistry review #2 that a List of Deficiencies and Comments (1 to 6) should be conveyed to the Applicant prior to approval. In my opinion, none of the comments/requests constitute approvability issues. The application can be approved from the standpoint of chemistry. However, the following are my comments to the chemist's comments in chemist's Review #2 for justifications.

Comment 1. The firm has responded to the chemist's comment #10 from chemist review #1.

Comment 2 & 3. The firm has responded to the chemistry comments (12-14) from chemist review #1. It is unnecessary to make the additional verification or clarification at this time point.

Comment 4. The drug product should not be marketed with unapproved container/closure system.

Comment 5. The firm has addressed the comment #27 in chemistry review #1. The firm could always obtain our review or conclusion for this matter if the applicant would still be interested in our conclusion regarding the acceptance of non-USP test method to obtain USP<671> data.

Comment 6. Regarding your comments 6 (a, b and c), I agree with reviewer's scientific findings which are correct based on their submitted the test data. The applicant could be requested to

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

Meeting Minutes

MEMORANDUM OF TELECON

Meeting Date:	August 2, 2000
Time :	3pm
Location:	S240, 9210 Corporate Blvd Rockville MD
Application:	NDA 19-860 NDA 21-140
Type of Meeting:	Age verse weight clarification for dosing directions
Meeting Recorder:	Daniel P. Keravich, MS., Pharm., MBA.

FDA Attendees Titles & Office Division:
Daniel Keravich, MS., Pharm., MBA., Project Manager, DOTCDP, HFD-560

External Constituents Attendees and titles:
Paula Oliver, Senior Director, Regulatory Compliance

Meeting Objective:
To clarify whether age or weight has precedence when dosing in the directions for Imodium A-D caplet and Imodium Advanced caplet

Discussion
The agency contacted the sponsor to seek clarification in the **Directions** portion of the labeling on whether age or weight would be the primary criteria when selecting a dose for Imodium. The current direction lists both age and weight for each age group. The agency wanted to know the sponsors intent on whether the consumer should select the dose by weight or age. The sponsor's response is that the label should reflect that the consumer should use weight to dose, and if weight was not available, the consumer should then use age. The sponsor indicated that they would send the DOTCDP a fax to formalize this response (See attached)

The meeting ended amiably.

Dan Keravich, M.S., Pharm., M.B.A.

Minutes Preparer: DPK 8-2-00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Memorandum

January 19, 2000

To: David Lepay, M.D.,
Director Division of Scientific Investigations,
Acting Branch Chief of Good Clinical Practices
Branch I, DSI, HFD-45
Metro Park North I, Rm# 103

From: Paul E. Levine, Jr., R.Ph.
Project Manager, HFD-180

Subject: Request for Domestic Clinical Inspections
NDA 21-140
McNeil Consumer Healthcare
Imodium Advanced (loperamide/simethicone) Caplet

NDA 21-140, received November 1, 1999, contains a bioequivalence study to establish a therapeutic alternative to the approved OTC chewable tablet formulation of Imodium Advanced (NDA 20-606, approved June 26, 1997). The study was conducted by McNeil Consumer Healthcare, located in 7050 Camp Hill Road, Fort Washington, PA 19034-2299, at (215) 273-7000.

The Division does not routinely request that sites involving bioequivalence studies be inspected. However, we have left the final decision, concerning whether or not to inspect this site, up to you. If you decide that this site should be inspected, we request that you notify us of your intent. Also, if the study is investigated, we request that the Inspection Summary Results be provided to us by July 15, 2000, since the 10-month goal date is September 01, 2000.

Should you require any additional information, please contact me at x38347.

cc: NDA 21-140
Division File
K.Malek
P.Levine

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 10, 1999
Time: 10:00-11:00 AM
Location: Conference Room 6B-45, Parklawn Building

MAR 8 2000

Application: NDA 21-140
Imodium® Advanced Caplet

Type of Meeting: 45-Day Filing Meeting

Meeting Chair: Dr. Lilia Talarico

Meeting Recorder: Paul E. Levine, Jr.

FDA Attendees:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Lilia Talarico, MD, Division Director
Steve Aurecchia, MD, Division Deputy Director
Liang Zhou, Ph.D., Chemistry Team Leader
Mike Adams Chemistry Reviewer
Kati Johnson, Supervisor, Project Manager Staff
Paul E. Levine, Jr., R.Ph, Regulatory Project Manager

Division of Pharmaceutical Evaluation II (HFD-870)

Ron Kavanagh, Biopharm Reviewer

Division of Biometrics II (HFD-715)

Paul Flyer, Ph.D., Statistician Team Leader

Division of Scientific Investigations (HFD-560)

Charles Ganley, M.D., Director, DOTCDP
Linda Katz, M.D., M.P.H., Deputy Director, DOTCDP
Andrea Leonard-Segal M.D., Medical Reviewer
Helen Cothran, Team Leader, DOTCDP
Gloria Chang, R.Ph., Interdisciplinary Scientist, DOTCDP
Al Rothschild, Regulatory Project Manager, DOTCDP

Background:

McNeil Consumer Healthcare, submitted this NDA on October 29, 1999, (received November 1, 1999) for Imodium Advanced Caplets (loperamide HCl/simethicone) Tablets with the following proposed indication: *to control symptoms of diarrhea; and bloating, pressure, and cramps commonly referred to as gas.* This application contains bioequivalence study reports used to establish the drug as a therapeutic alternative to the approved Imodium Chewable Tablet (NDA 20-606, approved June 26, 1997).

Meeting Objective:

To determine the fileability of this application, and to discuss any information requests that need to be issued to the sponsor.

Discussion Points:

I. Administrative
   A. Filing Issues: None
   B. Information Requests: None

II. Clinical - N/A

III. Pharm/Tox - N/A

IV Chemistry\Manufacturing\Controls (CMC)
   A. Filing Issues: None
   B. Information Requests: None

V Biopharm
   A. Filing Issues: None
   B. Information Requests: When the primary reviewer requested that a food-effects study be completed, there was some question as to whether this information was required of the previously approved application. We requested Al Rothschild (OTC) to determine if a food-effect study was done in NDA 20-606, and to forward the study information, if available, to this Division.

VI Division of OTC (HFD-560)
   A. Filing Issues: None
   B. Information Requests:
      1. OTC requested available information on global safety data, including an adverse events quantitative summary covering the months since the chewable tablet form (NDA 20-606), was approved. OTC requested that the firm contact HFD-560 directly for the specifics of this request.
      2. OTC will submit labeling requests directly to the firm. They will review the labeling and provide a copy of the review to the Division.

Conclusions:

1. It was determined that the application would be filed.

2. The internal goal date for the completion of finalized reviews is July 15, 2000. The 10-month FDAMA Goal Date is September 1, 2000.

3. The Division of OTC (HFD-560) will advise firm directly about labeling.

4. The Division of OTC (HFD-560) will do the Clinical Safety review for this application and forward a copy to our Division.

5. The Project Manager in HFD-180 will communicate to the firm in a telephone conference the information request from OTC. The firm will be instructed to contact OTC directly concerning this request.

7. It was agreed that all direct communications between the Division of OTC and the firm would be copied to this Division.

Minutes Preparer /S/ 3/3/00

Chair Concurrence /S/ 3/9/00 CT

Division of OTC Drug Products Labeling Review

NDA 21-140 /BL
Drug Product: Imodium Advanced Caplets
Active Ingredient: Loperamide Hydrochloride 2 mg
Simethicone 125 mg

Indication: Controls symptoms of diarrhea plus bloating, pressure, and cramps, commonly referred to as gas
Sponsor: McNeil CONSUMER HEALTHCARE
Date of Submission 8/24/00
Type of Submission: Minor draft labeling amendment
Reviewer: Gloria Chang, IDS/Pharmacist, HFD-560
Date of Label Review: 11/7/00
Project Manager: Daniel Keravich

Background: NDA 21-140 submitted 10/29/99 provides for a caplet dosage form of Imodium Advanced. In amendment 1 dated 5/24/00 to NDA 21-140, the sponsor submitted thermal copies of labeling for the 30 and 42-count bottles, 6, 12, and 18-count blister packages, 2-count pouch, and a dispensit box containing 18 (2-count) pouches. The Agency's comments on the sponsor's labeling submission were faxed to the sponsor on 8/7/00. (Attachment 1). On 8/24/00, in response to the Agency's comments, the sponsor submitted thermal labeling copies with type size information for the following package sizes: 6, 12, and 18-count blister unit packages, blister unit, 30 and 42-count bottle cartons and immediate bottle labels, 2-count pouch, and a dispensit containing 25 (2-count) pouches. (Attachment 2). This review is of that labeling.

Reviewer's Comments

I. Carton Label for the 6, 12, and 18-count blister units, 30 and 42 count bottle cartons, and dispensit

A. Principal Display Panel (PDP)

1. The placement of the Statement of Identity (SOI) in direct conjunction with the most prominent display of the proprietary name is acceptable.

2. The SOI is acceptable.

3. The sponsor should be reminded that the term "NEW" must be removed after 6 months of marketing.

4. As requested, the sponsor has removed the phrase "PATENTED FORMULA".

5. On the 30 count bottle carton, the statement "THIS PACKAGE FOR HOUSEHOLDS WITHOUT YOUNG CHILDREN" is in accordance with section 4(a) of the Poison Prevention Packaging Act (PPPA).

II. Blister Unit label

1. The SOI needs to include the pharmacological actions "Anti-Diarrheal/Anti-Gas" following the established names "Loperamide HCl/Simethicone".

III. Drug Facts Labeling

A. Content/Text

1. The sponsor's revision of the word "***Uses***" to "***Use***" in the ***Uses*** section is acceptable.

2. The revisions made in the***Warnings*** section are acceptable.

3. In the directions for the 6-count caplet carton, the last two boxes of the age groups are not lined up with the correct directions for use. The statement "children under 6 years of age (up to 47 lbs)" needs to be moved down to replace the statement "children 6-8 years (48-59 lbs)" as the last statement so that the appropriate sequence and corresponding dosing directions are correct.

4. Under the ***Other information*** section, the addition of the bulleted statement "▪ protect from light" and the tamper evident statements are acceptable.

B. Format (§ 201.66(d))

1. The sponsor's submitted format information regarding the font type and point type sizes for the Drug Facts title, Header, Subheader, Body Text, Drug Facts (continued) title, bullets, barlines, hairlines, and leading point type are acceptable in the standard format.

2. The 2-caplet sample pouch font type size and point type sizes for the Drug Facts title, Header, Subheader, Body Text, Drug Facts (continued) title,

bullets, barlines, hairlines, and leading point type are acceptable in the modified format. However, the following need to be revised:

a. In the ***Warnings*** section **"Stop use and ask a doctor if"**, the placement of the term "2 days" in the second bulleted statement right under the first bulleted statement may be confusing to consumers. There appears to be sufficient line spacing under this subheading to allow for each bulleted statement to be included on a separate horizontal line to read:
Stop use and ask a doctor if
- symptoms get worse
- diarrhea lasts for more than 2 days

b. The sponsor has not specified the location of the expiration date and lot number on each 2-count sample pouch.

Reviewer's Recommendations

I. The following labeling changes need to be made in order for this NDA supplement to be approved.

A. The SOI on the blister unit label needs to include the pharmacological actions "Anti-Diarrheal/Anti-Gas", following the established names "Loperamide HCl/Simethicone".

B. For the two-caplet sample pouch, the modified Drug Facts label needs to be revised as follows:

Under the subheading warning **"Stop use and ask a doctor if"**, the placement of the term "2 days" in the second bulleted statement right under the first bulleted statement may be confusing to consumers. There appears to be sufficient line spacing to allow for each bulleted statement to be included on a separate horizontal line, to read:

Stop use and ask a doctor if
- symptoms get worse
- diarrhea lasts for more than 2 days

C. In the directions for the 6-count caplet carton, the last two boxes of the age groups are not lined up with the correct directions for use. The statement "children under 6 years of age (up to 47 lbs)" needs to be moved down to replace the statement "children 6-8 years (48-59 lbs)" as the last statement so that the appropriate sequence and corresponding dosing directions are correct.

D. The sponsor has not specified the location of the expiration date and lot number on each pouch.

II. The following revision needs to be made after 6 months of marketing.

A. The sponsor should be reminded that the term "NEW" must be removed after 6 months of marketing.

The above recommendations can be conveyed to the sponsor.

Gloria Chang, R.Ph.
Interdisciplinary Scientist, HFD-560

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

11/14/00

Attachments

Labeling Review

NDA 21-140

Drug Product:	Imodium Advanced Caplet
Active Ingredients:	Loperamide Hydrochloride 2 mg Simethicone 125 mg
Indication:	Controls symptoms of diarrhea plus bloating, pressure, and cramps commonly referred to as gas
Sponsor:	McNeil Consumer Healthcare
Date of Submissions	10/29/99 and Amendment 1 (Revised Labeling) 5/24/00
Type of Submission:	NDA for new dosage form (caplet)
Review date:	7/20/00
Reviewer:	Gloria Chang, IDS/Pharmacist Division of OTC Drug Products
Project Manager:	Daniel Keravich

Background: NDA 21-140 provides for a caplet dosage form. Imodium Advanced Chewable Tablets (NDA 20-606) was approved on 6/27/97. In Amendment 1 to NDA 21-140, submitted 5/24/00, the sponsor included thermal labeling with type size information for the following package sizes: 30 and 42 count bottles, 6, 12, and 18-count blister packages, 2-count pouch, and a dispensit box containing 18 (2-count) pouches. (Attachment 1).

Reviewer's Comments:

I. Principal Display Panel

A. Move "Loperamide Hydrochloride/Simethicone" to right under the pharmacological categories to read:

Loperamide Hydrochloride / Simethicone
ANTI-DIARRHEAL / ANTI-GAS

B. The phrase "NEW" from the phrase "NEW Easy to Swallow" must be removed after 180 days of marketing.

C. Remove the phrase "PATENTED FORMULA".

D. The sponsor should be reminded that in accordance with section 4(a) of the Poison Prevention Packaging Act (PPPA), the statement "THIS PACKAGE FOR HOUSEHOLDS WITHOUT YOUNG CHILDREN" on the 30-count package is only allowed for a single size package. In accordance with section 4(a) of PPA, and for readability, we recommend the use of upper and lower case letters to read "This package for households without young children".

I. Drug Facts Label Content/Text in accordance with 21 CFR 201.66 (c)
See example Label (Attachment 2)

A. **Uses** section

1. Revise "**Uses**" to "**Use**"

A. **Warnings** section

1. Add as the first warning, the statement "**Allergy alert:** Do not use if you have ever had a rash or other allergic reaction to loperamide HCL."

2. Under the **Do not use** subheading delete all of the bulleted statements and add the statement "if you have bloody or black stool".

3. Under the **Ask a doctor before use if you have** subheading, revise the bulleted statements to read:
   - fever - mucus in the stool - a history of liver disease

4. Under the **Stop use and ask a doctor if** subheading, revise the bulleted statements to read:
   - symptoms get worse
   - diarrhea lasts for more than 2 days

5. In the Keep out of reach of children warning, delete the word "the" to read "**Keep out of reach of children.** In case of overdose . . .."

C. **Directions** section

1. Revise and bold the first bulleted statement to read:
   - **drink plenty of clear fluids to help prevent dehydration caused by diarrhea**

2. In the maximum daily dosage statements, revise the words "a day" to "in 24 hours".

3. Under the **Directions** heading, the sponsor needs to clarify the children dosing with regard to the children's age in years and the weight (lbs). For example, if a child is 70 lbs, but is 8 years old, the sponsor needs to clarify on the dosing table what takes precedence, the weight or the age.

D. **Other information** section

1. Add the bulleted statement: ▪ protect from light
   Likewise, this statement needs to be added to Imodium Advanced Chewable Tablets (NDA 20-606). For NDA 20-606, this revision can be made at the next printing, or within 180 days, whichever comes first.

2. Revise tamper evident statements as follows:
   a. For the cartons containing the blister units, revise to read "**do not use if the carton or if blister unit is open or torn**".

   b. For the sample pouches, revise to read "**do not use if pouch is open or torn**".

   c. Sponsor should be made aware that, although the tamper evident statement is acceptable here, the sponsor needs to comply with the tamper evident requirements on packages in accordance with 21 CFR 211.132.

E. **Questions or comments** section

1. The sponsor should consider adding "toll free" and including the hours available in this section.

I. Other Comments on Labeling

A. 2-Caplet Sample Pouch

1. The sponsor should be reminded that if the individual sample pouches are directly distributed by mail or in a retail establishment, the statement "Not for Retail Sale" needs to be included in a prominent location on each sample pouch.

2. The sponsor needs to specify the location of the expiration date and lot number on each of the 2-caplet sample pouches.

3. Under the **Directions** section, the directions for children 6-8 years and under 6 years, appear to be in a separate section from the rest of the Directions. Both sections need to be enclosed in a Drug Facts box and need to follow the requirements in 201.66(c)(1) and (d)(5). The first boxed section of the Directions (2nd Drug Facts Panel) needs to include a right justified arrow pointing down to show the continuation to the next adjacent panel.

4. The other section of the Directions (3rd Drug Facts Panel) needs to include the title "Drug Facts" (continued) and format in accordance with 201.66 (d)(1) through (10).

C. Blister Unit

1. The sponsor did not include labeling for the blister units. The sponsor needs to submit the blister pack units labeling for review.

Reviewer's Recommendations. The above comments can be conveyed to the sponsor.

/S/ 8/1/00

Gloria Chang, R.Ph.
Interdisciplinary Scientist, HFD-560

/S/ 8/1/00

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

Attachments