CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-140

MEDICAL REVIEW

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Division of Over-The-Counter Drug Products
Medical Review

NDA 21-140
Name: Imodium® Advanced Caplet
Pharmacologic Category: Anti-diarrheal/anti-flatulent
Proposed Indication: Control Symptoms of Diarrhea, and Associated Abdominal Bloating and Cramps
Dosage Form/Route of Administration: Caplet/Oral
Date of Submission: October 29, 1999
Date of Review: January 18, 2000
Reviewer: Andrea Leonard-Segal, M.D., M.S.

Background

This is a new drug application for Imodium® Advanced (Loperamide HCl and Simethicone Caplets). The caplet contains 2 mg of loperamide and 125 mg of simethicone, the same as the currently marketed Imodium® Advanced Chewable Tablet (2 mg of loperamide and 125 mg of simethicone). Loperamide is an antidiarrheal agent which has been used worldwide for over 20 years and was approved for over-the-counter (OTC) use in the United States in 1988. Simethicone is a silicon polymer defoaming agent that has been available in many countries since the 1960s and has been available OTC in the United States for relieving gas-related abdominal symptoms in divided doses of 500 mg per day. Simethicone is not systemically absorbed from the gastrointestinal tract. In 1997, the combination chewable tablet (NDA 20-606) was approved for OTC marketing in the United States.

The sponsor states that the combination caplet is intended for use by adults and children 6 years of age and older and will provide consumers with an alternative dosage form of the loperamide-simethicone combination, and as such will provide a clinical benefit with no increase in risk to the consumer. The sponsor provided information about chemistry, manufacturing and controls, dissolution, defoaming, and bioequivalence (McNeil bioequivalence protocols 98-058 and 98-051) (refer to the Chemist's Review). This review addresses the global safety of the marketed chewable tablet, and safety of the new combination caplet. The sponsor states that approximately [redacted] dosage units of the combination chewable tablet have been sold worldwide since 1997 and through March 25, 1999. The safety information provided about the new caplet is from the 2 bioequivalence studies.

McNeil Bioequivalence Study 978-068 (Pivotal)

This study had a single-dose, open-label, randomized, two-treatment crossover design. After an overnight fast, subjects received a single dose of 8 mg loperamide, and 500 mg simethicone administered as either 4 loperamide-simethicone caplets, 2 mg/ 125 mg, or 4 Imodium® Advanced Chewable Tablets, loperamide-simethicone 2 mg/125 mg. Each treatment was separated by a 2-week washout period. Twenty-nine healthy subjects were enrolled and included in the safety assessment. Twenty-eight subjects (15 males and 13 females) ranging in age from 19 to 55 years, completed the study. The sponsor states that one subject withdrew for personal reasons before the second study period.

Comment: The study design, single dose, and the number of subjects enrolled, 29, are inadequate to determine whether the product is safe unless bioequivalence is established to the currently marketed formulation. The personal reasons that one subject withdrew are not provided.

Nine adverse events were reported for 7 of 29 subjects. (See **Table 1**.)

Table 1. Adverse Events Reported During McNeil Study 98-068 (Pivotal)

Subject Number	Study Drug	Adverse Event	Intensity	Relationship to Study Drug
1	Caplet	Lightheadedness	Mild	Unlikely
4	Caplet	Vasovagal Episode	Mild	None
13	Caplet	Vasovagal Episode	Mild	None
3	Chewable Tablet	Cold Symptoms	Mild	None
5	Chewable Tablet	Headache	Mild	Possible
5	Chewable Tablet	Dizziness	Mild	Probable
17	Chewable Tablet	Fever	Mild	None
17	Chewable Tablet	Abdominal Cramp	Mild	None
27	Chewable Tablet	Cold Symptoms	Mild	None

Comment: The scale by which the investigator ranked the intensity of an adverse event was not provided. It is not clear what criteria the investigator used to determine a relationship between the study drug and an adverse event. Six of the nine adverse events were thought to be unrelated to the study drug. None were though to be definitely related.

McNeil Bioequivalence Study 98-051 (Pilot)

The objective of this study was to determine the bioequivalence of an early development formulation of loperamide-simethicone caplets with Imodium® Advanced chewable tablets. This study had a single-dose, open-label, randomized, 2-way crossover design. Sixteen healthy subjects (8 males and 8 females) ranging in age from 21 to 46 years were enrolled. Each subject received a single dose of 8 mg loperamide and 500 mg simethicone administered as 4 loperamide-simethicone caplets, 2 mg/125 mg, or 4 Imodium® Advanced Chewable Tablets, 2 mg/125 mg, after an overnight fast. Each treatment was separated by a 2-week washout period. All subjects completed both study periods and were included in the assessment of safety.

Three adverse events were reported in 3 of the 16 subjects. (See **Table 2.**)

Table 2. Adverse Events Reported During McNeil Study 98-051 (Pilot)

Subject Number	Study Drug	Adverse Event	Intensity	Relationship to Study Drug
4	Chewable Tablet	Dysmenorrhea	Mild	None
8	Chewable Tablet	Headache	Mild	Possible
16	Chewable Tablet	Headache	Mild	None

Comment: The protocols for the pilot and the pivotal trials appear to have been the same, though neither was described in detail. None of the 3 adverse events was definitely related to the study drug.

Safety Data from Commercial Marketing Experience – McNeil Drug Safety Reporting System

The sponsor provided a summary of safety data (including serious adverse event reports from the published literature and foreign sources) from the commercial marketing experience on Imodium® Advanced from McNeil's Drug Safety Reporting System since OTC approval in June, 1997 through March 25, 1999. (See **Table 3.**) The sponsor states that approximately 82% of the adverse events collected during this almost 2-year time period were received via the toll-free telephone number on the Imodium® Advanced carton label.

Table 3. Summary of Loperamide-Simethicone Combination Safety Data From Commercial Marketing Experience During the Period June 1997 Through March 25, 1999 (from McNeil Safety Reporting System).

Dosage Units Sold Worldwide (estimated)	[redacted]

Total Imodium® Advanced Reports of Adverse Event	470
Reports of Adverse Event with Serious Outcome	2
Deaths	0

The sponsor states that approximately 6% of the approximately [redacted] dosage units were sold outside of the United States. Two of 470 total reported adverse events were considered to be serious by the sponsor. One of these was a foreign report. The remaining 468 (99%) adverse event reports were rated as non-serious.

Of the 2 serious reports, one 34 year old male, developed an anaphylactic reaction that required treatment in the emergency room, after taking 3 doses of the product over 2 days for diarrhea. He was also taking ibuprofen softgel.

Comment: This case is confounded. The medical records are confusing; the emergency room records indicate that the subject took a generic form of loperamide whereas the 3 MedWatch reports say it was the combination product. One of the MedWatch forms indicates that he took simethicone plus the combination tablet and ibuprofen.

The second serious adverse event was a report from Ireland of a man (age unknown) with a history of diabetes mellitus and multiple cerebral infarcts who developed a transient ischemic episode on a day when he took medication for diarrhea. His physician did not believe the transient ischemic episode was secondary to Imodium® Plus.

Comment: It is not clear from the MedWatch report if the subject actually took Imodium® Plus.

Table 4 provides a body system summary of the 592 individual adverse events in the 468 reports. If a patient had more than one adverse event reported, McNeil tabulated each individual adverse event. The sponsor states that the most frequently reported individual adverse events were no drug effect (n = 194), taste perversion (n = 60), abdominal pain (n = 44), nausea (n = 44), vomiting (n = 29) and constipation (n = 26). Three of 4 non-serious reports of overdose did not describe symptoms associated with taking more than the recommended number of tablets to treat diarrhea. The fourth, of a subject with diarrhea secondary to chemotherapy who took 2 tablets every 2 hours for 6 days, mentions nausea and vomiting which resolved after the product was discontinued.

Comment: Treatment of diarrhea secondary to chemotherapy is not an indication for this product.

Table 4. Body System Summary for United States Adverse Event Reports With Non-Serious Outcome from McNeil's Drug Safety Reporting System for the Period June 26, 1997 through March 25, 1999 for Imodium® Advanced Chewable Tablets.

Body System Adverse Event	Number of Events
Body as a Whole	287

Allergic Reaction	2
Asthenia	1
Edema Face	3
Fever	1
Headache	7
No Drug Effect	194
Overdose	3
Overdose, Accidental	1
Pain	4
Pain, Abdominal	44
Pain, Chest	2
Reaction, Aggravation	10
Reaction, Unevaluable	15
Cardiovascular System	1
Palpitation	1
Digestive System	176
Constipation	26
Diarrhea	7
Discoloration Tongue	2
Dyspepsia	17
Dysphagia	6
Eructation	2
Esophagitis	2
Flatulence	14
Gastrointestinal Disorder	1
Glossitis	1
Hemorrhage, Rectal	1
Nausea	44
Nausea, Vomiting	7
Rectal Disorder	2
Stomatitis	3
Stool, Abnormal	11
Ulcer, Mouth	1
Vomiting	29
Metabolic and Nutritional	2
Hyperglycemia	2

Table 4 (Continued). Body System Summary for United States Adverse Event Reports with Non-Serious Outcome from McNeil's Drug Safety Reporting System for the Period June 26, 1997 through March 25, 1999 for Imodium® Advanced Chewable Tablets.

Body System Adverse Event	Number of Events

Nervous System	22
Dizziness	8
Dry Mouth	3
Hypertension	1
Hypertonia	1
Insomnia	2
Nervousness	2
Somnolence	4
Vasodilation	1
Respiratory System	5
Laryngismus	1
Pharyngitis	2
Burning of the Throat	2
Skin and Appendages	32
Dermatitis, Exfoliative	1
Pruritus	7
Rash	18
Skin discoloration	1
Sweat	3
Urticaria	2
Special Senses	63
Amblyopia	1
Pain, Ear	1
Taste Perversion	60
Vision, Abnormal	1
Urogenital System	4
Dysuria	1
Urine, Abnormal	2
Urine, Frequency	1

Comments: Adverse events requiring additional comments are listed below.

Body as a Whole:
Allergic Reaction – One of the 2 case descriptions lacked meaningful detail; the other described a rash in a subject on 6 concomitant pharmaceuticals.
Face Edema – Two reports may have been related to the use of the product. The third is a confounded study, and the allergic reaction resolved without discontinuation of the product.

Digestive System:
Dysphagia – The 6 subjects in the dysphagia category swallowed the pill whole, and/or claimed to choke swallowing it.
Rectal Hemorrhage – This was a 72 year old consumer who was taking 5 concomitant medications, among them Ticlid®, and ibuprofen, both of which cause platelet

dysfunction and can predispose to bleeding. An association between the Imodium® Advanced and the bleeding is unclear.

Nervous System:
Vasodilation: This 56-year old woman taking 4 concomitant medications noted that her "face is hot."

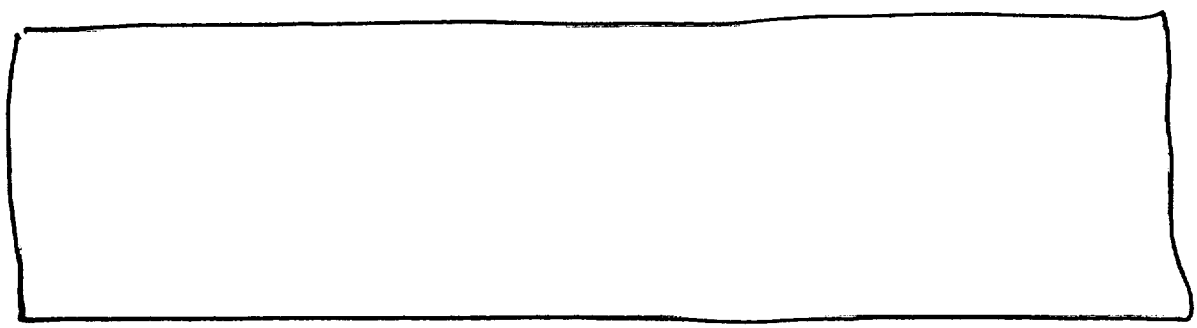
Respiratory System:
Laryngismus: This 67-year old man having radiation therapy for prostate cancer alleged that the use of Imodium® Advanced was associated with a dry and swollen throat. He was taking 4 concomitant medications. His symptoms resolved by discontinuing use of the product, drinking Gatorade®, Maalox® and water.

Skin and Appendages:
Exfoliative Dermatitis: This 37-year old man developed a red and inflamed mouth with skin peeling of the inside bottom lip. He discontinued the product and symptoms resolved by the next morning. There were no concomitant medications.

Special Senses:
Taste Perversion: Sixty subjects complained of a "bitter," "horrible," or "metallic" taste after chewing the product. This aftertaste lasted from minutes to 3 days.

The sponsor states that the most frequently reported adverse event in clinical trials of the chewable tablet was taste perversion and that loperamide in the Imodium Advanced® chewable tablet is coated with polymers to mask its bitter taste.

Comment: A decrease in "taste perversion" may result from a caplet formulation (which will be swallowed, not chewed).



*Comment: Among the 5 reported cases, there were 9 separate adverse events terms reported. (See **Table 5**.) The subject with an allergic reaction (urticaria) was using Atenolol concomitantly. The subject with and elevated blood sugar was a known diabetic.*

Table 5. Adverse Event Reports with Non-Serious Outcomes from Non-United States Sources Received by Janssen Research Foundation through March 25, 1999 for Loperamide-Simethicone Combination.

Body System Adverse Event	Number of Events
Body as a Whole	2
Allergic Reaction	1
Efficacy, Lack of	1
Digestive	3
Epigastric Pain	1
Nausea	1
Stomach Upset	1
Metabolic/Nutritional	1
Blood Sugar Increase	1
Nervous System	2
Headache	1
Dizziness	1
Skin/Appendages	1
Urticaria	1

Comment: The one report from foreign commercial marketing experience of the loperamide-simethicone combination with a serious outcome was described previously on page 4.

The sponsor states that efficacy and safety results of a pivotal study in NDA 20-606 for Imodium Advanced® chewable tablet have been published by McNeil as an abstract (Gastroenterology 1997;112:A21) and as a detailed report (Arch Fam Med 1999;8:243-248). The safety data from this pivotal study was included in NDA 20-606 and, as such was not included in NDA 21-140 for Imodium Advanced® caplet. Subsequent to submission of NDA 21-140, the same detailed report of the pivotal study (Arch Fam Med 1999;8:243-248) was abstracted in 3 different publications (ACP J Club 1999;131:66, Mod Med 1999;67:14, Evidence-Based Med 1999;4:176). The sponsor denies awareness of any other published reports of adverse events with this combination product.

Comment: The sponsor provided copies of the abstracts and article. The abstract in Gastroenterology did not address safety, only efficacy. The Arch Fam Med article, a summary of the pivotal NDA 20-606 trial, reported that the number of patients reporting adverse events among the 4 treatment groups in this study (placebo, loperamide-simethicone chewable tablet, loperamide, simethicone) was comparable and that no serious adverse events were noted. Three subjects withdrew from this study because of adverse events: 1 in the simethicone group had lumbar pain, and in the placebo group 1 had rheumatic pain and 1 had cough and pharyngitis. These were considered to be unrelated to the study medication.

Summary:
The safety data presented on the chewable form of Imodium Advanced® is not alarming. Of the 2 subjects with serious adverse events, the cerebrovascular incident was unrelated to the product. The anaphylactic reaction in the second patient may have been related, but this case is confounded by concomitant use of ibuprofen. There are 2 cases of allergic reactions that are likely related to the product, but the other reports of allergy are confounded and therefore the relationship with the product is unclear. It appears that consumers do not always understand that the tablet is supposed to be chewed. When it is chewed, many consumers suffer an unpleasant aftertaste.

Conclusion:
If bioequivalence is demonstrated, the safety profile of the chewable product is adequate to support the approval of the caplet formation. Taste perversion incidence may be reduced, as might the incidence of "dysphagia" in a caplet formulation. A better allergy warning on the label may be advisable, such as "Do not use if you have had a rash or other allergic reaction to loperamide HCl or simethicone." "Do not swallow this tablet whole," would be appropriate to add to the directions for the chewable product.

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