Review
Division of Surveillance, Research, and Communication Support

NDA #	21-229
Drug:	Omeprazole Magnesium Tablets
Sponsor:	The Procter & Gamble Co.
Identification:	Study 02255 Label Comprehension
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Reviewer:	Karen Lechter, J.D., Ph.D., HFD-410
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Overview

The results of this label comprehension study strongly suggest that the tested label does not adequately convey to consumers the product is not for episodic use and that it is only for prevention. Further, it is likely that many who take contraindicated medications and many with contraindicated conditions will believe they can take Prilosec 1 without checking with a health professional. Some of the high levels of correct responses may have been due to an artifact of the questioning by which almost all questions required responses that the product should not be used or a health professional should be consulted.

Communication Objectives

The following are the key communication objectives of the study:

1) Consumers understand the uses of the product
   a) Prilosec 1 is for prevention of frequent heartburn.
   b) Prilosec 1 is only for those who suffer heartburn two or more days a week.
2) Consumers understand who can and cannot use Prilosec 1 (warnings).
   a) Do not use if you are allergic to omeprazole.
   b) Notify your doctor if you have had heartburn for three months or longer and have not talked to your doctor about it.
   c) Do not use if you have trouble swallowing food, wheezing, a chronic cough or hoarseness, have vomited blood, black/tarry stools, chest pain, or unexplained weight loss.
   d) Do not use if you have a sudden increase of your heartburn symptoms with nausea and vomiting; chest pain; pain spreading to your arms, neck or shoulders; sweating; shortness of breath or lightheadedness.
   e) Do not use with other acid reducers.
3) Consumers understand under what conditions one must first ask their doctor or pharmacist before using Prilosec 1 (warnings).
   a) Ask a doctor or pharmacist before use if you are taking warfarin, phenytoin, diazepam, clarithromycin, itraconazole and/or ketoconazole.
   b) If pregnant or breast-feeding, ask a health professional before use.
   c) Children under 18 years of age: ask a doctor.
4) Consumers understand the condition under which Prilosec 1 can and cannot be used (warnings).

a) Stop use and ask a doctor if stomach pain continues or worsens.
b) Stop use and ask a doctor if heartburn continues or returns after using this product everyday for 14 days.

5) Consumers understand how to use Prilosec 1 safely and effectively (directions).
   a) For prevention of frequent heartburn, swallow 1 tablet with a glass of water in the morning.
   b) Take every day for 14 days.
   c) Do not continue beyond 14 days unless directed by your doctor.
   d) Do not take more than 1 tablet a day.

Methodology

Participants

There were five cohorts of adult males and females, 18 years of age and older.

1) General population adults (n=297)
2) High literate frequent heartburn sufferers (n=155)
   - above 8th grade reading level
   - experience heartburn 2 or more days a week or currently take prescription heartburn medication
3) Low literate frequent heartburn sufferers (n=162)
   - 8th grade reading level or lower
   - experience heartburn 2 or more days a week or currently take prescription heartburn medication
4) Drug interaction heartburn sufferers (n=96)
   - currently experience heartburn, have experienced it in the past 6 months, or currently take prescription heartburn medication
   - currently take warfarin, phenytoin, diazepam, clarithromycin, itraconazole, and/or ketoconazole
   - have no condition listed on the label that would prevent them from using the product or that would require them to consult a doctor or pharmacist before use, other than the drug interaction
5) Pregnant/Nursing heartburn sufferers (n=42)
   - currently experience heartburn, have experienced it in the past 6 months, or currently take prescription heartburn medication
   - pregnant or nursing
   - have no condition listed on the label that would prevent them from using the product or that would require them to consult a doctor or pharmacist before use, other than pregnancy or nursing

Procedure

Most participants were recruited in ten geographically dispersed shopping malls around the country. Participants recruited in malls were screened for qualifications. Those who qualified were taken to a facility in the mall and were interviewed. The majority of the drug interaction heartburn sufferers (Cohort 4) were recruited using advertising, screened by telephone, and asked to come to a central location for the interview. The pregnant and

nursing heartburn sufferers (Cohort 5) were recruited primarily by telephone using agency databases, and were asked to come to a central location for the interview.

All who qualified were given the Rapid Estimate of Adult Literacy in Medicine (REALM) literacy test. They then examined the label before they were asked questions about it. Non-sufferers were not asked all the questions. They were asked only about the purpose of the product, whether they could use it themselves, and they provided demographic and medical information relevant to product use. Pregnant or nursing participants were asked only about product use, whether they could use it themselves, and questions about use by pregnant and nursing women. They also provided demographic and medical information relevant to using the product. All others answered the full questionnaire. All had the label available to examine during questioning.

There were two different versions of the full questionnaire. Half of the drug interaction scenarios and half of the heartburn warning symptom questions were presented in each version to reduce the length of the questionnaire.

Recruitment Advertisement and Screening Questionnaire

Comments. An advertisement was used to recruit Cohort 4, the heartburn sufferers who are currently taking prescription medications listed on the label as requiring physician input. This advertisement listed only those classes of medications listed in the label. It is possible that the information in the advertisement, by not including other "false" medication classes, may have alerted consumers to the possibility that certain types of medications were important to the study. This may have biased the results by making participants' medications more salient to them as factors in the study, making it more likely they would answer questions about their own use of the product correctly. It would have been better to use a longer list of drug classes or to make a more general statement about taking any prescription medicines, or to say nothing about medicines. If nothing was on the advertisement about medicines, along with other questions, callers could have been asked if they took any medicines, to divert them from the true purpose of the questioning. This would not have given them specific clues about what the study was interested in, as the actual advertisement did.

Main Questionnaire

Comments. In the series of scenario questions (beginning with Q.2) about use for episodic heartburn, five questions should be answered "no" and only two "yes." It would have been better to have a more even balance so participants would not develop a nay-saying bias based on the pattern of questions. At some point, participants might realize that most questions should be answered "no." This feature of the questioning may be a possible source of bias. It is good practice to have more balance in such a series.

Q. 13 was asked only of the drug interaction cohort (Cohort 4). If, in response to the self-selection question (Q. 11), these participants answered incorrectly that they could use the product, they were asked Q. 13 in which they were provided with a list of contraindicated

drugs with their brand and generic names to help them respond. This question is troublesome for two reasons. First, consumers in retail settings would not be given a card with the contraindicated medications on it before examining the label. Second, both the generic and brand names are provided. In normal use, consumers would have to depend on their knowledge of their own medications to determine if they take a contraindicated medication. They would not have a reference list giving them the generic names for contraindicated products they might take. The results of Q. 13 are therefore of dubious value.

When scenario questions were answered incorrectly, participants were asked to give a reason for their response. It would have been better to ask the basis for all responses for two reasons. First, participants' reasons for giving the correct response may not be based on the label, and second, participants may notice that they are not always asked why they responded as they did. They may correctly conclude that the quality of their responses drives the interviewer's decision to ask for a reason, and this may provide them feedback that would affect the questioning process.

A series of 11 questions in a row (Q.15-Q.35) contains only one that should be answered affirmatively and ten that should not. This may have established a nay-saying bias that would make it more likely that responses would be correct. Correct responses may therefore be artificially inflated.

In the next series, a group of seven questions (Q.42-Q.50), all require that the person see a doctor or not use the product. A nay-saying bias could have affected these results, providing for more correct responses than would be the case if there were more balanced responses required.

Results and Discussion

Open-ended questions were scored as correct, acceptable, or incorrect. Correct responses were those that were correct initially or in a follow-up probe. Responses were acceptable if they did not reflect information on the label, but would not be incorrect product usage, such as asking a doctor when it is not necessary.

Product Purpose. In general, participants did not give full responses to the question about the purpose for product use. They either left out the idea of prevention or the idea of the necessity for frequent heartburn. When asked what the product is to be used for, only 39% of the general population responded with "prevent frequent heartburn. The literate frequent sufferers answered this question correctly 39% of the time, and the low literate frequent sufferers 36% of the time. Almost everyone else gave a partial response, even after probing, with answers such as "heartburn," "prevent heartburn," and "frequent heartburn."

Table 1. Responses to question about purpose of product.

Purpose	**General Population** (%) n=297	**Literate Frequent Sufferers** (%) n=155	**Low Literate Frequent Sufferers** (%) n=162
Complete: Prevent frequent HB	39	39	36
Incomplete: Heartburn	40	45*	24
Prevent HB	6	4	20*
Frequent or 2+ days/week HB	13	10	18
Acid reflux	2	2	2

*statistically significant difference between literacy groups at 95% confidence level

Questions about use for relief or prevention of heartburn episodes resulted in low proportions of correct responses. Approximately half of the general population believed the product was appropriate for relief and prevention of individual heartburn episodes. For three of the five questions in this area, the frequent sufferers, low and higher literacy, responded in the low to mid-sixty percent. Responses to this question indicate the label did not communicate the prevention message adequately. If there were no nay-saying response bias for this series of questions (discussed earlier), scores may have been even lower. These were all questions for which a correct response was that the product should not be used. Many participants seemed not to understand not to use the product episodically or for relief.

Table 2. Correct responses to episodic heartburn questions.

Q.	**Episodic**	**General Population** (%) n=297	**Literate Freq. Sufferers** (%) n=155	**Low Literate Freq. Sufferers** (%) n=162
2	relief	55	61*	49
3	relief	52	67	66
5	relief in freq. sufferer	48	51	59
6	prevent	54	57	63
8	prevent	61	65	65

*statistically significant difference between literacy groups at 95% confidence level

For two questions about using the product to prevent frequent heartburn, responses were generally above 80-90%. These were the two questions for which the correct response was that it was appropriate to use the product.

Table 3. Correct responses to frequent heartburn questions.

Q.	Frequent	General Population (%) n=297	Literate Freq. Sufferers (%) n=155	Low Literate Freq. Sufferers (%) n=162
4	prevent	93	94*	79
7	prevent	83	87	83

*statistically significant difference between literacy groups at 95% confidence level

Self-selection. When asked if they, themselves, could use the product, the range of correct responses in the group that should not use the product or should consult a physician varied from 41% to 91%. Of the total, 67% were correct overall. For one group, frequent heartburn sufferers with contraindicated medication, scores rose from 50% to 86% after seeing a list of the brand names of the drugs they use. However, in a purchase situation, these types of consumers would be unlikely to have access to a list of the brand and corresponding generic names. Thus, the 50% score is probably more representative of the types of decisions they would be likely to make based on the label. The highest scoring group was those who were allergic. There were only seven members of this group, so the results may not be representative. It is important to note that those who have contraindicated symptoms or who took contraindicated medication selected for themselves incorrectly at least 50% of the time.

Table 4. Responses to self-selection questions for those who should not use (Q9-14)

Participant Characteristics	Correct/Acceptable (%)	Incorrect (%)
Total (n=459)	67	33
Non HB sufferer (n=137)	80	20
Infrequent HB sufferer n=92	76	24
Frequent HB sufferer allergic to omeprazole(n=7)	86	14
Frequent HB sufferer with contraindicated symptom (n=85)	41	59
Frequent HB sufferer with contraindicated medication (n=96)	50	50
After see brand names	82	18
HB sufferers and pregnant or nursing (n=42)	91	10

Use with health conditions. Responses to scenario questions about whether individuals with particular health conditions could take the product were generally good, ranging

from 89%-91% in the general population, and from 90% to 100% in the two literacy groups. However, these questions were in a series that could have established a nay-saying bias, as mentioned earlier. These high scores may have been due, in part, to participants' realizing that almost every response should be not to use the product or to see a doctor.

Table 5. Correct/acceptable responses to scenarios about taking product with different conditions

Q.	**Condition**	**General Pop** (%) (base n)	**Literate Freq. Sufferers** (%) (base n)	**Low Literate Freq. Sufferers** (%) (base n)
15	Allergic	91 (158)	92 (155)	94 (162)
17	Heartburn 6 months; no doctor	89 (160)	95 (155)	95 (162)
18/19	trouble swallowing	89 (83)	90 (79)	95 (109)
20/21	chest pain, pain spreading to arms and shoulders, shortness of breath	94 (83)	96 (79)	95 (109)
22/23	chronic cough	89 (75)	93 (76)	94 (53)
24	black tarry stools	98 (83)	99 (79)	99 (109)
25	unexplained weight loss	96 (75)	97 (76)	100 (53)
27	heartburn worse; nausea, vomiting	98 (158)	98 (155)	96 (162)

There were very high percentages of correct responses to questions about use by pregnant and nursing women and by children. Again, these questions were in a nay-saying series.

Table 6. Use with pregnancy, nursing, children

Q.	**condition/ status**	**General Pop** (%) (base n)	**Literate Freq. Sufferers** (%) (base n)	**Low Literate Freq. Sufferers** (%) (base n)
48	breast-feeding	99 (90)	100 (81)	98 (86)
49	pregnant	98 (90)	100 (81)	99 (86)
50	age 15	96 (158)	99 (155)	96 (162)

Use with other products. Correct responses to questions about use with other products were generally very high, ranging from 91-100%. for some of these products, consumers should consult a physician or pharmacist before using Prilosec 1.

Table 7. Use with other products

Q.	Product	General Population (%) (base n)	Literate Freq. Sufferers (%) (base n)	Low Literate Freq. Sufferers (%) (base n)
28/29	other acid reducers	91 (158)	89 (155)	97* (162)
30	warfarin	98 (83)	99 (79)	98 (98)
31	phenytoin	100 (75)	100 (76)	98 (53)
34	diazepam	98 (83)	98 (79)	99 (109)
37	antibiotic clarithromycin	99 (75)	97 (76)	98 (53)
42	itraconazole	98 (42)	99 (79)	98 (109)
43	ketoconazole	97 (75)	100 (76)	100 (53)
35/36	Tylenol	93 (158)	97 (155)	93 (162)

*statistically significant difference between literacy groups at 95% confidence level

There seemed to be very good scores for what actions to take while using the product, including when to stop taking it, how long to use it, and when and how much to dose. However, some of these questions (33, 44, 46, 47) were in a nay-saying series.

Table 8. Actions During Use

Q.	Situation	General Pop Correct/ Acceptable (%) (base n)	Literate Freq. Sufferers Correct/Acceptable (%) (base n)	Low Literate Freq. Sufferers Correct/Acceptable (%) (base n)
44	stomach pain worse	100 (158)	100 (155)	100 (162)
47	more than 14 days	96 (158)	96 (155)	96 (162)
33	more than 14 days	89 (158)	94 (155)	93 (162)
38	time to take dose	85 (158)	88 (155)	83 (162)
39	# tablets daily	98 (158)	99* 155)	89 (162)
46	take an extra for episodic prevention	97 (158)	98 (155)	94 (162)
40	dosing frequency	98 (158)	98 (155)	88 (162)
41	how long take	94 (158)	95* (155)	82 (162)

*statistically significant difference between literacy groups at 95% confidence level

Because this questionnaire overwhelmingly contained questions that required responses that the product should not be used or that a doctor or pharmacist should be consulted, a strong nay-saying bias may have been responsible for the very high scores in these series. Thus, the scores are of questionable reliability and validity. It would have been much better to have more questions that did not preclude taking the medication or taking the other action that was mentioned in some of the questions.

Conclusion and comparison of tested label with proposed label

These results suggest that the tested label does not adequately convey to consumers the following:

- the product is not for episodic use and
- the product is only for prevention

Based on results of the self-selection question, it is not clear consumers will understand that the product should not be used with certain other medications or with certain health conditions unless one checks with a doctor or pharmacist.

Some of the high levels of correct responses to the scenario questions may have been due to an artifact of the questioning by which almost all questions required responses that the product should not be used or a health professional should be consulted.

If one compares the tested label with the proposed label for these areas of sub-optimal communication, one finds that there has been little or no change to the label to improve communication of some of these messages. In the proposed label, the prevention message is the same, with added wording about preventing symptoms and 24 hour coverage. The tested label says "for **prevention** of frequent heartburn." The proposed label says "for **prevention** of the symptoms of frequent heartburn for 24 hours." There is nothing on either label to indicate that episodic use is inappropriate, other than the directions to use it every day for 14 days. This message is the same on the tested and proposed labels.

The proposed label lists only three products that require consultation with a health professional, while the tested label had six. The section in the tested label that said "Do not use" contained lists of multiple conditions under two bullets that require the person consult a physician. In the proposed label, these are broken into five bullets, which may be easier to read and to process cognitively.

The "do not use" section of the tested label has been changed to "Ask a doctor before use if you have" in the proposed label. Furthermore, some conditions in the tested label are not in the proposed label. These include chronic cough or hoarseness, vomiting blood, black tarry stools, and sudden increase in symptoms with nausea and vomiting. The proposed label has five bullets in this section, while the tested label had only three covering more conditions. The resultant label section in the proposed label is shorter and easier to read and process. However, it has not strengthened the message about prevention or that it is not for episodic use. It is improved regarding use with other

medicines because that section is shorter. It is improved regarding use with certain medical conditions because that section is shorter and has more bullets.

Testing of the proposed label is necessary to conclude whether it communicates better than the tested label in critical areas.