DDMAC REVIEW

AUG 16 2000

NDA #	21-229
Drug:	Omeprazole Magnesium Tablets
Sponsor:	The Procter & Gamble Co.
Identification:	Study 3358 Label Comprehension
Date of Document:	January, 1998
Reviewer:	Karen Lechter, J.D., Ph.D., HFD-42
Review Completed:	August 16, 2000

Attached is a detailed review of the label comprehension study for omeprazole magnesium tablets. The attached review was written by DDMAC staff in 1998 in response to the study report submitted under IND [redacted] The IND label comprehension report is identical to the one submitted under this NDA.

The tested label was changed in content and organization after the label comprehension study. The labels used in the actual use studies differed substantially from the one studied for comprehension. The label proposed as the final draft for the NDA is similar, but not identical, to the actual use study labels. Therefore, at this point, there is no label comprehension study that evaluates comprehension of the most recent draft of the label.

The attached detailed review from 1998 makes the following general points:

- The most significant concern raised by this study was the potential for use by persons with conditions that require physician consultation according to the label. A substantial proportion (74%) of persons who should contact a physician before use said they would use the product, and did not mention contacting a physician.

  As a result of these findings about use by persons who should contact a physician, the sponsor conducted an addendum study. The addendum study was designed to determine whether the wording of the question about using the product accounted for the high incorrect rate among persons who should have consulted a physician before use. The results of the addendum study suggest that the wording of the question did, to some extent, cause some of the incorrect responses. However, when the question was worded in a better way, incorrect response rates were still high among this group (43% incorrect using original question; 31% incorrect using revised wording).

  Further questioning resulted in lower rates for incorrect responses. However, these additional questions were leading. The agency believes the responses to the leading questions do not reflect normal consumer understanding of the label. Therefore, the agency does not rely on responses to these questions as indicators of comprehension. Furthermore, the sample size for this study was small—only 29 participants saw the newly worded initial question and 29 saw the question as it was worded in the main study. As a result of the findings in both studies, the agency is concerned that

DDMAC REVIEW

IND #	[redacted]
Drug:	Omeprazole Magnesium Tablets
Sponsor:	The Procter & Gamble Co.
Identification:	Serial: 014
Date of Document:	February 27 , 1998
Reviewers:	Karen Lechter, J.D., Ph.D., HFD-40 Kathryn Aikin, Ph.D., HFD-40
Review Completed:	June 3, 1998

Two studies are included in this submission--the original study and an addendum study designed to determine whether some results in the original study were due to the way in which the questions were asked.

ORIGINAL STUDY (Study 1)

Study Objectives

Objectives for Self-Selection

- Consumers understand that this product is intended for use by adults 12 years of age or older for the prevention and/or relief of heartburn, acid indigestion, and sour stomach.

Objectives for Product Use

- Consumers understand not to use or to ask a health professional before using if they:
  - Have trouble swallowing
  - Are taking warfarin, phenytoin, or diazepam
  - Are pregnant or breast-feeding
- Consumers understand that they should stop using the product and ask a doctor if:
  - Their stomach pain does not go away
  - They need to use 1 tablet a day for more than 14 days in a row
- Consumers understand how to use the product to PREVENT symptoms on days they expect to have symptoms
- Consumers understand how to use the product to PREVENT symptoms before consuming food and/or beverage they expect to cause symptoms
- Consumers understand how to use the product to RELIEVE symptoms
- Consumers understand that the product should be used only once a day (1 tablet in 24 hours)
- Consumers understand what to do in case of an overdose

Methodology

Participants

There were 504 participants, males and females age 18 and older, in 4 cohorts:

1. General population of men and women 18 years or older, who believe they suffer from heartburn, acid indigestion or sour stomach ("Sufferers"; n=197).
2. General population of men and women 18 years or older who do not suffer from heartburn, acid indigestion, or sour stomach ("Non-Sufferers"; n=104).
3. Men and women sufferers and non-sufferers who are of a 7th-8th grade reading level or lower, as determined by the REALM (Rapid Estimate of Adult Literacy in Medicine) test ["Low Literacy"; n(sufferers)=101; n(non-sufferers)=54]. Some of these participants were from the general population and overlapped with Cohort 1; some were specially recruited.
4. Men and women who take one or more of the following prescription drugs: diazepam, phenytoin, warfarin; and female sufferers who are pregnant or breast-feeding ("Special Population"; n=117).

Of the 504 participants, 189 were male and 315 female. One hundred eighty (180) were under 61 years of age; 324 were 61 years of age and older.

Materials

Participants were shown a carton for Prilosec.

Three questionnaires and a literacy test were used:

Screening Questionnaire

Self-Selection Questionnaire (asks what the product is used for; whether the participant would use the product to prevent or relieve heartburn; what persons should do if they have heartburn and wanted to use Prilosec and were taking phenytoin, diazepam, or warfarin, or were women who are breast feeding, or persons who have trouble swallowing)

Product Use Questionnaire (label comprehension)

REALM Test (Rapid Estimate of Adult Literacy in Medicine)

Questions on the Self-Selection and Product Use questionnaires included both open-ended and closed-ended questions.

Procedure

Potential participants in the two general cohorts were recruited at 10 sites, in shopping malls throughout the country. To recruit the necessary number of participants for each cohort, additional recruitment was conducted at convenience stores, grocery stores, literacy centers, community centers or other locations that provided the desired demographic characteristics for the study. Cohort 4 was recruited primarily through advertising and existing databases.

Potential participants were screened to determine whether or not they qualified to participate and to help assign them to the appropriate cohorts. The REALM test was then administered. Participants were given a copy of the carton for the product and were asked to read it. They were then asked if they would personally use the product, if they would ask a doctor/health

professional first, or would not personally use it. They were asked why they gave the answers they did.

At this point, non-sufferers and persons in the Special Population cohort were asked demographic questions and were dismissed, as were sufferers who indicated they would not use the product. Only sufferers who indicated they would use the product or would ask a doctor before use continued beyond this point.

After reading the carton label as they would read it in a retail store, the remaining sufferers were asked further label comprehension questions by the interviewer. They were permitted to refer back to the label to answer questions, if necessary. They were then asked a series of demographic questions. The package insert was not studied.

Results

Table 1 presents a summary of questions with relatively high correct/acceptable response rate. The following tables separately address the remainder of the questions.

Table 1.
Responses to Questions with a Relatively High Correct/Acceptable Response Rate.

Question	Respondents	Response			
		Correct	Acceptable	Correct/Acceptable	Incorrect
Q2. What is Prilosec 1 used for?	Sufferers	99.5%	--	99.5%	2.0%
	Non-Sufferers	98.1%	--	98.1%	1.9%
	Low Literacy Sufferers	100%	1.0%	100%	3.0%
	Low Literacy Non-Sufferers	96.3%	1.9%	96.3%	3.7%
	Special Condition	100%	0.9%	100%	3.4%
Q5. You suffer from seizures and are taking a medicine called Phenytoin to help control your seizures. You also routinely suffer from heartburn several times a week. You have just heard about this new product, Prilosec 1 for the prevention and relief of heartburn. If you were the person described in this situation and you wanted to use Prilosec 1 to prevent or treat your heartburn, what would you do now?	Sufferers	84.8%	8.1%	92.9%	6.1%
	Non-Sufferers	79.8%	11.5%	89.4%	9.6%
	Low Literacy Sufferers	81.2%	2.0%	83.2%	9.9%
	Low Literacy Non-Sufferers	87.0%	11.1%	92.6%	3.7%
	Special Condition	83.8%	7.7%	89.7%	9.4%
Q6. You had a baby 6 weeks ago and you are breastfeeding the baby. You are currently suffering from heartburn several times a week. If you were the woman described in this situation and you wanted to use Prilosec 1 to prevent or treat your heartburn, what would you do now?	Sufferers	90.8%	6.7%	97.5%	1.7%
	Non-Sufferers	84.7%	10.2%	94.9%	--
	Low Literacy Sufferers	93.5%	3.2%	96.8%	1.6%
	Low Literacy Non-Sufferers	96.8%	3.2%	100%	--
	Special Condition	89.9%	10.1%	96.6%	2.2%

Question	Respondents	Correct	Acceptable	Correct/Acceptable	Incorrect
Q8. You have been using Prilosec 1 for 3 days to treat your heartburn. You have started to have stomach pain that does not go away. You are still having heartburn symptoms. With this situation in mind, and based on the label you read, what should you do now?	Sufferers	98.8%	1.2%	98.8%	1.2%
	Low Literacy Sufferers	95.8%	1.4%	95.8%	1.4%
Q9. You are currently a few months pregnant. The pregnancy has apparently caused you to have an upset stomach and frequent heartburn. If you were the woman described in this situation and you wanted to use Prilosec 1 to prevent or treat your heartburn, what would you do now?	Sufferers	92.2%	5.9%	98.0%	--
	Low Literacy Sufferers	85.1%	6.4%	91.5%	2.1%
Q11. What should you do in case of an overdose of Prilosec 1?	Sufferers	92.7%	1.2%	93.3%	6.1%
	Low Literacy Sufferers	94.4%	--	94.4%	4.2%
Q12. Your 10-year old child ate pizza for lunch, and is now complaining of symptoms that you believe to be heartburn. Prilosec 1 has worked well for you, and you would like to give it to your child. Thinking about this situation and the label you read, what should you do now?	Sufferers	61.0%	32.3%	91.5%	3.7%
	Low Literacy Sufferers	72.2%	18.1%	88.9%	8.3%
Q14. Your doctor has recently prescribed warfarin (also known as Coumadin- a blood thinning drug) for you to take on a daily basis. You have also been experiencing heartburn lately and you would like to treat and prevent heartburn by using Prilosec 1. If you were the person described in this situation and you wanted to use Prilosec 1 to prevent or treat your heartburn, what would you do now?	Sufferers	87.2%	7.9%	95.1%	3.0%
	Low Literacy Sufferers	90.3%	2.8%	93.1%	2.8%

Question	Respondents	Correct	Acceptable	Correct/Acceptable	Incorrect
Q16. You went out for dinner and had chili, tortilla chips and a cola. You are ready to go to bed but you have a bad case of heartburn. You want to treat this heartburn with Prilosec 1. With this situation in mind and based on the label you read, how many tablets of Prilosec 1 will you take, if any?	Sufferers	94.5%	--	96.3%	2.4%
	Low Literacy Sufferers	88.9%	--	90.3%	2.8%
Q20. Your doctor has prescribed Diazepam (also known as Valium, an anxiety-reducing drug) for you to take on a regular basis. You have also been experiencing some heartburn lately and would like to take Prilosec 1 to prevent and treat your heartburn. Thinking about the label you read, and this situation, would it be OK or NOT OK for you to take Prilosec 1?	Sufferers	--	--	88.4%	5.5%
	Low Literacy Sufferers	--	--	90.3%	4.2%

The results indicate that, in general, respondents have a fairly good understanding of what Prilosec 1 is to be used for, that persons using Phenytoin and nursing mothers should not use it without consulting a doctor, and that a doctor should be consulted if heartburn pain does not go away. However, it appears that certain information may be misinterpreted, especially by individuals who should consult a physician before using the product. Responses to questions that may indicate misinterpretation of label information are summarized separately below.

Table 2.
Responses to Question 4a: **If you wanted to relieve heartburn, would you use Prilosec 1 yourself?**

	Response		
Respondents	Yes	No	Don't Know
Sufferers	76.1%	12.7%	11.2%
Non-Sufferers	73.1%	20.2%	6.7%
Low Literacy Sufferers	67.3%	17.6%	14.9%
Low Literacy Non-Sufferers	66.7%	22.2%	11.1%
Special Condition	74.4%*	21.4%	4.3%

*incorrect

A large number of Special Condition respondents (approximately 75%) who should consult a physician before using Prilosec 1 appear not to understand that they should not use the product (including those who indicated "don't know").

Table 3.
Responses to Question 7: **You have trouble swallowing. You also routinely suffer from heartburn. If you were the person described in this situation and you wanted to use Prilosec 1 to prevent or treat your heartburn, what would you do now?**

	Response			
Respondents	Correct	Acceptable	Correct/Acceptable	Incorrect
Sufferers	69.5%	8.1%	77.6%	20.3%
Non-Sufferers	72.1%	7.7%	79.8%	15.4%
Low Literacy Sufferers	77.2%	2.0%	79.2%	13.9%
Low Literacy Non-Sufferers	75.9%	11.1%	87.0%	11.1%
Special Condition	74.4%	11.1%	85.5%	14.5%

Between 11% and 20% of respondents in all conditions reported incorrectly that they would use the product if they had trouble swallowing. Based on this percentage, it is possible that the swallowing warning is either unclear or is being misinterpreted.

Table 4.
Responses to Question 10: **You have been using Prilosec 1 to prevent your heartburn symptoms every day for the last 2 weeks in a row. You are pretty sure your heartburn will come back if you stop taking the medicine. Prilosec 1 has been working well for you and you want to continue to use the product. Again, thinking about this situation and based on the label you read, what should you do?**

	Response			
Respondents	Correct	Acceptable	Correct/Acceptable	Incorrect
Sufferers	78.7%	4.9%	83.6%	14.0%
Low Literacy Sufferers	79.2%	1.4%	80.6%	12.5%

A majority of respondents understood that they should not use Prilosec 1 continuously for more than 2 weeks. Approximately 12% of the Low Literacy Sufferers and 14% of the entire Sufferer respondent population incorrectly indicated that they would continue to use Prilosec 1 after two weeks.

Table 5.
Responses to Question 13a: **You expect to have a very stressful day at work. You usually get heartburn on stressful days like this. You want to take Prilosec 1 to prevent your heartburn on this day. Thinking about this situation, when is the best time to take Prilosec 1?**

	Response			
Respondents	Correct	Acceptable	Correct/Acceptable	Incorrect
Sufferers	51.2%	30.5%	81.7%	19.5%
Low Literacy Sufferers	54.2%	26.4%	80.6%	16.7%

The correct/acceptable totals are relatively high; however, it is interesting to note the disparity in correct (51% for Sufferers, 54% for Low Literacy Sufferers) and acceptable (31% for Sufferers, 26% for Low Literacy Sufferers) responses in this question, compared to others. Approximately 20% of Sufferers and 17% of Low Literacy Sufferers incorrectly indicated the time at which they should take Prilosec 1 to prevent heartburn on a stressful day. Of those who responded incorrectly, 12.8% of the Sufferers and 9.7% of the Low Literacy Sufferers indicated they would take Prilosec 1 when symptoms first begin. Although taking Prilosec 1 in this manner is consistent with the directions to relieve heartburn, it is incorrect for prevention of symptoms.

Table 6.
Responses to Question 15a: **You are going out for pizza and cola with friends. You expect to start eating at 7:30 pm. Pizza and cola almost always give you heartburn. You would like to prevent these heartburn symptoms by using Prilosec 1. Based on your reading of the label, what is the best time for you to take Prilosec 1 in order to prevent heartburn symptoms?**

	Response			
Respondents	Correct	Acceptable	Correct/Acceptable	Incorrect
Sufferers	78.7%	4.9%	83.6%	11.0%
Low Literacy Sufferers	70.8%	2.8%	73.6%	19.4%

A majority of respondents understood the correct time to use Prilosec 1 to prevent heartburn symptoms in this situation. Approximately 19% of the Low Literacy Sufferers and 11% of the entire Sufferer respondent population incorrectly indicated the time at which Prilosec 1 should be taken to prevent heartburn in this situation. Among the Sufferers, 3% indicated they would take Prilosec 1 first thing in the morning and 2.4% indicated they would take it just before eating. Among Low Literacy Sufferers, 4.2% indicated they would take it just before eating, and 4.2% when symptoms start.

Table 7.
Responses to Question 17a: **You decide to take a Prilosec 1 at 10:30 pm for the heartburn caused by the chili, tortilla chips and cola you had earlier this evening. The next morning, you think you may have heartburn sometime that day because you are going out for pizza at lunch. You would like to take Prilosec 1 again to prevent heartburn. Would it be OK or NOT OK for you to take another Prilosec 1 tablet to prevent heartburn?**

	Response		
	Question 17a.		Question 17b. **Why do you say that?**
Respondents	Correct	Incorrect	Most frequent incorrect responses*
Sufferers	(83.5%)	(14.6%)	It's two different days (19%) Will relieve/prevent heartburn (15%)
Low Literacy Sufferers	(73.6%)	(22.2%)	Wouldn't hurt/it's ok (21%) Will relieve/prevent heartburn (16%)

*Base=Number of respondents who provided an incorrect answer

Approximately 15% of the Sufferers and 22% of the Low Literacy Sufferers incorrectly indicated that it would be OK for them to take another Prilosec 1 within 24 hours of their previous dose. Of the participants who incorrectly stated whether it would be OK for them to take Prilosec 1 under these circumstances, 19% of the Sufferers responded that it was two different days, and 21% of the Low Literacy Sufferers responded that it wouldn't hurt them to take the drug.

Table 8.
Responses to Question 18a. **You took one Prilosec 1 tablet this morning at 7:00 am to prevent heartburn symptoms throughout the day. You went out for dinner, had Mexican food and now at 8:00 pm you have heartburn. Would it be OK or NOT OK for you to take another Prilosec 1 tablet to treat this 8:00 pm episode of heartburn?**

	Response		
	Question 18a.		Question 18b. **Why do you say that?**
Respondents	Correct	Incorrect	Most frequent incorrect responses*
Sufferers	(84.1%)	(14.0%)	Because a whole day has passed/enough time has passed (27%) It has been 10 to 12 hrs/more than 12 hrs (15%)
Low Literacy Sufferers	(80.6%)	(18.1%)	It has been 10 to 12 hrs/more than 12 hrs (29%) It is an acid reliever/heartburn reliever (29%) Can take in am and pm/twice a day (14%)

*Base=Number of respondents who provided an incorrect answer

Approximately 14% of the Sufferers and 18% of the Low Literacy Sufferers incorrectly indicated that it would be OK for them to take another Prilosec 1 within 24 hours of their previous dose.

Of the participants who incorrectly stated whether it would be OK for them to take Prilosec 1 under these circumstances, 27% of the Sufferers responded that a whole day had passed, and 29% of the Low Literacy Sufferers responded that it had been 10 to 12 hours since the last dose.

Table 9.
Responses to Question 19a: **Your doctor has prescribed Prozac (an anti-depressant drug) for you to take on a regular basis. You have also been experiencing some heartburn lately and would like to take Prilosec 1 to prevent and treat your heartburn. Keeping this situation in mind, would it be OK or NOT OK for you to take Prilosec 1?**

	Response		
	Question 19a.		Question 19b. **Why do you say that?**
Respondents	Correct	Incorrect	Most frequent incorrect responses*
Sufferers	(35.4%)	(53.0%)	Consult doctor/pharmacist first (52%) Should not take with other medications (18%) Might cause drug interaction (13%)
Low Literacy Sufferers	(37.5%)	(55.6%)	Consult doctor/pharmacist first (38%) Might cause drug interaction (20%) Don't know (18%) Should not take with other medications (13%)

*Base=Number of respondents who provided an incorrect answer

A slight majority of respondents in both the Sufferer and Low Literacy Sufferer groups responded incorrectly that it would not be OK to use Prozac with Prilosec 1. Of those who responded incorrectly, 52% of the Sufferers and 38% of the Low Literacy Sufferers indicated that they would consult a doctor or pharmacist first before taking the two drugs together.

Table 10.
Responses to Question 21a: **You are having a late-night episode of heartburn. You cannot remember if you took a Prilosec 1 tablet earlier in the day. You would like to take a Prilosec 1 to help relieve your heartburn. If you were the person described in this situation, would it be OK or NOT OK for you to take Prilosec 1?**

	Response		
	Question 21a.		Question 21b. **Why do you say that?**
Respondents	Correct	Incorrect	Most frequent incorrect responses*
Sufferers	(78.0%)	(18.9%)	To relieve my heartburn (25%) Would be ok (14%)
Low Literacy Sufferers	(81.9%)	(15.3%)	Probably did not take earlier since it lasts 24 hrs (23%) To relieve my heartburn (15%) Wait- time might not be right (15%)

*Base=Number of respondents who provided an incorrect answer

A majority of respondents correctly indicated that they should not take another Prilosec 1 if there was a possibility they had taken one earlier in the day. However, approximately 19% of the Sufferers and 15% of the Low Literacy Sufferers incorrectly responded that they could take another dose if they couldn't remember taking one earlier. Of those who responded incorrectly, 25% of the Sufferers reported that it would relieve their heartburn, and 23% of the Low Literacy Sufferers reported that they probably didn't take Prilosec 1 earlier in the day since it lasts 24 hours.

Comments

Comments on the Questionnaire

Of the three questions regarding use of Prilosec with concomitant prescription medications, one question (Q 19a) could be answered correctly that the two products could, indeed, be used together. The results showed that a majority (53.7%) of sufferers incorrectly stated Prilosec should **not** be used by a person taking Prozac. This question came after a series of questions that asked what a person should do or whether it was "okay or not okay" to take Prilosec in a variety of situations, all of which were correctly answered that the product should not be used or a doctor should be consulted. Interspersed among these questions were 5 that asked about the appropriate amount to take or the time when the drug should be taken. One other question asked what to do about overdosing. There were two additional questions after the Prozac question asking whether it was appropriate to take Prilosec in the situation described. These, also, would be correctly answered by saying the product should not be used. Therefore, all questions in this series about the appropriateness of use other than the Prozac question should have been answered correctly by a response that the product should not be used or that a doctor should be consulted.

It is possible that the large proportion of incorrect responses to the Prozac question was due to the effect of prior questions and answers that established a response bias--the expectation that all such questions should be answered that the product should not be used or a doctor should be consulted. This calls into question whether or not participants truly understood when the product should not be used. This problem could have been avoided if more questions were posed for which the correct response was that the drug could be used. It is also possible that participants erred on the side of caution--it is prudent to ask a physician about drug interactions. However we cannot determine from these results whether participants answered as they did due to a response bias or a tendency to consult a doctor when considering drug interactions, or for some other reason.

In the series of questions that posed a variety of scenarios and asked participants whether it would be "OK or NOT OK for you to take" Prilosec in a variety of hypothetical situations, only those participants who answered incorrectly were asked to give reasons for their responses. Those who responded correctly were not asked why they answered as they did. It would have been useful to know whether participants who gave the correct response did so for appropriate reasons. Further, it is possible that being asked why a response was given for only some responses served as a cue about the question--that it had been answered incorrectly. This possibility probably did not have a large effect, as most participants answered most questions correctly, so the cue would not have been given often, and, further, the cue was given after the question was answered. However, use of the question for incorrect responses may have served as feedback to the participants as to how they were doing, and may have affected their performance.

Comments on the Results

The results indicate that respondents have a fairly good understanding of the information in the label. However, it appears that certain information may be misinterpreted, especially by individuals who have contraindicated conditions.

Participants in all cohorts scored relatively high on a number of questions. They understood what Prilosec is used for and that persons taking phenytoin, diazepam, or warfarin, and breast-feeding or pregnant women should consult a doctor before use or not use it at all. In reading the scenarios of hypothetical situations, they understood that they should consult a doctor if stomach pain does not diminish. They knew what to do in case of overdose and that Prilosec should not be used for children. They understood how much to take in a dose.

The results were moderate, but not stellar (in the 80% range) for several questions, including the following: what to do if you have trouble swallowing, and what to do after 14 days of use. Based on the percentage of respondents who answered incorrectly, it is possible that the swallowing warning and the time limit on continuous dosing are either unclear or are being misinterpreted.

There were several questions about the timing of dosing that also scored in the 80% range. These included the best time to take it before a meal you expect to cause problems, or on a day you expect to be stressful, whether it can be taken the morning after an evening dose, and

whether it can be taken in the evening after a morning dose. The responses to questions dealing with 24 hour dosing may reflect participants' problems with understanding this concept. Despite the fact that the label said not to take more than 1 tablet every 24 hours, some of those who had answered incorrectly on timing questions gave as reasons the fact that "a whole day has passed/ enough time has passed" or "it has been 10 to 12 hours/ more than 12 hours," or it "wouldn't hurt/ it's okay," or "it's two different days." The labeling for these timing items should be considered for revision.

Of those who responded incorrectly to questions about when to take the medication if one expects a stressful day, and when it should be taken before a meal that one expects to cause problems, most stated that it should be taken when symptoms begin. This response is correct for relief, but not prevention of symptoms. This may reflect a misinterpretation of the label or confusion on the part of respondents between "prevention" and "relief" of symptoms.

One question that was answered correctly by only 36% overall was the one dealing with the use of Prilosec with Prozac. As discussed earlier, these results may have been due to caution on the part of the participants, or it may have been an artifact of the design of the questionnaire. Fortunately, incorrect responses to this question would result in no public health hazard, but would merely deter some potential users from taking the product.

For all of the questions, for the most part, responses were similar among the cohorts. However, for the question about when to dose before a meal that may be a problem, the low literate sufferers were incorrect more often than the general group of sufferers. They also scored lower on whether they could take Prilosec the morning after an evening dose. Thus, the low literate group appeared to have more problems in determining the correct timing of dosing than the other participants.

The package insert was not tested in this study, so we cannot determine whether that part of the labeling might pose communication problems.

Conclusions--Study 1

Most questions were answered correctly by all cohorts. The low literate cohort had some problems in determining timing of dosing, and there were several questions that suggest that modifications to the label should be considered.

Of most concern in these results is the possibility that persons who should seek medical advice before use may not do so. The Addendum Study was designed to shed light on this issue.

ADDENDUM STUDY (Study 2)

Study Objectives

This study was conducted to determine whether the high proportion of persons in the Special Population Cohort who incorrectly responded that they would use the product was a result of the wording of the question, rather than a true reflection of whether or not they believed they would use the product.

Communication Objectives

Consumers understand when not to use or when to ask a health professional before using, as follows:

- Ask a doctor before use if taking warfarin, phenytoin, or diazepam
- Ask a health professional before use if pregnant or nursing

Methodology

Participants

Participants were 60 men and women who were pregnant or nursing or who were taking one or more of the following drugs: diazepam, phenytoin, or warfarin. Recruitment was done through a database or referrals. All were recruited from the same geographic area. Forty-nine (49) were under age 65; 11 were 65 or older. Two of these were eliminated from the analysis because they were using Prilosec along with at least one contraindicated medication.

Materials

A screening questionnaire was used to determine sex, age, suffer/non-sufferer, medical conditions, and prescription product use. The REALM test was used to determine literacy.

There were two versions of the questionnaire. Version 1 included some questions identical to those tested in the original study, to serve as a control, and also included more probing questions. Version 2 started off with a probing question ("Would it be okay for you, personally to use Prilosec 1 yourself or not?"). This was followed by the same more probing questions asked in Version 1.

The questionnaires asked the following questions:

2. What is Prilosec 1 used for?

3a. (version 1) If you wanted to prevent heartburn, would you use Prilosec 1 yourself?
(version 2) If you were a heartburn sufferer and you wanted to prevent heartburn, would it be okay for you, personally, to use Prilosec 1 yourself, or not?

3b. Why do you say that?

4a. (version 1) If you wanted to relieve heartburn, would you use Prilosec 1 yourself?
(version 2) If you were a heartburn sufferer and you wanted to relieve heartburn, would it be okay for you to use Prilosec 1 yourself, or not?

4b. Why do you say that?

5a. Is there anything you would do prior to taking this product, or not?
5b. Why do you say that?

6a. Considering your current health and medications you are currently taking, would it be necessary for you to contact a doctor prior to using this product yourself, or not?
6b. Why do you say that?

7a. Are you currently taking any of the following medications? Diazepam, warfarin, phenytoin
7b. Are you currently taking any of the following medications? Valium, coumadin, dilantin

8. When taking a new drug, how likely are you to read the warning label for drug interactions?
Extremely likely, very likely, somewhat likely, not at all likely

9. In general, how concerned are you about drug interactions with different medications?
Extremely concerned, very concerned, somewhat concerned, not at all concerned

10. In general, how safe do you consider over-the-counter medications?
Extremely safe, very safe, somewhat safe, not at all safe

11-15. Demographic questions

Procedure

After completing a screening questionnaire by telephone, potential participants who met the criteria for the study were invited to participate in the label comprehension study. At the study site, after completing the REALM literacy test, participants were given the carton to read. Half of the participants were then given Version 1 of the questionnaire; half were given Version 2.

If participants answered questions 3a and 4a (would you use?) with "no," they were asked no further questions other than the demographic items (11-15). If they responded that they would use the product for either prevention or relief, they were asked question 5a (would you do anything prior to use?). If they correctly responded that they would ask a doctor before use, they were asked no more use questions. If they did not respond that they would ask a doctor before use, they were asked questions 6a and 6b which asked directly whether they would contact a doctor prior to use.

Results

An addendum study was conducted with Special Condition respondents; those currently taking Diazepam, Phenytoin, or Warfarin, and pregnant or nursing women. Two versions of the questionnaire were used to evaluate the possibility that the results of Study 1 in this population were due to wording effects, rather than comprehension of label information.

Table 12.
Responses to Questions 4a and 4b

	Response		
	Question 4a.		Question 4b. **Why do you say that?**
Questionnaire	Correct	Incorrect	Most frequent incorrect responses*
Version 1: If you wanted to relieve heartburn, would you use Prilosec 1 yourself?	n=9 (31.0%)	n=19 (65.5%)	Safe for children/safe for adults (16%) It works/feel better fast (16%)
Version 2: If you were a heartburn sufferer and you wanted to relieve heartburn, would it be OK for you to use Prilosec 1 or not?	n=17 (58.6%)	n=12 (41.4%)	Relieves heartburn (17%) Just to try it/try something new (17%)

*Base=Number of respondents who provided an incorrect answer

As with Question 3a, a larger percentage of Special Condition respondents answering Version 2 of the questionnaire correctly understood that they should not use Prilosec 1 (59%), compared to special population respondents answering Version 1 (31%)

Table 13.
Responses to Questions 5a: **Is there anything you would do prior to taking this product for yourself, or not?**

	Response			
	Question 5a.			Question 5b. Why do you say that?
Questionnaire	No	Ask doctor	Other (ns)	Most frequent incorrect responses*
Version 1	n=5 (29.4%)	n=5 (29.4%)	n=5 (29.4%)	Read directions/warnings (42%) Don't know (33%)
Version 2	n=4 (36.4%)	n=1 (9.1%)	n=6 (54.5%)	Don't know (40%) Eat crackers/food before taking (30%)

*Base=Number of respondents who provided an incorrect answer

Respondents who have answered previous questions correctly have been dropped from the survey at this point. The n's in each cell continue to dwindle as the questionnaire progresses. Of those who remain, slightly more Special Condition respondents in Version 2 incorrectly indicate that they would not do anything before taking Prilosec 1 (36%), compared to Version 1 (29%). Given the small cell n's, this difference may not be meaningful.

Table 14.
Responses to Questions 6a: **Considering your current health and medications you are currently taking, would it be necessary for you to contact a doctor prior to using this product yourself, or not?**

	Response		
	Question 6a.		Question 6b. **Why do you say that?**
Questionnaire	Correct	Incorrect	Most frequent incorrect responses*
Version 1	n=6 (50.0%)	n=5 (41.7%)	Don't know (67%) Warning labels don't apply to me (37%)
Version 2	n=5 (50.0%)	n=5 (50.0%)	Don't know (60%) Warning labels don't apply to me (20%)

*Base=Number of respondents who provided an incorrect answer

Slightly more Special Condition respondents answering Version 2 incorrectly indicated that it would not be necessary for them to contact a doctor prior to using Prilosec 1 (50%), compared to respondents answering Version 1 (42%). However, as noted above, this difference may not be meaningful.

The results were also analyzed with the 9 participants who did not realize the were taking a contraindicated medication removed from the analysis. This resulted in slightly higher correct percentages for all questions.

Comments

The use of a second study to determine whether or not responses in the first study were due the wording of the question was an appropriate action to take. However, the questionnaire in the second study contains increasingly leading questions about whether or not the participant would use the product without consulting a physician. The analysis of what the results mean in this context are unclear. It does appear, however, that while part of the findings in the first study may be explained by the wording of the questions, the wording is not the entire explanation for the results.

It should be noted that the numbers receiving each version of these questions is relatively small--29 for each version and that each subsequent question was answered by fewer persons than the previous questions, as those who responded correctly were asked no more questions.

The results showed that 35% of those who received Version 1 of questions 3a (would you use for prevention?) and 4a (would you use for relief?) correctly indicated they would not use the product. These questions correspond to the wording in the original study, in which 21% of persons in the special population said they would not use the product. Responses to revised questions 3a and 4a in Version 2 of the questionnaire resulted in 69% saying they would not use

the product for prevention or would consult a doctor before using it; 59% stated they would not use it for relief, or would consult a doctor first. Thus, it appears that participants can identify the indications, but they seem to be unaware that their own condition is contraindicated.

Interestingly, it should be noted that the wording of the Version 2 questions for prevention (3a) and relief (4a) was not parallel. In the former case, the question was about prevention. It asked "...would it be okay for you **personally** to use Prilosec 1 yourself...?" In the latter case, dealing with relief, the question was "...would it be okay for you to use Prilosec 1 yourself...?" The results showed more correct responses when the question included the word "personally" (70%) than when it did not (59%). These differences could have been due to the word "personally," or to different perceptions about the use of Prilosec for prevention and relief, natural variation, or some other reason. However, these results may suggest that the more the participants personalized the question to themselves, the more likely they were to respond correctly. This hypothesis would require further testing, and might be worth exploring in future research.

Participants who had not indicated that they would not use the product continued on to respond to question 5a, which asked if they would do anything prior to using the product. This question was the same for both versions. At this point, only 26 participants remained in the study, 15 from Version 1 and 11 from Version 2. In response to this question, 6 gave a correct response of consulting a doctor (21%). They exited the study and the remaining 22 participants were asked directly if it would be necessary for them to consult a doctor prior to use. Half of these (11) correctly stated that they should do so. Here, it is unclear whether participants are unaware of their contraindicated condition (although this seems unlikely, given the leading nature of the question), or whether they believed that warnings in general do not apply to them.

Of the remaining 11 participants, 9 did not know if they were taking any of the active ingredient medications. At this point, there should not have been any pregnant or nursing women left in the group, as they had all answered correctly by the time question 6 was asked.

The sponsor has suggested that these results indicate that after all the questions are asked, 81% of those in the high risk group eventually answered correctly. However, it may be inappropriate to use responses to all of the questions when drawing conclusions about the effectiveness of the label.

The use of the reworded questions 3a and 4a, asking whether or not it would be "okay" for the participant personally to use the product if he or she suffered from heartburn is probably acceptable and is not unnecessarily leading. The results show that the reworded question, which emphasizes the personal aspect of the query, results in 69% giving a correct response on the prevention question and 59% on the relief question, as opposed to 35% and 31%, respectively, when the original wording was used. However, these results of 59%-69% are still rather low, and suggest that a substantial proportion of potential users who should consult a doctor before use will not follow the label instructions.

The further questioning of those who did not respond correctly initially involves increasingly leading questions. The value of the results for these questions diminishes as they become more leading.

We are most comfortable with the results of questions 3 and 4, which indicate there are still many persons in the risk population that may not understand the label instructions or may not intend to follow them.

In considering whether or not this product is appropriate for non-prescription use, the potential for use without a doctor's review should be considered as a real possibility for a substantial portion of users. The issue is whether or not the product would be safely used in an over-the-counter setting if this were the case.

Even taken in the best light, using all the questions posed in the second study, including the leading questions, only 81% of at risk participants who responded to Version 2 correctly responded that they should see a doctor before use. This level of correct response suggests there may be a problem with applying the information on the label to oneself. Responses to the scenario questions asking about the same issues suggest that there is understanding that persons taking the three medications, and pregnant and nursing women should consult a physician before use, but there appears to be a disconnect either in understanding when the labeling applies to oneself or in accepting that it does. It should also be kept in mind that the series of scenario questions used in the first study may have created a response set that made it more likely that these scenario questions would be answered that the medication should not be taken or that a physician should be consulted. Therefore, what appears to be a high level of understanding of when a doctor should be consulted may be, in part, due to artifacts of the questionnaire, making the true understanding of the label lower than the scores indicate. Thus, there may not be as great a difference between understanding of the label for purposes of the scenarios and in application to one's own situation.

Conclusions--Original Study and Addendum Study

The results of both studies suggest that persons who should consult a doctor before using Prilosec may not do so, although they appear to understand the warnings on the labeling. Pregnant and nursing women would be more likely to consult a physician than persons taking the

medications listed on the label. Consideration should be given to whether or not it would present a public health concern if persons who are taking warfarin, phenytoin, or diazepam, and perhaps some pregnant or nursing women used this medication without a doctor's advice.

The results of the original study suggest portions of the label that could be considered for strengthening, including a clarification of the 24-hour limitation on timing of dosing, and other timing issues. The labeling language concerning what to do after 14 days of continuous use and if one has difficulty swallowing should also be reviewed for possible improvements.

We have no information about comprehension of the package insert; however, one would expect higher comprehension after reading both the carton label and the insert.

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DDMAC ADDENDUM REVIEW

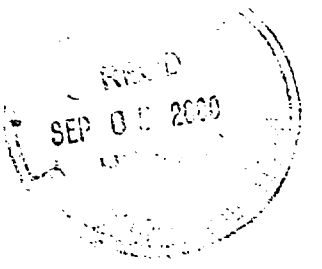
AUG 31 2000

NDA #	21-229
Drug:	Omeprazole Magnesium Tablets
Sponsor:	The Procter & Gamble Co.
Identification:	Study 3358 Label Comprehension
Date of Document:	January, 1998
Reviewer:	Karen Lechter, J.D., Ph.D., HFD-42
Review Completed:	August 31, 2000

Attached are two labels for this product. The first is the label studied in the Label Comprehension study. The second is the label proposed with the NDA.

Karen Lechter, J.D., Ph.D.

Label Comprehension Study Label



Safety Feature–Do not use if tablet blister unit is open or broken.

Active Ingredient (In Each Tablet)	Purpose
Omeprazole 20 mg.....	Acid Preventer

Uses

- **for Prevention** of heartburn, acid indigestion, and sour stomach
- **for Relief** of heartburn, acid indigestion, and sour stomach

Warnings

Ask a doctor before use if you:

- have trouble swallowing.
- are taking **warfarin** (blood thinning medicine), or **phenytoin** (seizure medicine), or **diazepam** (relief of anxiety medicine). Ask when you are not sure if your medication contains one of these drugs.

n using and ask a doctor if:

stomach pain does not go away.

u need to use 1 tablet a day for more than 14 days in a row. This could mean you have a more serious problem.

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or a Poison Control Center immediately.

Directions

Adults and children 12 years of age and older:

- **For Prevention** of symptoms for 24 hours on days you expect to get symptoms, swallow 1 tablet with water. Or, if you prefer to wait until you think food or beverage may cause symptoms, swallow 1 tablet with water one hour in advance.
- **For Relief** of symptoms: Swallow 1 tablet with water.
- Do not take more than 1 tablet every 24 hours.

Children under 12 years of age: Ask a doctor.

Other information:

- store at room temperature
- protect from light and moisture

Inactive Ingredients: Hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, talc, starch

Before Use Read:

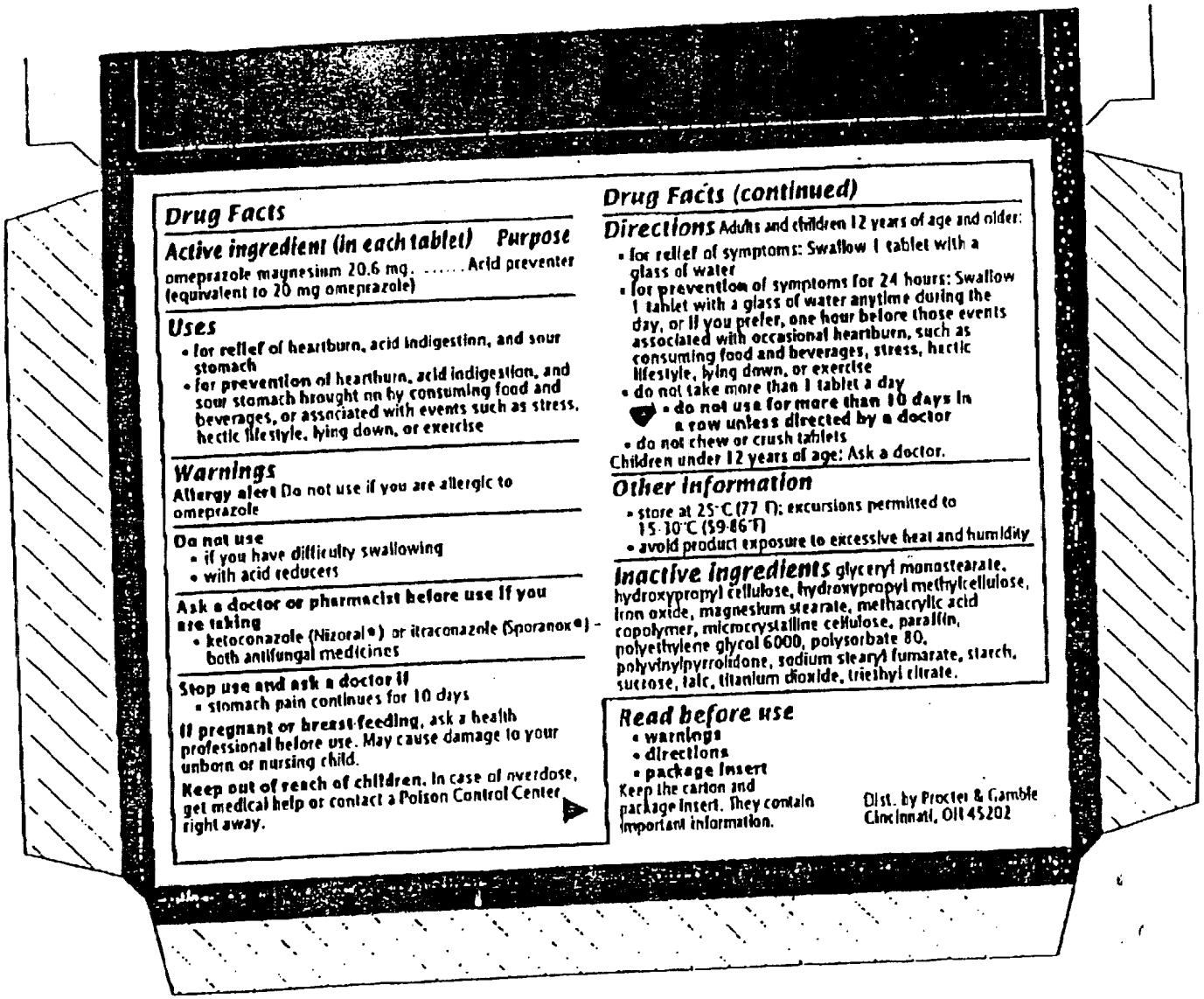
- the directions • information sheet • warnings

Keep the carton and information sheet. They contain important information.

Questions?

Call toll-free 1-800-395-0689

Proposed Market Label



Drug Facts

Active ingredient (in each tablet) **Purpose**

omeprazole magnesium 20.6 mg. (equivalent to 20 mg omeprazole) ..... Acid preventer

Uses

- for relief of heartburn, acid indigestion, and sour stomach
- for prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise

Warnings

Allergy alert Do not use if you are allergic to omeprazole

Do not use

- if you have difficulty swallowing
- with acid reducers

Ask a doctor or pharmacist before use if you are taking

- ketoconazole (Nizoral®) or itraconazole (Sporanox®) - both antifungal medicines

Stop use and ask a doctor if

- stomach pain continues for 10 days

If pregnant or breast-feeding, ask a health professional before use. May cause damage to your unborn or nursing child.

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

Drug Facts (continued)

Directions

Adults and children 12 years of age and older:

- for relief of symptoms: Swallow 1 tablet with a glass of water
- for prevention of symptoms for 24 hours: Swallow 1 tablet with a glass of water anytime during the day, or if you prefer, one hour before those events associated with occasional heartburn, such as consuming food and beverages, stress, hectic lifestyle, lying down, or exercise
- do not take more than 1 tablet a day
- **do not use for more than 10 days in a row unless directed by a doctor**
- do not chew or crush tablets

Children under 12 years of age: Ask a doctor.

Other information

- store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
- avoid product exposure to excessive heat and humidity

Inactive ingredients

glyceryl monostearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin, polyethylene glycol 6000, polysorbate 80, polyvinylpyrrolidone, sodium stearyl fumarate, starch, sucrose, talc, titanium dioxide, triethyl citrate.

Read before use

- warnings
- directions
- package insert

Keep the carton and package insert. They contain important information.

Dist. by Procter & Gamble Cincinnati, OH 45202