DDMAC REVIEW

NDA#:	21-198
Drug:	Pravachol 10 (pravastatin sodium)
Sponsor:	Bristol-Myers Squibb Co.
Study:	Label Comprehension Study
Study Report Date:	December 9, 1999
Reviewer:	Karen Lechter, J.D., Ph.D.
Reviewing Div:	HFD-42
Review Completed:	June 6, 2000

This review presents a summary and analysis of the label comprehension study for Pravachol 10 mg tablets for over the counter (OTC) use.

Review Summary

This section is a short summary of this review. The study examined consumer comprehension of an earlier version of the label than the one eventually submitted with the NDA. Both of these labels are attached.

The results of the study provide information about basic understanding of some of the concepts on the label. Based on the results, we can conclude that participants understood
- The product is for lowering cholesterol.
- Pregnant women and those who drink 3 or more alcoholic beverages on most days should not use the product.
- Persons with hepatitis or normal cholesterol should not use the product.
- Consult a physician if unusual muscle pain or tenderness develops.
- Have a doctor check cholesterol after 8 weeks.

There was moderate understanding of the age at which men (77%) and women (80%) can use the product. There is insufficient information to determine if consumers would understand that there are several simultaneous requirements necessary to use the product.

Consumers probably understand which medical conditions preclude use of the product (heart disease, liver disease, and diabetes). One set of questions on this topic produced results that were unclear; another set suggested adequate understanding.

Due to the wording of the questioning, it is not clear that consumers understand they must see a doctor before use and see a doctor after taking the product for a year. Further, participants were not asked under what special circumstances written on the label they must see a doctor before use, other than the general advice for everyone to see a doctor before use.

Scores were relatively low (73%) regarding use by persons with total cholesterol above 240 and by those taking erythromycin (65%).

Due to the simplicity of the questions asked, we do not know if consumers can apply the information to a variety of use situations or can appropriately self-select to use the product based on their own situations.

Because the label was substantially modified after this study was conducted, the results of this label comprehension study do not provide information on the adequacy of the currently proposed label.

Communication Objectives

The **primary objective** of the study was to determine whether consumers understand that they should see a doctor before using Pravachol 10 mg.

The **secondary objectives** were to determine whether consumers understand:
- product purpose
  - to lower total cholesterol if it is between 200 and 240 mg/dl after a program of diet and exercise
- who should not use Pravachol 10 mg
  - people who have diabetes or coronary heart disease
  - people already taking prescription cholesterol lowering medication
  - people who have liver disease and/or drink ≥ 3 alcoholic beverages per day
  - people taking erythromycin
  - pregnant females
- who should use Pravachol 10 mg.
  - non-pregnant females ≥ 55
  - males ≥ 35
  - people who have total cholesterol between 200 and 240 mg/dl
- the need for follow-up evaluations
- muscle pain should be reported to a doctor

Method

Participants
Participants were age 25 or older. They did not necessarily have interest in or knowledge of cholesterol. They were excluded if they or a family member was employed by advertising agency, market research firm, or a company that manufactures health care products. Also excluded were persons who participated in a consumer research study in the past six months, those currently participating or those who have a family member currently participating in a consumer diary panel, those who wore reading glasses that were not available, and persons known personally to the interviewer.

There were 612 participants in the final data set, including 546 in the basic "random" sample and 66 supplemental low-literacy participants. There were quotas for men and women (50% each), ages 25-34 (20%), ages 35-49 (25%), and age 50 or older (55%). There were 163 low-literacy participants, with reading levels below 9th grade. Sixty-six

(66) of these were supplemental. The mean age of the total sample was 51.8. Seventy-six percent (76%) were Caucasian, 9% African American, and 2% Hispanic. Fifty-one percent (51%) were female, and 73% had literacy levels of 9th grade or above.

Materials
The following materials were used in the study:
- screening questionnaires to determine eligibility to participate
- the Rapid Estimate of Adult Literacy in Medicine (REALM) literacy test
- a package label
- the main questionnaire. This began with 5 open-ended questions administered by an interviewer. Open-ended questions do not provide alternate choices of responses; participants must generate their own responses. The remainder of the questionnaire, containing questions 7-22, was self-administered by the participants, without an interviewer. These consisted of closed-ended (multiple-choice) questions. A final set of questions asked about the participants' medical conditions, their concern about cholesterol, diet and exercise, other health habits, and demographic information.

Procedure
Participants were recruited in shopping malls in 20 geographically diverse locations, with 5 locations in each of the four geographic quadrants of the country. The protocol did not explain how supplemental screening was conducted to reach the quota for low-literate participants.

After screening, participants completed the REALM literacy test. They were then given a package with labeling and were asked to read it as if they were deciding whether or not to purchase the product.

The interviewer asked the first 5 questions. The first two were administered without the package in view, to test recall. The remaining three questions were asked with the label available. Once the participants answered the first five questions administered by the interviewer, they completed the remainder of the questionnaire themselves, with the package available at all times.

Results

Statistical analyses were performed on the closed-ended questions using t-tests, $p \leq .05$. There were no adjustments for the use of multiple comparisons.

The first five questions contained two questions that were repeated with similar or identical wording. They were asked once without the package present, and again when the package could be examined during the questioning. They were :

1. What should you do before you start to use Pravachol 10? (Q.2) What does the package say you should do before starting to use Pravachol 10?" (Q.6).

2. What does the package say is the reason for using Pravachol 10? (Q.3, Q.5)

A closed-ended question (Q.12) asked "Which of the following does the package say you should do before you start to use Pravachol 10? Ask for advice from friends or relatives who have used Pravachol 10 before; get your blood pressure checked; see your doctor; none of the above, anyone can buy Pravachol 10 and begin using it immediately."

*Comment: The first open-ended question asked "What should you do before you start to use Pravachol 10?" This wording suggests to participants that there is something they must do. It does not test if they know they must do something before taking the medication. Q. 12 asks what the **package** says should be done before using Pravachol 10. These questions are different. The choices in Q.12, a multiple-choice question, include one that appears obviously wrong ("ask for advice from friends or relatives who have used Pravachol 10").*

The results of these questions show that without the label present, 82% of participants were able to generate a response indicating that a doctor should be consulted before use. When the question was asked with the label present, the correct scores rose to 95%. The score for the corresponding multiple choice question was 94%. There were no differences in scores between the low-literate and high-literate participants on the two open-ended questions. However, for the multiple-choice question, the high literate scored higher (96%) than the low literate (91%).

The two open-ended questions about reasons to use the product (Q. 3, Q.5) resulted in 90% and 95% providing a response indicating cholesterol lowering. There were no differences between literacy groups on these questions. Summaries of these results are in Tables 1-3.

Table 1. Responses to Two Open-Ended Questions, Package Not Present

Questions	% Correct (N=612)
2. What should you do before you start to use Pravachol 10? (see Dr.)	82
3. What does the package say is the reason for using Pravachol 10? (cholest.)	90

Table 2. Responses to Two Open-Ended Questions, Package Present

Questions	% Correct (N=612)
5. What does the package say is the reason for using Pravachol 10? (cholest.)	95
6. What does the package say you should do before starting to use Pravachol 10? (see Dr.)	95

Table 3. Responses to Closed-Ended Question About Actions Before Use

Question	% Responding (N=612)
12. Which one of the following does the package say you should do before you start to use Pravachol 10?	
See Your Doctor (Correct)	<u>94</u>
Get blood pressure checked	3
Ask for advice from friends or relatives who have used Pravachol 10 before	–
None of the above/anyone can buy Pravachol 10 and begin using it immediately	1

Comment: *Once participants are alerted by the question that there is something they should do before using the product, the participants respond at fairly high levels that they should see a doctor. Their awareness is somewhat lower when they do not have the label in view.*

Two questions asked about diseases and the use of Pravachol 10. They were both open-ended, as follows:
Q. 4a. The package states that people with certain diseases should not use Pravachol 10. What are those diseases?
Q. 4b. What other diseases are mentioned on the package, if any?

The results for both of these questions were combined. Seventy-one percent (71%) of participants mentioned all three diseases—heart disease, diabetes, and liver disease. Ninety-seven percent (97%) mentioned at least one of these. There were no differences between the two literacy groups on these questions.

Table 4. Combined Responses to Two Questions About Use with Diseases, Closed-Ended, Package Present

Questions	% Responding (N=612)
4a. The package states that people with certain diseases should not use Pravachol 10. What are those diseases? 4b. What other diseases are mentioned on the package, if any?	
Disease/Conditions (net)	97
Heart problems/disease	93
Diabetes	82
Liver disease	80
Completely Correct (all 3)	71
Partially correct (1 or 2 of 3)	25
Incorrect (none of 3)	4
Other Conditions Mentioned	
High blood pressure	19
Pregnancy/pregnant	18
Drink alcohol	11
Allergies	7
Smoking	4
Under 18	3

Comment: It is not clear what responses to Q.4b mean. Do they mean the participant believes that if a disease is mentioned on the package, that disease precludes use of the product? We do not know. The label says not to use the product unless told to do so by a doctor if you have heart disease, diabetes, or liver disease. However, other diseases or conditions mentioned on the label are pregnancy, nursing, allergy to pravastatin or other ingredients, drink 3 or more alcoholic drinks /day (do not use). Also mentioned are high blood pressure (ask a doctor before use) and family history of heart disease (ask a doctor before use), cold, flu, injury or sprain (see doctor if have muscle pain or tenderness not caused by these conditions), feel weak or have a fever (see doctor if these develop). The label also mentions heart disease and menopause for women, stating that after menopause, the risk of heart disease increases in women. Therefore, if any of these conditions or diseases are mentioned in response to Q.4b, we cannot assume participants believe they are reasons not to use Pravachol. Unfortunately, the sponsor combined responses to both of these questions, so we cannot be sure how many participants correctly answered 4a. The results show that in response to Q.4a and Q.4b, 19% mentioned high blood pressure, 18% pregnancy, 11% drinking alcohol, 7% allergies, and 4% smoking.

Three questions in a row (Q. 7-9) asked which of the 3 conditions listed in the question were types of people who should not use Pravachol 10. In addition to the three specific choices, there was a choice of "none of the above." Ninety percent (90%) correctly stated people with heart disease (as opposed to asthma or ulcers) should not use the product; 89% correctly said people with diabetes (not arthritis or heartburn), and 88% correctly stated people with liver disease (rather than those with frequent headaches or glaucoma). There were no differences in responses for the two literacy groups.

Table 5. Responses About People Who Should Not Use Pravachol 10, Closed-Ended, Package Present

Questions	% Responding (N=612)
7-9. Which one of the following types of people should *not* use Pravachol 10?	
People with Heart Disease (Correct)	90
People with asthma	2
People with ulcers	1
None of the above	6
People with Diabetes (Correct)	89
People with arthritis	1
People with heartburn	3
None of the above	6
People with Liver Disease (Correct)	88
People with frequent headaches	1
People with glaucoma	1
None of the above	8

Comment: These questions provided reasonable incorrect choices. Therefore, it is likely that correct responders did understand the information on the label concerning these issues at the cognitive level at which the questions were asked. Later in this review we will discuss the absence of questions requiring higher-level understanding of the label information.

Several additional multiple-choice questions asked about persons who should not take the product (Q.15-Q.19). These covered the warnings about use by pregnant women, persons who drink 3 or more alcoholic beverages on most days, people with cholesterol levels above 240, and persons taking erythromycin or other cholesterol-lowering medications. The results showed 87% understood the pregnancy warning and the alcoholic beverage warning. Fewer understood the other warnings. Only 73% understood persons with cholesterol levels above 240 should not use the product and

understood the warning about use with other cholesterol-lowering medications, and 65% understood the erythromycin warning. There were no significant differences between the literacy groups on these questions.

Table 6. Responses to Questions About Who Should Not Use, Closed-Ended, Package Present

Questions	% Responding (N=612)
15.-16. Which one of the following types of people should <u>not</u> use Pravachol 10?	
<u>Pregnant Women (Correct)</u>	<u>87</u>
People with migraine headaches	2
People with colitis	2
None of the above	8
<u>People Who Drink 3 or More Alcoholic Beverages per Day (Correct)</u>	<u>87</u>
People who drink 3 or more glasses of diet soda per day	2
People who drink 3 or more glasses of milk per day	1
None of the above	8
17. According to the label, which one of the following types of people may need a prescription cholesterol-lowering medication?	
<u>People with Total Cholesterol Levels More Than 240 (Correct)</u>	<u>73</u>
People with total cholesterol levels of 220	13
People with total cholesterol levels under 180	3
None of the above	9
18.-19. People who are taking one of the following medications should <u>not</u> take Pravachol 10. Which one of the following medications is that?	
<u>The Antibiotic Erythromycin (Correct)</u>	<u>65</u>
The pain reliever Tylenol	4
The antacid Mylanta	1
None of the above	29
<u>Prescription Cholesterol Lowering Medications (Correct)</u>	<u>73</u>
Medications to control the thyroid	6
Prescription headache remedies	5
None of the above	15

Comment: Q.15, Q. 18, and Q.19 had reasonable alternative choices. Correct responses probably indicate a basic understanding of the labeling on these issues. Q.16

involved questions about drinking different types of beverages. It is likely that participants could guess that alcohol drinkers, as opposed to milk and diet soda drinkers, should not use the product. Q. 17. involved persons with varying cholesterol levels. The first choice was "a person with a total cholesterol level of 220." Another is "a person with a total cholesterol level of more than 240." On its face, it is unlikely that the 220 response would be correct if there is also a choice of 240. If a person with a level of 220 can't use it, then certainly a person with 240 cannot as well. If 220 is correct, then above 240 is probably also correct. However, they both cannot be correct, as there is only one correct response per question. Therefore, 220 cannot be correct. Participants following this line of reasoning can eliminate one choice without knowing anything about the label information, thus increasing their chance of a correct response on this item.

Four questions dealt with who could use the product (Q. 10-11, Q. 13-14). Questions 10-11 ask which of the following types of people Pravachol 10 is meant for. Q. 10 gives several choices of cholesterol ranges. Q.11 gives a list of people with normal cholesterol or various conditions, with the correct response being "none of the above." Seventy-six percent (76%) correctly stated the cholesterol range of 200-240. Seventeen percent (17%) stated 250-300. For Q.11, 85% knew that Pravachol 10 is not meant for persons with any of the conditions listed. For these questions, there were no significant differences between literacy groups.

Table 7. Responses to Questions About People for Whom Pravachol 10 is Intended, Closed-Ended, Package Present

Questions	% Responding (N=612)
10. Which one of the following types of people is Pravachol 10 meant for?	
People with Total Cholesterol Levels Between 200-240 (Correct)	<u>76</u>
People with total cholesterol levels of 250-300	17
People with total cholesterol levels of 160	2
None of the above	5
11. Which one of the following types of people is Pravachol 10 intended for?	
None of the Above (Correct)	<u>85</u>
People with normal cholesterol	7
Pregnant women	5
People with hepatitis	1

Comment: The fact that over 15% appeared to believe the product could be used for cholesterol levels above 250 suggests a potential problem in limiting the use of the product to the appropriate cholesterol ranges.

Q.13 and Q.14 ask for the ages at which men and women "should" take Pravachol 10. Seventy-seven percent (77%) correctly stated for men that it is age 35 and older; 80% correctly gave the age of 55 for women. There were no differences in these responses by literacy group.

Table 8. Responses to Age at Which Pravachol Should Be Taken, Closed-Ended, Label Present

Questions	% Responding (N=612)
13. At what age should <u>men</u> take Pravachol 10?	
<u>Ages 35 and Older (Correct)</u>	<u>77</u>
Ages 18 and older	6
Ages 55 and older	12
None of the above	3
14. At what age should <u>women</u> take Pravachol 10?	
<u>Ages 55 and Older (Correct)</u>	<u>80</u>
Ages 18 and older	7
Ages 35 and older	8
None of the above	4

Comment: The wording of questions 13 and 14 would have been better if they had asked about ages at which persons "could" take the product, rather than the ages at which they "should" take it. The incorrect responses for men were primarily age 55 and older. This type of misunderstanding of the age requirements does not pose a public health concern.

Q. 20 asked what should be done if a Pravachol 10 user experiences unusual muscle pain or tenderness. Ninety-three percent (93%) correctly responded that they should see a doctor.

Table 9. Responses to Question about Muscle Pain, Closed-Ended, Label Present

Questions	% Responding (N=612)
20. If you are taking Pravachol 10 and you experience unusual muscle pain or tenderness, what should you do?	
See Your Doctor (Correct)	93
Decrease the dosage of Pravachol 10	4
Increase the dosage of Pravachol 10	-
None of the above, just keep using it as before	1

Q. 21 related to the use of the product without checking with a doctor or use for only 8 weeks and asked which of 3 statement is true, or none of them. Eighty-two percent (82%) correctly said that users should see a doctor for a cholesterol check after 8 weeks of use.

Q.22 asks what to do after taking Pravachol 10 for a year. Eighty-six percent (86%) correctly said their cholesterol should be checked.

For Q.10-22, there were no differences between literacy groups.

Table 10. Responses Concerning Future Cholesterol Checks, Closed-Ended, Label Present

Questions	% Responding (N=612)
21. Which one of the following statement, if any, is true?	82
<u>8 Weeks after You Start Using Pravachol 10 You Should Have Your Doctor Check Your Cholesterol Level (Correct)</u>	<u>82</u>
8 weeks after you start using Pravachol 10 you should not use it anymore	5
It is safe to use Pravachol 10 for as long as you wish without checking with your doctor	2
None of the above	9
22. What do you need to do after you have been taking Pravachol 10 for a year?	
<u>Have Your Cholesterol Level Checked (Correct)</u>	<u>86</u>
Stop taking Pravachol 10	3
Take Pravachol 10 less frequently	2
Take Pravachol 10 more frequently	1
None of the above	7

Comment: The question about what to do after one year has the same problem as the earlier question about what to do before use. It suggests to participants that something must be done after one year, when we do not know if they realize that fact.

The remaining questions dealt with personal information, lifestyle, medical conditions, and similar topics.

Comment: There appears to be no rationale for some of the personal questions, such as marital status and occupation. Other questions, such as level of concern about cholesterol could have been used to separate respondents to see if those more concerned with cholesterol issues scored better than those who were less concerned. However, such an analysis was not reported. Some of the questions appear to be standard marketing-type questions that were not useful or not used in this analysis.

Label Modifications Based on the Study Results
After the study, the sponsor made changes to the label to strengthen the messages about who should not use the product, particularly consumers with cholesterol levels above 240 and those taking prescription cholesterol medication or erythromycin. In addition, the

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sponsor changed an icon on the label that was designed to represent the cholesterol range for which the product is intended.

Additional label changes were made based on the 1999 FDA rule on labeling requirements for OTC drugs and based on additional consumer use trials and clinical studies. The result is a label that is quite different from the one tested in this study. The tested label and the label proposed with the NDA application are attached.

Conclusion
In general, the questions presented to the participants were simple and straightforward. They did not require participants to apply the information on the label to hypothetical situations, which would have been a more challenging and useful test of comprehension. None of the questions tested whether participants understood there must be a combination of total cholesterol level **and** a particular minimum age, which differs for men and women. As the label did not mention HDL or LDL levels as requirements for use, these were not mentioned in the questioning.

The scores are a function of the labeling and the type of questioning, among other factors. Many of the questions were very basic and did not require any reasoning processes to answer. Others assumed participants already knew information they may not have known before the question was asked (e.g., "What should you do before you start to use Pravachol 10?"). Some questions provided reasonable false alternatives in the multiple choice questioning, while a few had incorrect choices that may have been obvious to some participants.

Participants were not asked if they could use the product themselves, with responses analyzed according to responses given to medical history questions. Such a question would have been useful to see if they could apply the information on the label to the important question of self-selection. The issue of self-selection in this study is not as critical if we can be assured that almost all potential users will consult a physician before using the product. Another study addresses consumer behavior in response to the label.

Participants clearly understood the purpose for using the product. It is not clear from the results that participants would understand, without prompting, that they must do something (consult a physician) before using the product. Due to the scoring method, it is not clear how well participants understood who should not use the product based on their medical conditions. Participants did not understand well the appropriate cholesterol range for the product or the warning about use with erythromycin. Approximately 79% understood the ages for use by men and women.

We do not know if participants knew they must meet several criteria at once to use Pravachol 10—a certain total cholesterol and a different age for men and women. There were no questions testing if participants understood that a combination of factors must be met. It is possible that a significant number of participants would not understand that all 3 requirements must be met before use. This study does not provide us with that critical information because it does not ask.

The communication objectives did not include, and the questionnaire did not ask, about conditions listed on the label under "Ask your doctor before use if." These include cholesterol above 240 and/or very low HDL, smoking, high blood pressure, and a family history of heart disease. Therefore, we do not know how well participants would understand this section of the label.
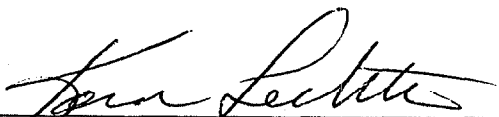
Although there are questions asking about use by persons with certain medical conditions, the questionnaire did not ask about persons who could not use the product, based on cholesterol levels, age, and sex. Thus, we do not know if participants understood that persons with certain characteristics should **not** use the product . We do not know if participants understood who could not take the product if that information was not specifically on the label.

Most questions produced fairly high scores. These scores are a function, in part, of the difficulty of the questions, whether the questions are leading, and other aspects of the questioning. The scores are not unbiased measures of comprehension. It is likely that questions requiring participants to apply the information on the label to hypothetical situations would have produced lower scores, but would have given us a better assessment of how well the label is understood.

The fact that there was only one question for which the low literate scored differently and lower than the "high literate" suggests that the label tested is equally understandable to both groups at the simple cognitive levels at which the questions were aimed.

Comprehension of who should and should not use Pravachol 10 is problematic for the label studied here. The sponsor appropriately modified the label in response to the findings in this study. However, the most recent version of the label is so different from the one tested, that this study does not provide us with insight about how well the new label would be understood.

If this product is approved, a new label comprehension study would be useful to evaluate the most recent version of the label. The study reviewed here has little bearing on the latest labeling. Any new label comprehension studies should include scenario questions with hypothetical situations to determine how well consumers can apply the label information.

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Label Tested in the Label Comprehension Study

Drug Facts

Active ingredient (in each tablet)   Purpose
Pravastatin sodium, 10mg...Cholesterol reducer

Use
- lowers mildly elevated cholesterol.
- helps manage a risk factor for heart disease.
- to be used with a program of diet and exercise.

You have mildly elevated cholesterol if your total level is between
200-240mg/dl and your "bad" cholesterol (LDL) is over 130mg/dl.

Warnings
Do not use

- if you have liver disease or regularly drink 3 or more alcoholic beverages daily.
- if you are allergic to pravastatin or any of the inactive ingredients.
- if you are under 18 yrs.

Before use; ask a doctor about
- your cholesterol levels (total, HDL, LDL, triglycerides).
- your risk factors for heart disease.

Ask a doctor before use if you have any of the following conditions because you
may need the prescription strength of this product:
- heart disease
- diabetes
- total cholesterol that is above 240mg/dl

Ask a doctor or pharmacist before use if you are already taking prescription medication
to lower your cholesterol .

Stop use and ask a doctor if
- you have any unusual muscle pain or tenderness that is not caused by a cold, flu,
  recent injury or sprain. This is very important if you also feel weak or have a fever.

If pregnant or breast feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a
Poison Control Center right away.

Directions
- take 1 tablet every day
- 8 weeks after starting, check your cholesterol again
  - If you have reached a healthy cholesterol level, keep taking one tablet
    daily to stay at a healthy level.
  - If you haven't reached a healthy cholesterol level, you may need the
    prescription strength of this product.
- once a year check your cholesterol level.
- continue to exercise and stay on a low-fat diet.

Other information
- This product is very low in sodium.
- Read all product information before using.
- Keep this box and educational leaflet for important information.
- Tamper resistant inner unit. Do not use if foil seal is torn or broken.
- Do not store above 86° F (30° C). Protect from moisture and light.

Inactive ingredients croscarmellose sodium, lactose, magnesium oxide,
magnesium stearate, microcrystalline cellulose, povidone and red ferric oxide.

Questions or comments? Free enrollment in Pravachol Partners Program.
Call 1-877-PRAVA10 (1-877-772-8210) or log on to www.prava10.com