

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-887

SOCIAL SCIENCE REVIEW(S)



SOCIAL SCIENCE REVIEW

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

DATE: Original Review: December 10, 2005; Amended Review: March 10, 2006

FROM: Susanna Weiss, Ph.D., J.D.
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THROUGH: Charles Ganley, M.D.
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RE: NDA 21-887
GlaxoSmithKline Healthcare
Orlistat 60 mg capsules (for weight loss)

SUBJECT: Amended Review of Orlistat Label Comprehension Study.

BACKGROUND

Hoffmann-LaRoche, Inc. first submitted an investigational new drug application (IND) for orlistat capsules on May 12, 1988 (received May 13, 1988). Xenical® (orlistat) 120 mg capsules were subsequently approved for prescription marketing on April 23, 1999, under NDA 20-766.

On June 14, 2001 (received June 19, 2001), Hoffmann-LaRoche submitted IND 62,758, to investigate the feasibility of an over-the-counter (OTC) version of orlistat, to be marketed as Xenical® 60 mg capsules. An End of Phase II meeting was held on July 17, 2002, between representatives of Hoffmann-LaRoche, the Division of Metabolic and Endocrine Drug Products, and the Division of Over-the-Counter Drug Products (now the Office of Nonprescription Products).

GlaxoSmith Kline subsequently acquired ownership of IND 62,758 from Hoffmann-LaRoche and a Type B – Pre-NDA meeting was held on December 8, 2004 between representatives of GlaxoSmithKline, the Division of Metabolic and Endocrine Drug Products, and the Division of Over-the-Counter Drug Products (now the Office of Nonprescription Products).

During the July 17, 2002 End-of-Phase II meeting with Hoffmann-La Roche, and during the December 8, 2004 TypeB – Pre-NDA meeting with GlaxoSmithKline, several issues were raised which have a bearing on the subsequent package labeling, supplemental materials, and label comprehension study that was developed for submission under NDA 21-887 for OTC Orlistat (the amended name for the OTC product). The meeting minutes refer to the following key issues:

1. Potential drug-drug interaction, e.g., cyclosporine-orlistat must be addressed.

2. A label comprehension study would have to show that consumers who have co-morbidities contraindicated on the label, such as gallbladder disease, would know not to use the product.
3. Adequate safety in a non-obese population.
4. Safety considerations in specific populations such as pregnant women, the elderly, and renally/hepatically impaired patients.
5. Vitamin malabsorption and the waste of fat-soluble vitamins:
 - a. The need for vitamin supplementation and the potential for consumers to wrongly take vitamins concomitantly with Orlistat, instead of 2 hours before or 2 hours after taking Orlistat.
 - b. A "worst-case-scenario" whereby overweight, post-menopausal women at risk for osteoporosis might take vitamin D and Calcium at the wrong times.
 - c. Consumers who might concomitantly use Orlistat and also significantly ingest foods containing Olestra.
6. The need for consumers to understand the importance of appropriate diet and exercise in conjunction with use of Orlistat, so that they optimize and maintain their weight loss.
7. Potential misuse by those under the age of 18.
8. Potential misuse by non-overweight individuals, especially those with eating disorders such as anorexia and bulimia who abuse laxatives.

GlaxoSmithKline (GSK) provided the following responses to these concerns:

- *Long term (up to 4 years) Rx clinical trials showed that vitamin levels decrease but remain within reference ranges with orlistat usage. GSK indicated that the drug facts label will recommend vitamin use while taking orlistat. GSK also noted that data from the Actual Use Study trial demonstrates that the majority of consumers were already taking a multivitamin and, of those who were not, roughly 50% started to take one.*
- *GSK indicated that they are not aware of any clinical data describing concomitant use of Olestra and orlistat. However, they noted that Olestra products are currently formulated to include vitamins and orlistat will be labeled to encourage vitamin use. In the event that gastrointestinal effects are additive, GSK believes it is unlikely that consumers would elect to use them together.*
- *In the 'worst case scenario' of vitamin deficiency, i.e., if orlistat was used chronically by overweight, post-menopausal women at risk for osteoporosis, or persons taking vitamin D and calcium at the wrong times, GSK referred to the 4 year Xenodos study which demonstrated that patients experienced an initial decrease in vitamin levels during the first 1 to 2 months of use, after which they re-established a new steady state vitamin level.*
- *GSK believes that use in those under 18 should be under physician supervision.*
- *GSK described the incidence of reported misuse and abuse from Rx experience as negligible, even in the environment of internet availability. GSK noted that only four cases of abuse by bulimic patients using Xenical® have been reported worldwide. Among these four cases, there were no clinically significant safety issues or adverse health consequences. GSK also noted that Orlistat is not a good cathartic and only inhibits fat absorption.*

STUDY OVERVIEW

This was a multi-site (13 geographic locations) mall-intercept study. Interviewing began on January 31, 2005 and ended on February 11, 2005. A total of 410 interviews were conducted.

Primary Objectives

1. To measure consumers' understanding of the key label objectives – uses, warnings, directions for use, and the front panel information indicating inside-package components.
2. To measure consumers' understanding of where to locate additional information included in the package.

Study Population

Inclusion/Exclusion Criteria:

- Male/Female of any race/ethnicity.
- At least 18 years of age.
- Expressed an interest (“somewhat” or “very interested”) in weight loss.

Two cohorts of individuals:

1. General Population (GP) of 304 subjects, 54 (18%) of which qualified as Low Literate and were also counted in Cohort #2 (the low literacy group).
2. Low Literacy (LL) group of 160 subjects, 54 of which were from the General Population group and 106 of which were specifically recruited as low literate subjects.

Gender Breakdown:

- General Population (GP) – 36% male and 64% female.
- Low Literacy (LL) – 39% male and 61% female.

Race/Ethnicity:

General Population

75% Caucasian/White
18% African American/Black
1% Native American
1% Asian
5% Other

Low Literacy Group (REALM test)

39% Caucasian/White
52% African American/Black
---% Native American
---% Asian
---% Other

Reviewer Comments

There is no specific mention of Hispanic/Latino Americans, even though this is the fastest growing segment of the U.S. population and constitutes almost 14% of the population according to latest census figures. It may also be worth noting, although this is just an observation, that 84 (53%) of the 160 subjects in the Low Literacy cohort reported that they had completed high school, and 19 (12%) reported that they had completed some college or technical school, even though their REALM scores indicated that they read at about a seventh-to-eighth-grade level.

The Questionnaire and Interviewing

Scenarios were developed to test consumers' understanding of product package labeling. The questions following those scenarios were open-ended. A variety of question structures were used to minimize subjects' opportunity to detect correct response patterns. Additional questions were deployed to measure the respondents' ability to locate information in the Table of Contents materials for the various Guides that are included inside the product package.

Reviewer Comments

Review of the questionnaire and the interviewing scripts and methods indicate that questions and techniques were objective, non-leading, and were conducted to minimize opportunity for bias.

Data Reporting

Coding Problems -- Reviewer Comments

There are some problems with the Sponsor's coding of "correct" vs. "acceptable" vs. "incorrect" responses, as well as with the presentation of the results. These issues are described in the table that runs from pages 10-24 of this document.

Tabulated Data -- Reviewer Comments

When first submitted, data was reported by Sponsor only as percentages. At FDA request, new tables were submitted in which results were reported by number of subjects as well as percentages. For purposes of exemplification only, the breakdowns in the tables were requested to be as follows:

Base: Total Responding	General Population N = 304		Low Literacy N = 160	
	N	%	N	%
Correct (total)	?	?	?	?
<i>Correct initially Q90</i>				
Not okay	?	?	?	?
Ask her doctor	?	?	?	?
<i>Correct after probe Q91</i>				
Ask a doctor first	?	?	?	?
Ask a doctor/pharmacist	?	?	?	?
Acceptable (total)	?	?	?	?
<i>Acceptable initially Q90</i>				
Call the 800#	?	?	?	?
<i>Acceptable after probe Q91</i>				
Look in User Guide	?	?	?	?
Incorrect (total)	?	?	?	?
Is not contraindicated	?	?	?	?
Okay to use	?	?	?	?
Package does not mention	?	?	?	?
Lower dosage	?	?	?	?
Don't know	?	?	?	?

SUMMARY OF OBSERVATIONS

Data Coding and Data Reporting Flaws

The primary objectives of this label comprehension study were to measure consumers' understanding of key communication objectives contained in the Drug Facts Label, including: (a) what the product is used for, (b) warnings, e.g., "do not use" and "ask a doctor/pharmacist before use," (c) directions for use, e.g., dose, duration of use, and multivitamin use, (d) what to expect during product usage, and (e) where to find additional information, i.e., in the supplementary materials contained inside the package.

Bearing this in mind, and given the fact that the study participants were specifically informed that: (A) this was a test of the package labeling; (B) they would not be questioned about previous knowledge or commonsense but about what has been learned from reading the information in the package labeling; (C) they should respond according to the information in the label, and (D) they would be able to view and read all the package labeling throughout the test, it is not justifiable (with very few exceptions) to code responses that are not based precisely on the label information as "acceptable" or, worse still, "correct."

For example, it is not appropriate to inflate the label's comprehension value by coding the "default" response – "*ask a doctor, pharmacist or healthcare professional*" – as an "acceptable" answer, unless that instruction was given in the label. OTC medicines are rarely designed to be purchased or used with concurrent or frequent input from healthcare professionals (other than limited advice from a doctor or pharmacist, and only where specified in the label instructions).

However, this being said, the study contained some scenarios and questions which called for responses based on information that was not presented in the Drug Facts Label or other areas of package labeling. In those particular instances, then, it was understandable and acceptable that subjects would defer to "I don't know," or "it's not mentioned anywhere on the box," or "she/he should talk to a doctor or pharmacist." These particular issues are described in detail later in this review.

Sponsor's Results tables were organized into three sections, based on the communication objectives of the package labeling. A similar organizational system has been followed by this reviewer.

Drug Facts Label – Product Usage and Warnings.

Drug Facts Label – Directions and Product Information.

Front Panel and Guides – Tables of Contents of the *User's Guide*, the *At Home Guide*, and the *Away from Home Guide*.

Comprehension of Information Contained in the Drug Facts Label

27 scenarios and accompanying questions were designed to elicit responses concerning information contained specifically in the Drug Facts Label portion of the packaging.

The General Population group achieved the following scores by answering questions correctly or acceptably:

95% to 100% on 11 scenarios
90% to 94% on 4 scenarios
82% to 89% on 7 scenarios
75% to 79% on 3 scenarios
69% on one scenario and question
48% on one scenario and question

The Low Literacy group achieved the following scores by answering questions correctly or acceptably:

90% to 100% on 12 scenarios
80% to 89% on 5 scenarios
74% to 79% on 3 scenarios
62% to 69% on 4 scenarios
50% on two scenarios and questions
34% on one scenario and question

The ability of the Drug Facts Label to transfer information to the reader was generally very good. Results show that, for the most part, i.e., with the exception of two sets of responses, almost all of the General Population (GP) respondents grasped the basic concepts, warnings and directions contained in the label. The GP group scored at or above 90% on 15 out of 27 scenarios/questions; from 82% to 89% on seven of the scenarios/questions; from 75% to 79% on three of the scenarios/questions, and scored poorly – 69% and 48% – on two scenarios/questions. The latter scenarios require additional explanation and will be discussed in detail later in this review. Low Literacy (LL) respondents scored between 90% - 100% on 12 scenarios; 80% - 89% on five scenarios; 74% - 79% on three scenarios; 62% - 69% on four scenarios, 50% on two, and 34% on one scenario. For additional information also see the table on page 9.

Where to Find Information in the Supplementary Educational Materials

Nine scenarios and questions were designed to elicit responses about information contained in the **supplementary educational materials**. There was about a 60% versus 40% split between reasonably good and rather poor responses.

General Population subjects scored from 66% - 90% on five of the nine scenarios/questions, and between 37% - 43% on the four remaining scenarios/questions. Low Literacy subjects scored between 65% - 90% on six of the scenarios, and 23% - 41% on four of the scenarios.

Note: At the time the study was conducted, the educational booklets and other supplementary materials had not been completed. In their place, the study utilized just the Tables of Contents of what would later become the set of educational materials. These Tables of Contents were printed on individual sheets of paper and were separate from the Drug Facts panel that was the primary focus of all the other questions in the study. The Tables of Contents for the educational materials can be seen in the Appendices of this review (pp. 41-43), and results concerning these materials will be discussed later in this document.

<u>Where to Find Information in the Educational Materials</u>	<u>Sponsor</u>		<u>Reviewer</u>	
	GP %	LL %	GP %	LL %
<u>Results Listed in Descending Order for General Population Group Per Reviewer's Analysis</u>				
Q48 Information on fast food restaurants	90	90	90	90
Q49 Information on setting realistic goals	90	86	90	86
Q51 Information on understanding personal eating habits	82	76	82	76
Q47 Information on snacking tips	80	69	77	69
Q50 Information on learning to navigate the grocery store	67	66	66	65
Q52 Information on the food and activity tracker	45	43	43	41
Q35 Information on fat and calories	74	57	42	26
Q26 Information on preparing meals	84	63	42	24
Q19 Information on what to order when dining out	75	58	37	23

Possible Explanation for Low Scores on Some Questions about the Educational Materials

There might be a fairly simple explanation for the low scores on some of the questions regarding the location of specific information in the supplementary educational materials, and it concerns the wording of the questions. For example, following the scenario for Question 19 which states: “*Steve is overweight. He has been using Orlistat. Steve is going out to dinner tonight but is not sure what would be best for him to order,*” the wording of Question 19 said: “*Based on the **package labeling**, where could Steve find information?*” [emphasis added]. It is possible that many of the respondents thought that the term “package labeling” meant the Drug Facts label that they had been reviewing in order to answer the preceding label comprehension questions. They may not have understood that the term referred to all of the package panels, as well as to the Tables of Contents for the educational materials, and it may have taken them several “tries” before they grasped the need to look somewhere other than in the Drug Facts label for the required information to answer questions about the supplementary educational materials.

General Observations about the Study’s Results

The overall number of “incorrect” responders in the study was fairly small on most of the scenarios, but there appear to be three broad types of “incorrect” responders: (1) those who state that key information points are not present anywhere in the package labeling, even though they are in fact there, (2) those who read information in the label but who do not understand and/or do not recall it accurately, and (3) those who, despite reading certain instructions in the Drug Facts Label, ignore those instructions and instead construct their own rationalizations or internal narratives as to why it would be “okay” to behave contrary to the label instructions. These nuances in the data may need further exploration and explanation in future.

CONCLUSIONS AND RECOMMENDATIONS

➤ Overall comprehension of information in the Drug Facts Label was very good:

The ability of the Drug Facts Label to transfer information to the reader was generally very good. Results indicate that the General Population (GP) scored above the 90th percentile on 15 out of the 27 scenarios/questions concerning the Drug Facts label, and between 82% to 89% on seven of the scenarios/questions. This suggests a good grasp of most of the information and instructions about the product’s use, warnings and directions that were contained in the label. The Low Literacy (LL) group scored above the 80th percentile on 17 out of the 27 scenarios/questions associated with the Drug Facts Label. The two cohorts scored relatively poorly on only two important concepts – those concerning vitamin absorption and the recommended timing for taking a daily multivitamin. These will be discussed later in this summary.

➤ Need for clarification that Orlistat is intended for use only by overweight adults:

Seventy-nine percent of the General Population and 78% of the Low Literate group responded correctly that it is “not okay” to use Orlistat if a person is not overweight. These somewhat lower scores may be due to the slightly ambiguous nature of the label that was used in the study – a label which left room for some subjective interpretation. A little over 20% of all the respondents rationalized that, since there was no specific warning on the box stating that non-overweight people should not take Orlistat, and if a person is over 18 and healthy, then it would be “okay” to take Orlistat.

- **New warning has been added to the NDA Drug Facts Label:** In light of the propensity for some study participants to ignore the label instructions and rationalize that Orlistat is not just for *overweight* adults, and that it is up to individual purchasers to determine what their weight should be and whether or not they should use Orlistat, the Sponsor has added a specific warning to the Drug Facts Label in its NDA application. The revised label contains the Warning “Do not use . . . if you are not overweight.”

- Guidance about what it means to be “overweight” is needed on the exterior of the product container: There needs to be some type of guidance on the external packaging about how consumers can determine what constitutes being “overweight.” For example, some type of “BMI chart” or “BMI wheel” needs to be provided to help consumers make a more objective and accurate assessment of who is a suitable candidate for taking Orlistat. The supplementary educational materials, included inside the box, contain information about weight loss in general and describe numerous ways to maintain a low fat, reduced calorie diet. However, information about being “overweight” is needed on the outside of the box, so that consumers have appropriate guidance prior to purchasing the product.
- Potential use by consumers younger than 18 years of age and those who are not overweight: Although, at least initially, Orlistat may be used by teenagers and non-overweight consumers, this will probably self-resolve because: (a) the price of the product may be a prohibitive factor for most teenagers (see the “Teenager Final Report” self-selection study submitted by GSK on January 24, 2006); (b) there is no *rapid* weight loss, so the appeal to consumers who do not really need to take the product may be greatly diminished, and (c) there are some unpleasant (though not risky) side effects associated with overuse or incorrect use of the product which may serve as deterrents.

➤ **Vitamin absorption:**

A disappointing aspect of the label comprehension study results concerns the instructions about vitamin absorption and the proper timing for taking a daily multivitamin. On the first try, only 69% of the General Population and 50% of the Low Literacy group responded correctly that a multivitamin should be taken once a day, and only 48% of the GP and 34% of the LL group understood that in order to ensure adequate vitamin absorption, the multivitamin must be taken 2 hours before or 2 hours after taking Orlistat. Eventually, after two opportunities to review the label information and respond accurately, 73% of the 304 General Population subjects, and 58% of the 160 Low Literacy understood the correct timing for taking the multivitamin.

In order to increase the likelihood that consumers will read the instruction about taking a daily multivitamin, 2 hours before or 2 hours after taking Orlistat, it might be better to move the instruction higher up in the “Directions” section of the label, or even move it into the section of Warnings that is sub-headed “When using this product.” The order in which information is presented is an important factor in whether or not it is noticed, read at all, and/or recalled.

➤ **Results concerning other Directions and Warnings:**

Results for the other Drug Facts Directions and the Warnings about what to expect when using the product were generally positive. In the General Population, scores ranged from 75% to 95%, with seven of the eleven sets of scores occurring between 82% and 89%. Among the Low Literates group, scores ranged from 50% to 86%, with six of the eleven sets of scores reaching above the 70th percentile.

Recommendations

If changes and additions are made to the Orlistat Drug Facts Label and outer packaging as summarized above, I would recommend approval of orlistat for OTC use, based on the generally positive results reported in the Label Comprehension Study.

Orlistat Drug Facts Label Communication Objective: Results Reported by % of Total Correct + Acceptable Responses	Sponsor		Reviewer	
	GP%	LL%	GP%	LL%
Product Use	100	100	100	100
Not okay to use Orlistat if having gallbladder problems	99	97	99	97
Not okay to use Orlistat if had kidney stones in the past	97	97	97	97
Not okay to use Orlistat if currently taking medicine for diabetes	97	96	97	97
Not okay to use Orlistat if allergic	99	97	97	94
Okay to use Orlistat if experiencing problems sleeping	93	91	97	94
Not okay to use Orlistat if under 18 years old	98	98	96	95
Okay to take Orlistat if not currently taking any other medication for weight loss	98	98	96	94
Not okay to use Orlistat while taking cyclosporine	96	90	96	90
Not okay to use while breastfeeding	96	93	95	92
Changing your eating patterns before starting Orlistat	96	93	95	86
Not okay to use Orlistat while taking Warfarin	94	93	94	93
Recommended dosage to start taking Orlistat	95	91	93	90
Okay to use Orlistat if experiencing a headache	90	77	92	80
Not okay to use Orlistat if diagnosed with problems absorbing food	92	89	90	86
When to increase dose from 1 capsule to 2 capsules with each meal	89	80	89	81
Where to find information on using Orlistat	96	95	88	85
Okay to continue using Orlistat if experiencing loose stool and bowel changes	93	85	86	74
Maximum capsules of Orlistat in one day	86	67	86	67
How Orlistat works to promote weight loss	84	64	85	64
Why weight loss may vary between people taking Orlistat	83	64	82	62
Timeframe of when to expect results when taking Orlistat	82	69	82	69
Not okay to take Orlistat if not overweight	79	78	79	78
Weight loss goal not met after 6 months	78	74	78	74
How to decrease the likelihood of loose stool and bowel changes	86	69	75	50
Concern about vitamin absorption	93	88	69	50
Recommended timing for taking a multivitamin	79	66	48	34

Results Relating to Drug Facts Label – Use

Three questions directly concerned the use of Orlistat (per the Drug Facts Label) and were designed to test consumers’ understanding that:

- The product is intended to promote weight loss in overweight adults when used along with a reduced calorie and low fat diet.
- It is “not okay” to use Orlistat if under 18 years of age.
- It is “not okay” to use Orlistat if not overweight.

<u>PRODUCT USE – Drug Facts Label Communication Objective</u> <u>Results Reported by % of Total Correct + Acceptable Responses</u>	Sponsor		Reviewer	
	GP%	LL%	GP%	LL%
Q1 Product Use: “to promote weight loss in overweight adults when Used along with a reduced calorie and low fat diet.”	100	100	100	100
Q44 / Q45 Not okay to use Orlistat if under 18 years old	98	98	96	95
Q15 / Q16 Not okay to use Orlistat if not overweight	79	78	79	78

Scores for Question 1 concerning the product’s intended use, and Questions 44/45 testing the concept that it is not okay to use Orlistat if under 18 years of age, were very positive – 100% and 96%, respectively, for the General Population (according to the reviewer’s calculations). However, the scores concerning the instruction that Orlistat is for overweight adults require further explanation and are discussed below.

Information Transfer Objectives, Scenario and Study Questions	General Population (n=304)		Low Literacy (n=160)		Comments, Observations and Open-Ended Responses
	%	%	%	%	
Table C / Card H (Q15/Q16) <u>Not okay to use Orlistat if not overweight</u> Jane is 25 years old and not overweight. Jane is considering using Orlistat. Q15/Q16 Based on the package labeling, is it okay or not okay for Jane to use Orlistat?	<u>Sponsor</u> Correct 78 Acceptable 1 Total 79	<u>Reviewer</u> Correct 78 Acceptable 1 Total 79	<u>Sponsor</u> Correct 74 Acceptable 3 Total 78*	<u>Reviewer</u> Correct 74 Acceptable 3 Total 78*	Although the label states that Orlistat is for “ <i>weight loss in overweight adults</i> ” the Drug Facts panel does not indicate what constitutes being overweight. There may, therefore, be room for subjective interpretation of whether or not it is appropriate to take Orlistat. Much would depend on individual perceptions of whether one is “overweight” or not. One general train of thought was that, since there is no specific warning on the box stating that non-overweight people should not take Orlistat, and if the consumer is over 18 and healthy, then it’s okay to take it. Another set of responses reflected the idea that it would be good for <i>maintaining</i> desired weight. Ask a doctor, pharmacist or healthcare professional may be an acceptable response in this scenario.

As mentioned above, the “Jane” scenario and Questions 15/16 were designed to test the concept that it is not okay to use Orlistat if a person is not overweight. The lower correct + acceptable scores achieved on this scenario – only 79% of the General Population and 78% of the Low Literates answered correctly that it is NOT okay to use Orlistat if a person is not overweight – may be due to the somewhat ambiguous nature of the label instructions, which leave room for subjective interpretation.

The Drug Facts Label that was used in the Label Comprehension Study did not include a specific warning telling consumers that they must not use Orlistat unless they are overweight. This omission led several study participants to interpret the product’s desired indication – “to promote weight loss in overweight adults” – very loosely and subjectively. They rationalized that, since there is no warning on the box stating that non-overweight people must not take Orlistat, then it would be “okay” to take it. Ambiguity about the product’s intended use by “overweight” adults was exacerbated by the complete absence of anything written or pictorial on the package telling consumers how to assess what is “overweight.”

Drug Facts	
Active ingredient (in each sealed capsule)	Purpose
Orlistat 60mg.....	Weight Loss Aid
Use • promote weight loss in overweight adults when used along with a reduced calorie and low fat diet	
Warnings	
Do not use	
<ul style="list-style-type: none"> • if you are taking cyclosporine (a drug given after organ transplant) • if you have been diagnosed with problems absorbing food • if you are allergic to any of the ingredients in orlistat capsules 	

Verbatim Responses For Questions 15/16

A small percentage of all respondents (1% GP and 4% LL) suggested that Jane should consult her doctor first, but a fairly large percentage of respondents – just over 20% from each cohort – rationalized that, since “Jane” in the scenario was over 18 and healthy, and since there was no specific warning on the box stating that non-overweight people should not take Orlistat, then it would be “okay” to take Orlistat:

- *Is not contraindicated*
- *Package / label does not mention*
- *Don't have to be overweight to use*
- *Over 18 years old / old enough*
- *Healthy / isn't sick*
- *Safe to use*

Another set of verbatim responses reflected the idea that it would be good for maintaining desired weight:

- *“It could help her not to be overweight.”*
- *“If she wants to maintain her weight. It's fine to use.”*
- *“If she uses it moderately, it will help her maintain her weight.”*
- *“It could help her stay thin.”*
- *“She just might want to keep her weight the way it is.”*
- *“It's only a fat reducer and it would keep her thin.”*
- *“Helps block fat so you don't gain weight.”*

The verbatim responses further reveal respondents' thoughts about who is an appropriate candidate for Orlistat and suggest that consumer perceptions of what may be "overweight" or "not overweight" are quite subjective:

- *"If she really wants to go for that Calista Flockhart look, she can. It doesn't say specifically not to, and it probably won't be any worse for her than if she just goes bulimic."*
- *"If she wants to, it could help to lose cellulite but she really doesn't need it but she has no health problems to keep her from using the product."*
- *"Some people may want to lose weight no matter what they weigh. Nowhere on this box does it say for those that are overweight only."*
- *"She can see if it will cut down her appetite."*
- *"It just says a well-balanced diet and I don't think it says you can't use it unless you are overweight."*
- *"She doesn't need to take it, but it doesn't say not to take it if not overweight."*

Warning Added Later to the Drug Facts Label

In light of the apparent propensity for the study participants to ignore the label instructions and rationalize that Orlistat is not just for *overweight* adults, and that it is up to individual purchasers to determine what their weight should be and whether or not they should use Orlistat, the Sponsor added a specific warning to the Drug Facts Label in its application. The revised label adds the words: Do not use "if you are not overweight." See the highlighted text in the example below.

Drug Facts	
Active ingredient (in each sealed capsule)	Purpose
Orlistat 60 mg.....	Weight Loss Aid
Use	
• promote weight loss in overweight adults when used along with a reduced calorie and low fat diet	
Warnings	
Do not use	
• if you are taking cyclosporine (a drug given after organ transplant)	
• if you have been diagnosed with problems absorbing food	
• if you are allergic to any of the ingredients in orlistat capsules	
• if you are not overweight	

In addition to this warning that was added to the label, there needs to be some type of guidance on the external packaging about how to determine what constitutes being "overweight." The supplementary educational booklets contain information about weight loss in general and describe numerous helpful ways to maintain a low fat, reduced calorie diet. Nevertheless, the "incorrect" responses on Questions 15/16 indicate that 21% of GP and 23% of LL consumers maintained subjective perceptions about what constitutes being "overweight" and believed that it is up to individual purchasers to determine what their weight should be and whether or not they should use Orlistat.

Results Relating to Drug Facts Label – Warnings

Thirteen questions directly concerned the Drug Facts Label “Warnings” and, overall, the results were very positive, with 12 of the 13 sets of scores in the 90th percentile, and 9 of them above the 95th percentile.

<u>WARNINGS – Drug Facts Label Communication Objective</u> <u>Results Reported by % of Total Correct + Acceptable Responses</u>	Sponsor		Reviewer	
	GP%	LL%	GP%	LL%
Not okay to use Orlistat if having gallbladder problem	99	97	99	97
Not okay to use Orlistat if had kidney stones in the past	97	97	97	97
Not okay to use Orlistat if currently taking medicine for diabetes	97	96	97	97
Not okay to use Orlistat if allergic	99	97	97	94
Okay to use Orlistat if experiencing problems sleeping *	93	91	97	94
Not okay to use Orlistat if under 18 years old.	98	98	96	95
Okay to take Orlistat if not currently taking any other medication for weight loss	98	98	96	94
Not okay to use Orlistat while taking cyclosporine	96	90	96	90
Not okay to use while breastfeeding	96	93	95	92
Not okay to use Orlistat while taking Warfarin	94	93	94	93
Okay to use Orlistat if experiencing a headache *	90	77	92	80
Not okay to use Orlistat if diagnosed with problems absorbing food	92	89	90	86
Okay to continue using Orlistat if experiencing loose stool and bowel changes	93	85	86	74
* These conditions were not referred to in the Drug Facts Label. GSK’s Briefing Document, submitted on December 19, 2005, for the Advisory Committee Meeting, states on page 81 “[t]hese conditions do not pertain to orlistat and were included as control questions.”				

Warnings concerning use of concomitant medications such as cyclosporine, Warfarin, and diabetes drugs, and warnings concerning concomitant or prior conditions such as kidney stones and gallbladder problems, are selected out from the table above and discussed in more detail below.

Warnings →	<u>Cyclosporine</u>		<u>Warfarin</u>		<u>Kidney Stones</u>		<u>Gallbladder</u>		<u>Diabetes</u>	
Responses ↓	GP%	LL%	GP%	LL%	GP %	LL%	GP%	LL%	GP%	LL%
Correct Exactly Per Label Instruction	91	89	29	22	59	50	61	47	45	39
Acceptable Alternatives: “Not okay to use” or “Ask Dr. or Healthcare Professional”	5	1	65	71	38	47	38	50	52	58
Total % correct + acceptable responses	96	90	94	93	97	97	99	97	97	97

Warnings – Cyclosporine – Do not use

Warnings

Do not use

- if you are taking cyclosporine (a drug given after organ transplant)
- if you have been diagnosed with problems absorbing food
- if you are allergic to any of the ingredients in orlistat capsules

Although responses concerning cyclosporine were generally very positive, there is still concern about the number of study participants who answered incorrectly. For example (as illustrated above), even though the label states under **Warnings: Do not use if you are taking cyclosporine (a drug given after organ transplant)**, several respondents missed or misunderstood the warning, including nine respondents who said there was nothing on the package/label about cyclosporine. Examples of some incorrect responses:

- *I can't find anything that says he cannot take it if he takes cyclosporine.*
- *Not on package saying not to.*
- *It doesn't say anything about cyclosporine that I can see.*
- *Don't see anything on the package about this medication.*
- *It didn't mention cyclosporine.*
- *It wasn't on the box.*

Problem Regarding the Wording of Questions 2-3, 11-14, 24-25, 32-33, 40-41

The wording of Questions 2-3, 11-14, 32-33, and 40-41 concerning warnings about Cyclosporine, Warfarin, kidney stones, diabetes medication, and gallbladder problems was as follows:

“Based on the package labeling, is it okay or not okay for [name from scenario] to use Orlistat?”

This wording led many respondents to answer the question literally, i.e., “**Not okay**,” rather than responding using the language of the label instructions: e.g., “ask a doctor or pharmacist” (about Warfarin or diabetes medication), or “ask a doctor” (about kidney stones or gallbladder problems). The question should have asked: **“Based on the package labeling, what should [name from scenario] do now?”**

Strictly speaking, it would not generally be acceptable to answer “Not okay,” since that is not the information provided in the label. However, since the “not okay” responses appear to have stemmed from the wording of the questions, and since no harm would come to a consumer who selects NOT to take the product, this response could be acceptable in these particular instances. The results relating to these specific questions are discussed in more detail below.

Warnings – Gallbladder Problems or Kidney Stones – “Ask a doctor before use if you have . . .”

Two scenarios were designed to test understanding of the important warning that a doctor must be consulted before using Orlistat if the consumer has gallbladder problems or kidney stones.

Warnings
Do not use
<ul style="list-style-type: none">• if you are taking cyclosporine (a drug given after organ transplant)• if you have been diagnosed with problems absorbing food• if you are allergic to any of the ingredients in orlistat capsules
Ask a doctor before use if you have
<ul style="list-style-type: none">• gallbladder problems or kidney stones

The label specifically states: **Ask a doctor before use if you have gallbladder problems or kidney stones . . .**, yet only 61% of the GP and 47% of the LL group gave the strictly correct answer “ask a doctor,” while 38% and 50%, respectively, said it’s “not okay” to take the product if you have gallbladder problems. Similarly, regarding kidney stones, only 59% of the GP and 50% of the LL group gave the strictly correct answer “ask a doctor,” while the 38% and 47%, respectively, responded that it would not be okay to take Orlistat.

Nevertheless, as mentioned above, since the “not okay” responses appear to have stemmed from the wording of the questions, and since no harm would come to consumers who opt not to take Orlistat, the safety concern seems to be alleviated. The combined correct and acceptable responses were at or above the 97th percentile for the General Population and the Low Literacy group.

Warnings – Diabetes Medicine or Warfarin – “Ask a doctor or pharmacist before use if you are ...”

- taking medicine for diabetes. Your medication dose may need to be adjusted during weight loss.
- taking Warfarin (blood thinning medicine).
- taking other weight loss drugs.

Warnings
Do not use
<ul style="list-style-type: none">• if you are taking cyclosporine (a drug given after organ transplant)• if you have been diagnosed with problems absorbing food• if you are allergic to any of the ingredients in orlistat capsules
Ask a doctor before use if you have
<ul style="list-style-type: none">• gallbladder problems or kidney stones
Ask a doctor or pharmacist before use if you are
<ul style="list-style-type: none">• taking medicine for diabetes. Your medication dose may need to be adjusted during weight loss.• taking warfarin (blood thinning medicine)• taking other weight loss drugs

The label specifically states: **Ask a doctor or pharmacist before use if you are taking medicine for diabetes . . . or taking Warfarin . . .**, yet only 45% of the GP and 39% of the LL group gave the strictly correct answer “ask a doctor or pharmacist,” while 52% and 58%, respectively, said it’s “not okay” to take the product if you are taking medicine for diabetes. Similarly, regarding Warfarin, only 29% of the GP and 22% of the LL group gave the strictly correct answer “ask a doctor or pharmacist,” while the 65% and 71%, respectively, responded that it would not be okay to take Orlistat while taking Warfarin.

Again, however, as mentioned above, since the “not okay” responses appear to have stemmed from the wording of the questions, and since no harm would come to consumers who opt not to take Orlistat, the safety concern seems to be alleviated. The combined correct and acceptable responses regarding diabetes medicine were at the 97th percentile for the General Population and the Low Literacy group, and were at the 94th and 93rd percentiles, respectively, regarding Warfarin.

Warning – “Not Okay” to Take Orlistat While Breastfeeding

Although 95% of the General Population group and 92% of the Low Literacy group correctly responded that it is “not okay” to use Orlistat if breastfeeding, 11 subjects responded that the label did not contain the warning and 8 subjects offered a variety of their own rationalizations why it would be okay to take Orlistat even though the Drug Facts Label states (perhaps not clearly enough) “**If pregnant or breastfeeding, do not use.**” These are examples of the rationalizations revealed in the verbatim responses:

- *She just wants to lose weight.*
- *She couldn't use it when pregnant, but can use it now.*
- *She isn't really sick or nothing. She just wants to lose weight.*
- *It's not a danger to her.*
- *She's not high risk, baby out of her, and not old.*
- *After 6 to 8 weeks you can diet to lose baby fat.*

In trying to understand the reasons for these incorrect responses, several questions and possible explanations come to mind:

- Were the “incorrect” responses predominantly given by male respondents? Males may have overlooked a warning referring to pregnancy and breast-feeding, saying to themselves that the warning doesn’t pertain to them so they can skip over the information. Younger, unmarried males may be even more likely to ignore the warning.
- If women were among the “incorrect” responders, and particularly if there were women who are mothers or who are of childbearing potential, this is a serious issue and we need to know and ask: “Why would they ignore such an important warning?”
- Perhaps some consumers do not comprehend the nature of systemic drugs – if it were explained, their thinking might change.
- Maybe the urge to be thin (e.g., lose the extra pounds gained during pregnancy) is more important in a person’s mind than the health of a baby.

Answers to some of these questions might be obtained by examining “who” (gender/age/marital status/ethnicity) gave “incorrect” responses, and then by asking follow-up questions to delve more deeply into “why” they answered as they did.

Warning – “Not okay” to Use Orlistat if Diagnosed With Problems Absorbing Food

The “Jenna” scenario (Table G / Card D on page 13 above) indicates that the “correct” response rate on the food absorption scenario was high (90% GP and 86% LL) but as with the scenario about cyclosporine, several respondents incorrectly said that the warning about problems absorbing food was not mentioned on the box/ package/ label, even though it was clearly stated in the Drug Facts Label. Other respondents gave explanations which seemed to imply that Jenna’s wish to lose weight was more important than her inability to absorb food, and several respondents appear to have misunderstood this instructions entirely. Examples of verbatim responses include:

- *It’s good for dieting if you eat the right food.*
- *It might help her.*
- *It doesn’t have anything to do with absorbing food problems.*
- *It won’t make her sick or interfere with the program.*
- *She can take only part of the dosage and see what happens.*
- *The drug helps with absorption.*
- *This product could help your digestion.*
- *I’ve never heard of not absorbing food.*
- *It doesn’t say anything under warnings about it.*
- *I didn’t read it.*
- *I don’t see anywhere that it is a red flag.*
- *Well, the box does not say anything about absorbing food.*
- *I didn’t see anything about it not being okay.*
- *Only if she has trouble absorbing fat.*
- *She wants to lose weight.*
- *This is supposed to be good for weight loss.*

Directions – The Need to Take a Multivitamin Each Day at Specific Times

Directions

- for overweight adults 18 years and older
- before using this product, read the enclosed User’s Guide for complete directions and other important information
- 1 to 2 capsules with each meal
 - start with 1 capsule. After you have gained experience with choosing meals that contain less than 30% fat, you can increase to 2 capsules with each meal for maximum weight loss.
- do not exceed 6 capsules daily
- continue daily use for up to 6 months. If you have not reached your weight loss goal by 6 months, talk to your doctor.
- to ensure adequate vitamin absorption, you should take a multivitamin once a day, 2 hours before or after taking orlistat capsules

The key information transfer objective from the Drug Facts Label is this: Orlistat can prevent the absorption of fat soluble vitamins, therefore it is important for those taking Orlistat to supplement their diets with a daily multivitamin, but the vitamin supplement will be wasted if not taken in the precise time-frame instructed in the label – either 2 hours before or 2 hours after taking Orlistat.

Q27 Concern About Vitamin Absorption: Responses Coded by Sponsor as Correct / Acceptable	General Population N=304	Low Literacy N=160
GSK's Total of Correct + Acceptable Responses	93%	88%
Correct	69%	50%
Take a multivitamin once a day, 2 hours before or after taking Orlistat	47%	36%
Take a multivitamin	21%	14%
Take a multivitamin once daily/ Take a multivitamin	1%	0%
Acceptable	24%	38%
Ask a doctor		
Ask a doctor / pharmacist		
Eat better foods / More balanced diet / Watch diet		
Call 1-800#		
Look in User's Guide / Manual / Directions on label/ Reference cards		

The Table directly above shows the results for Question 27. We can see that the Sponsor has a combined total of correct and acceptable answers of 93% for the General Population and 88% for the Low Literacy group. However, if we look at the responses coded by the Sponsor as "acceptable" we can see that they are really just "default" answers that have no relationship to the actual label instructions. For example:

- Ask a doctor
- Ask a doctor or pharmacist
- Eat better foods or a more balanced diet
- Call the 800#
- Look in the Users Guide or the Manual or the Directions on the label or in the Reference cards

None of these answers show that consumers understood the specific label instructions concerning the need and timing for taking a multivitamin. We can therefore reject these so-called "acceptable" answers and eliminate 24% from the General Population total and 38% from the Low Literacy group total. This leaves us with the following totals: 69% of the General Population and 50 % of the Low Literacy group understood the need to take a daily multivitamin.

Now, because 160 respondents in the General Population and 102 respondents in the Low Literacy group did not understand the proper timing for taking the multivitamin, they were given a second opportunity to provide the correct answer, and the scenario about "Terry" was repeated and a new question was posed to the study subjects. The new question, Question 28, was more specific than Question 27, and specifically asked: "Based on the package labeling, what is the recommended timing for taking a multivitamin to ensure adequate vitamin absorption?"

Q28 "... what is the recommended timing for taking a multivitamin to ensure adequate vitamin absorption?" Responses Coded by Sponsor as Correct / Acceptable	General Population N= 160	Low Literacy N=102
GSK's Total of Correct + Acceptable Responses	79%	66%
Correct	48%	34%
2 hours before or 2 hours after taking capsule	48%	34%
One to two hours before meals	1%	0%
Acceptable	31%	31%
2 hours before [incomplete answer]		
2 hours after [incomplete answer]		
Six months; Once a day; Once a day for six months		
Before a meal; After you eat		
Ask a doctor or pharmacist; Call 1-800#		
Once a day 2 hours before [incomplete answer]		

The Table directly above reports the Sponsor's calculation of results for Question 28. It shows that GSK's combined total of correct and acceptable responses for the General Population was 79% and for the Low Literacy group it was 66%. However, as with the previous question (Q27), a variety of so-called "acceptable" answers are not appropriate, for example: "2 hours before" and "2 hours after" are incomplete answers and neither the wording of the scenario nor the question provide the necessary language (specific wording) to complete the sentences to "2 hours before or after taking Orlistat."

The responses such as "Six months, once a day, and once a day for six months" indicate that subjects were picking-up the instructions for how often and for how long to take the multivitamin, but were still missing the specific instruction to take the multivitamin 2 hours before or after taking Orlistat. General answers such as "Before a meal, or after you eat" or "Ask a doctor or pharmacist, or call the 800#" show absolutely no understanding of the label instruction and are nothing more than "default" responses. If we eliminate the 31% of unacceptable answers in each group, we are left with the following "correct" responses: 48% for the General Population and 34% for the Low Literacy group.

The following Table summarizes the reviewer's revised totals for "correct + acceptable" responses for Questions 27 and 28.

<u>DIRECTIONS – Drug Facts Label Communication Objective:</u> <u>Results Reported by % of Total Correct + Acceptable Responses</u>	Sponsor		Reviewer	
	GP% n=304	LL% n=160	GP% n= 304	LL% n=160
Concern about vitamin absorption	93%	88%	69%	50%
Recommended timing for taking a multivitamin	79%	66%	48%	34%

As indicated above, 69% of the General Population and 50% of the Low Literacy group correctly responded that a multivitamin should be taken once a day, but only 48% of the GP and 34% of the LL group understood that in order to ensure adequate vitamin absorption, the multivitamin must be taken 2 hours before or 2 hours after taking Orlistat. Even though this instruction was stated in the Directions section of the Drug Facts Label, 24% of GP and 38% of LL respondents reverted to "default" answers such as "ask a doctor" or "ask a doctor or pharmacist" or "call the 1-800#" on the package labeling or "look in the User's Guide/Manual/ Reference Card" in answering Q27 about vitamin absorption.

Question 27	GP Total n=304	LL Total n=160
"Take a multivitamin once a day, 2 hours before or after taking Orlistat capsules"	(n=144) 47%	(n=58) 36%
Question 28	GP n=160	LL n=102
"2 hours before or 2 hours after taking capsule"	(n=76) 48%	(n=35) 34%
Total number of subjects who responded correctly on Q27 and Q28	(n=220) 73%	(n=93) 58%

Ultimately, then, if you combine the scores for the correct answer from Question 27 with the scores for the correct answer from Question 28, you can see that even after two opportunities to review the label information and respond accurately, 27% of the 304 General Population subjects, and 42% of the 160 Low Literacy subjects still did not understand the correct timing for taking the multivitamin.

Need for Label Revisions Concerning Multivitamins

The order in which information is presented is an important factor in whether or not it is noticed, read at all, and/or recalled. In order to boost the likelihood that consumers will read the crucial instruction about taking a daily multivitamin, 2 hours before or 2 hours after taking Orlistat, it might be better to move the instruction higher up in the "Directions" section, or even move it into the section of Warnings that is sub-headed "When using this product."

Results Concerning Other Directions and Warnings

Although the results concerning vitamin absorption were disappointing, results for the other Drug Facts Directions and the Warnings about what to expect when using the product were mostly quite positive. In the General Population, scores ranged from 75% to 95%, with eight out of eleven sets of scores falling between 82% and 89%.

<u>Drug Facts Label Communication Objective:</u> <u>Results Reported by % of Total Correct + Acceptable Responses</u>	<u>Sponsor</u>		<u>Reviewer</u>	
	<u>GP%</u>	<u>LL%</u>	<u>GP%</u>	<u>LL%</u>
Changing your eating patterns before starting Orlistat	96	93	95	86
When to increase dose from 1 capsule to 2 capsules with each meal	89	80	89	81
Where to find information using Orlistat	96	95	88	85
Okay to continue using Orlistat if experiencing loose stool and bowel changes	93	85	86	74
Maximum capsules of Orlistat in one day	86	67	86	67
How Orlistat works to promote weight loss	84	64	85	64
Why weight loss may vary between people taking Orlistat	83	64	82	62
Timeframe of when to expect results when taking Orlistat	82	69	82	69
Not okay to take Orlistat if not overweight	79	78	79	77
Weight loss goal not met after 6 months	78	74	78	74
How to decrease the likelihood of loose stool and bowel changes	86	69	75	50

The lowest scores were achieved for comprehension of how to decrease likelihood of loose stool and bowel changes: only 75% of GP and 50% of LL subjects understood that “You can decrease the likelihood [of loose stool and bowel changes] by reducing the fat in your diet.” There were several idiosyncratic verbatim responses for this scenario, including:

- “She should drink more fluids/ Drink a lot of water/ Increase water intake.”
- “Eat less calories/ eat less.”
- “Take a multivitamin.”
- “Take something to firm her up/ Take other medication to help with this problem.”
- “She should take less fiber, not prune juice/ cut back on fruit because it irritates your bowels.”

For the communication objective concerning what to do if the weight loss goal is not met after 6 months of using Orlistat, comprehension levels were 78% for the GP and 74% for the LL group. This is not particularly good given the straightforward nature of the label instruction to “talk to your doctor” about the situation. An acceptable response was to call the 1-800 phone number for advice.

SCENARIOS DESIGNED TO ENCOURAGE EXTRAPOLATION

According to GSK’s Briefing Document (page 81), submitted on December 19, 2005, for the Advisory Committee Meeting, two medical conditions that do not pertain to Orlistat were included in the scenarios and accompanying questions to serve as control questions. These conditions were: experiencing “problems sleeping” and experiencing “a headache.”

The Reviewer’s initial review of the Orlistat Label Comprehension (dated December 10, 2005) described the inclusion of those two scenarios as follows: they “would require the subjects to extrapolate from the label information and make the kinds of *ad hoc* decisions that often face consumers of OTC drugs in the real world.” The subjects did reasonably well on these scenarios – on Questions 4/5 concerning problems sleeping, the GP scored 97% and the LL group scored 94%. On Questions 17/18 concerning experiencing a headache, the GP scored 92% and the LL group scored 80%. However, these scores reflect a specific analytical perspective regarding the scenarios and questions, one which encompasses the view that the scenarios generated some unforeseen problems. The analyses are described in detail below.

1. Okay to use Orlistat if experiencing problem sleeping (Card C scenario in Table B):

Lisa is overweight and is interested in losing a few pounds. She has been having problems sleeping lately. Lisa is thinking about using Orlistat for weight loss.

Q4/Q5 Based on the package labeling, is it okay or not okay for Lisa to use Orlistat?

Subjects were specifically told by the study interviewers (per their script) that it is the content of the package labeling that is being tested, not previous experience or common sense. The scenario was designed to test whether or not consumers would realize that it is alright to take Orlistat even if a person is having trouble sleeping, in other words, insomnia is not generally a contraindication for using Orlistat. Neither the Drug Facts Label, nor anything in the Tables of Contents for the various Guides, disclosed any directions or information concerning insomnia and the use of Orlistat. That being the case, a correct answer to the scenario question is, in fact, that **the package/label does not mention this**. Yet the subjects who gave that response were coded as having answered incorrectly.

There are actually **two** correct responses to this question:

1. The first is the response that the Sponsors were looking for, which would have been something like this: "It doesn't mention anywhere in the labeling that you shouldn't take Orlistat if you are having trouble sleeping, therefore it would be okay for Lisa to take Orlistat even if she's been having problems sleeping lately."
2. The second correct response is actually that none of the packaging, labeling or guides mention anything about this issue (insomnia). A total of 13 respondents gave CORRECT variations on this answer but were coded as "INCORRECT." Examples coded as "incorrect" include:
 - Don't see anything about sleeping.
 - I couldn't find on the back of the package where the information is stated.
 - I don't remember reading anything about that.
 - Didn't see it on the box.
 - It doesn't say anything about problems with sleeping.

An "acceptable" alternative to the latter response would have been one supplemented with additional caveats such as: "The labeling doesn't say anything about trouble sleeping. She should check with her doctor or a pharmacist in case she's taking some medication to help her sleep that might not be good to take along with Orlistat."

What *should* have been coded as "incorrect" but was, in fact, coded as "acceptable" was a response which fabricates something which is NOT in the labeling at all: "**It says if you have problems sleeping, don't take it until you consult your doctor.**" It is just as worrying that respondents make up things that are not in the labeling as it is that they forget or ignore things that are there.

2. **Okay to use Orlistat if experiencing a headache (Card I scenario in Table D):**

Frank is overweight and would like to use Orlistat. Frank has a headache today and is not sure if he should start taking Orlistat.

Q17/Q18 *Based on the package labeling, is it okay or not okay for Frank to start taking Orlistat today?*

Obviously, this scenario was designed to elicit the response that it would be "okay for Frank to start taking Orlistat today" because headaches are not mentioned anywhere in the labeling as a contraindication for Orlistat. However, although neither the label nor guides mentions headaches, several respondents erred on the side of caution when answering this question and, in fact, provided logical and rational reasons for their responses. The open-ended responses revealed three predominant trains of thought:

1. The cause of the headache is unknown, it might be a symptom of something more serious, and Frank should first find out from a doctor what's causing the headache before starting to take Orlistat.
2. People who suffer from headaches, particularly migraine headaches, often take medicine for the pain. If Frank is taking medicine for his headache he should check with a doctor or pharmacist before starting Orlistat, in case there is a potential drug interaction problem.
3. Frank should wait until his headache has gone before starting to use Orlistat.

Since neither the package labeling nor the Guides refer to headaches, an OTC consumer could hardly be faulted for taking the precautionary steps described above, nor can the study subjects be faulted for choosing to respond that the package/labeling does not mention headaches when, indeed, it does not. Several responses originally coded as "incorrect" should therefore be switched to "acceptable."

REVISIONS AND ADDITIONS NEEDED TO THE PACKAGING AND LABELING

Some elements of the Drug Facts Label need to be changed and I defer to Arlene Solbeck, M.S., the Senior Regulatory Review Scientist, for more complete details. These are simply my brief suggestions:

1. In the **Uses** section, it might help to state the age factor, as follows, since this is an important element of the appropriate use (and purchase) of the drug:

Use

- Promote weight loss in overweight adults, 18 years and older, when used along with a reduced calorie and low fat diet.
2. The **Directions** about multivitamins must be given greater prominence and clarity. Obviously they are being missed and/or misunderstood in their present form and location.
 3. There must be some indication on the external packaging as to what constitutes being "overweight." Consumers need guidance to help them make more informed and appropriate self-selection decisions and to (hopefully) deter them from making subjective assessments about who should use Orlistat.

Information Transfer Objectives, Scenario and Study Questions	General Population (n=304) %	Low Literacy (n=160) %	Comments and Observations, Including Open-Ended Responses																																
<p>Table A / Card A (Q1)</p> <p>Product Use</p> <p>Q1 Based on the package labeling, what is the product used for?</p>	<table border="1"> <tr><td>Sponsor Correct</td><td>%</td></tr> <tr><td>Acceptable</td><td>97</td></tr> <tr><td>Total</td><td>3</td></tr> <tr><td>Reviewer Correct</td><td>%</td></tr> <tr><td>Acceptable</td><td>97</td></tr> <tr><td>Total</td><td>3</td></tr> <tr><td>Total</td><td>100</td></tr> </table>	Sponsor Correct	%	Acceptable	97	Total	3	Reviewer Correct	%	Acceptable	97	Total	3	Total	100	<table border="1"> <tr><td>Sponsor Correct</td><td>%</td></tr> <tr><td>Acceptable</td><td>94</td></tr> <tr><td>Total</td><td>6</td></tr> <tr><td>Reviewer Correct</td><td>%</td></tr> <tr><td>Acceptable</td><td>94</td></tr> <tr><td>Total</td><td>6</td></tr> <tr><td>Total</td><td>100</td></tr> </table>	Sponsor Correct	%	Acceptable	94	Total	6	Reviewer Correct	%	Acceptable	94	Total	6	Total	100	<p>Responses coded as “acceptable” were appropriate based on the label language/content.</p> <p>Acceptable Responses:</p> <ul style="list-style-type: none"> • For dieting. • To block/prevent/decrease fat absorption. 				
Sponsor Correct	%																																		
Acceptable	97																																		
Total	3																																		
Reviewer Correct	%																																		
Acceptable	97																																		
Total	3																																		
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Acceptable	94																																		
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Reviewer Correct	%																																		
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<p>Table B / Card C (Q4 / Q5)</p> <p>Okay to use Orlistat if experiencing problems sleeping.</p> <p>Lisa is overweight and is interested in losing a few pounds. She has been having problems sleeping lately. Lisa is thinking about using Orlistat for weight loss.</p> <p>Q4/Q5 Based on the package labeling, is it okay or not okay for Lisa to use Orlistat?</p> <p>Note: This concomitant condition is not mentioned in the label.</p>	<table border="1"> <tr><td>Sponsor Correct</td><td>%</td></tr> <tr><td>Acceptable</td><td>87</td></tr> <tr><td>Total</td><td>6</td></tr> <tr><td>Reviewer Correct</td><td>%</td></tr> <tr><td>Acceptable*</td><td>87</td></tr> <tr><td>Acceptable**</td><td>6</td></tr> <tr><td>Total</td><td>4</td></tr> <tr><td>Total</td><td>97</td></tr> </table>	Sponsor Correct	%	Acceptable	87	Total	6	Reviewer Correct	%	Acceptable*	87	Acceptable**	6	Total	4	Total	97	<table border="1"> <tr><td>Sponsor Correct</td><td>%</td></tr> <tr><td>Acceptable</td><td>79</td></tr> <tr><td>Total</td><td>12</td></tr> <tr><td>Reviewer Correct</td><td>%</td></tr> <tr><td>Acceptable*</td><td>79</td></tr> <tr><td>Acceptable**</td><td>12</td></tr> <tr><td>Total</td><td>3</td></tr> <tr><td>Total</td><td>94</td></tr> </table>	Sponsor Correct	%	Acceptable	79	Total	12	Reviewer Correct	%	Acceptable*	79	Acceptable**	12	Total	3	Total	94	<p>* Since problems with sleep and use of Orlistat are not mentioned in the label, a response such as “ask a doctor, healthcare professional or pharmacist” may be an acceptable and understandable response for this scenario.</p> <p>** 13 subjects (8 GP and 5 LL) who were coded by the Sponsor as responding “incorrectly” actually gave a logical and technically correct response that the package/label does not mention anything about sleeping problems.</p> <p>It is interesting that another 12 respondents gave completely incorrect answers, including a couple who said that the label specifically indicated not to take Orlistat if you are having trouble sleeping. In fact the label does not mention anything at all about sleep problems.</p> <p>Examples of incorrect responses:</p> <ul style="list-style-type: none"> • It says if you have problems sleeping, don't take it until you consult your doctor. • Sleeping disorders – you can't take it. It says on the label. • Sleeping problems will affect it. • May be causing her sleep loss if not eating right. • The medicine might keep her up all night. • The insomnia might get worse with it and it doesn't say otherwise.
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Table C / Card H (Q15 / Q16) <u>Not okay to use Orlistat if not overweight</u>	Sponsor Correct Acceptable Total	Sponsor Correct Acceptable Total	The "Jane" scenario and questions (Card H, Q15/Q16) were designed to test the concept that it is not okay to use Orlistat if a person is not overweight. However, the scenario and question present information that is a little ambiguous and leaves room for subjective interpretation.
<p>Jane is 25 years old and not overweight. Jane is considering using Orlistat.</p> <p>Q15/Q16 Based on the package labeling, is it okay or not okay for Jane to use Orlistat?</p>	<p>% 78 1 79</p>	<p>% 74 3 78*</p>	<p>79% of the General Population and 78% of the Low Literates gave the correct answer that it is NOT OKAY. A few respondents suggested that Jane should consult her doctor or healthcare professional first, but just over 20% of the study participants offered a variety of reasons why it would be "okay" for Jane to use Orlistat.</p> <p>One general train of thought was that, since there is no specific warning on the box stating that non-overweight people should not take Orlistat, and if the purchaser is over 18 and is healthy, then it's okay to take it:</p> <ul style="list-style-type: none"> • Is not contraindicated / Package/label does not mention (25) • Don't have to be overweight to use (3) • Over 18 years old/old enough (13) • Okay to use / Healthy/'sn't sick / Safe to use / Other (22)
<p>Although the label states that Orlistat is for "<i>weight loss in overweight adults</i>" the Drug Facts panel does not indicate what constitutes being overweight. There may, therefore, be room for subjective interpretation of whether or not it is appropriate to take Orlistat. Much would depend on individual perceptions of whether one is "overweight" or not.</p> <p>Ask a doctor, pharmacist or healthcare professional may be an acceptable response in this scenario. Many of the responses that were coded as "incorrect" were quite logical given the label content.</p>	<p>Reviewer Correct Acceptable Total</p> <p>% 78 1 79</p>	<p>Reviewer Correct Acceptable Total</p> <p>% 74 3 78*</p> <p>* Percentages are rounded and do not always sum.</p>	<p>There were a variety of other interesting open-ended responses, including several that reflected the idea that Orlistat would be good for <i>maintaining</i> desired weight:</p> <ul style="list-style-type: none"> • If she really wants to go for that Calista Flockhart look, she can. It doesn't say specifically not to, and it probably won't be any worse for her than if she just goes bulimic. • Some people may want to lose weight no matter what they weigh. Nowhere on this box does it say for those that are overweight only. • There's nothing on the box that says not overweight people can't take it. There's no warning. • It might be unhealthy, but it doesn't explicitly say not to. • If she wants to maintain her weight, it's fine to use it. • It could help her not to be overweight. • I think it's good for everyone even if they are not really overweight. It could help them to maintain. • If she uses it moderately, it will help her maintain her weight. • It could help her stay thin. • She might just want to keep her weight the way it is.

Table D / Card I (Q17 / Q18)			
<p>Okay to use Orlistat if experiencing a headache</p> <p>Frank is overweight and would like to use Orlistat. Frank has a headache today and is not sure if he should start taking Orlistat.</p> <p>Q17/Q18 Based on the package labeling, is it okay or not okay for Frank to start taking Orlistat today?</p>	<p>Sponsor</p> <p>Correct 80 %</p> <p>Acceptable 10 %</p> <p>Total 90 %</p> <p>Reviewer</p> <p>Correct 80 %</p> <p>Acceptable 10 %</p> <p>Acceptable 2 %</p> <p>Total 92 %</p>	<p>Sponsor</p> <p>Correct 66 %</p> <p>Acceptable 11 %</p> <p>Total 77 %</p> <p>Reviewer</p> <p>Correct 66 %</p> <p>Acceptable 11 %</p> <p>Acceptable 2 %</p> <p>Total 80 %</p>	<p>Note: This concomitant condition is not mentioned in the label.</p> <p>Experiencing a headache at the same time as wanting to take Orlistat is not mentioned in the label. A response such as "ask a doctor, pharmacist or healthcare professional" is, therefore, an acceptable and understandable response for this scenario. 10% GP and 11% LL gave this response.</p> <p>Sponsor coded as "incorrect" respondents who said that the label does not mention this concomitant condition.</p> <p>However, since neither the package labeling nor the Guides refer to headaches, the study subjects cannot be faulted for choosing to respond that the package/labeling does not mention headaches when, indeed, it does not.</p>
<p>Table E / Card L (Q21 / Q22)</p> <p>Okay to continue using Orlistat if experiencing loose stool and bowel changes.</p> <p>Peggy is overweight and has been talking Orlistat for 1 week. She has noticed that she is having loose stool and bowel changes.</p> <p>Q 21/Q22 Based on the package labeling, is it okay or not okay for Peggy to continue using Orlistat?</p>	<p>Sponsor</p> <p>Correct 86 %</p> <p>Acceptable 7 %</p> <p>Total 93 %</p> <p>Reviewer</p> <p>Correct 86 %</p> <p>Acceptable 0 %</p> <p>Total 86 %</p>	<p>Sponsor</p> <p>Correct 74 %</p> <p>Acceptable 11 %</p> <p>Total 85 %</p> <p>Reviewer</p> <p>Correct 74 %</p> <p>Acceptable 0 %</p> <p>Total 74 %</p>	<p>The label specifically describes these symptoms/side effects, explains that they are related to how the product works, and will lessen in a few weeks. The default response "ask a doctor, pharmacist or other healthcare professional" is therefore NOT an acceptable response for this scenario and should be coded as "incorrect."</p> <p>14% of GP respondents and 26% of LL respondents gave incorrect responses which seem to indicate that they <i>completely missed</i> the point on the label that loose stools and bowel changes are related to how the product works, usually lessen in a few weeks, and you can reduce the likelihood of these effects by reducing the fat in your diet.</p> <p><u>Examples of incorrect responses:</u></p> <ul style="list-style-type: none"> • It could mean something serious. • . . . it means something is wrong in your system. • . . . Don't think it would be healthy. • I don't think it's good for your body... I would quit using it. • Maybe it's an allergic reaction. • It doesn't seem to agree with her. • Not healthy. • That is an adverse reaction. • Problems absorbing food will mess with the bowels.
<p>Correct responses after probe Q22:</p> <ul style="list-style-type: none"> • It is related to how the product works. • It is related to how the product works and usually lessens in a few weeks. • It will lessen in a few weeks. • This will happen after high fat meals. • Side effect / reaction to drug. • Normal / what to expect. 			

<p>Table F / Card BB (Q44 / Q45)</p> <p>Not okay to use Orlistat if under 18 years old.</p> <p>Stacey is 16 years old and overweight. Stacey is interested in trying Orlistat to lose weight.</p> <p>Q44/Q45 Based on the package labeling, is it okay or not okay for Stacey to use Orlistat?</p>	<p>Sponsor Correct 96 Acceptable 2 Total 98</p> <p>Reviewer Correct 96 Acceptable 0 Total 96</p>	<p>Sponsor Correct 95 Acceptable 3 Total 98</p> <p>Reviewer Correct 95 Acceptable 0 Total 95</p>	<p>The label states in Directions: "for overweight adults 18 years and older." Therefore, the only correct response for this scenario and question is "not okay."</p> <p>Ask a doctor or pharmacist is NOT an acceptable response for this scenario. The label specifically states that Orlistat is for overweight adults 18 years and older.</p> <p>For clarity and emphasis, it may be helpful to move this instruction to the top of the Drug Facts Label under the heading "Uses."</p> <p>For example: Use . . . promote weight loss in overweight adults 18 years and older, when used along with a reduced calorie and low fat diet.</p>
<p>Table G / Card D (Q6/Q7)</p> <p>Not okay to use Orlistat if diagnosed with problems absorbing food.</p> <p>Jenna is overweight and wants to reduce her weight. Jenna has previously been diagnosed as having problems absorbing food.</p> <p>Q6/Q7 Based on the package labeling, is it okay or not okay for Jenna to use Orlistat?</p> <p>The label states in the Warnings section: Do not use . . .</p> <ul style="list-style-type: none"> • if you have been diagnosed with problems absorbing food. 	<p>Sponsor Correct 90 Acceptable 3 Total 92*</p> <p>* Percentages are rounded and do not always sum.</p> <p>Reviewer Correct 90 Acceptable 0 Total 90</p>	<p>Sponsor Correct 86 Acceptable 3 Total 89</p> <p>Reviewer Correct 86 Acceptable 0 Total 86</p>	<p>The label specifically states in the Warnings section: Do not use if you have been diagnosed with problems absorbing food.</p> <p>Ask a doctor or pharmacist is NOT an acceptable response for this scenario.</p> <p>The overall "correct" response rate on the food absorption scenario was fairly high (86%-90%) but 8 respondents incorrectly said that the warning about problems absorbing food was not mentioned on the box/package/label, even though it is clearly stated in the Drug Facts Label. A further 21 subjects gave explanations which seemed to imply that Jenna's wish to lose weight was more important than her inability to absorb food, or that it's okay for Jenna to use Orlistat even though she has problems absorbing food. Some examples of incorrect responses include:</p> <ul style="list-style-type: none"> • It's good for dieting if you eat the right food. • It might help her. • It doesn't have anything to do with absorbing food problems. • It won't make her sick or interfere with the program. • She can take only part of the dosage and see what happens. • The drug helps with absorption. • This product could help your digestion. • I've never heard of not absorbing food.

<p>Table H / Card E (Q8 / Q9)</p> <p>Not okay to use while breastfeeding.</p> <p>Marsha had a baby two months ago and is currently breastfeeding. She would like to use Orlistat to help her get rid of the extra baby weight.</p> <p>Q8/Q9 Based on the package labeling, is it okay or not okay for Marsha to start using Orlistat?</p> <p><u>The Drug Facts Label states:</u> "If pregnant or breast-feeding, do not use."</p>	<p><u>Sponsor</u> Correct Acceptable Total</p> <p>% 95 1 96</p>	<p><u>Sponsor</u> Correct Acceptable Total</p> <p>% 92 1 93</p>	<p>Although 95% of the General Population group and 92% of the Low Literacy group correctly responded that it is "not okay" to use Orlistat if breastfeeding, 12 subjects responded that the label did not warn against taking Orlistat if breastfeeding, and 8 subjects offered a variety of their own rationalizations why it would be okay to take Orlistat even though the label states (perhaps not clearly enough) that breastfeeding is contraindicated:</p> <ul style="list-style-type: none"> • She just wants to lose weight. • She couldn't use it when pregnant, but can use it now. • She isn't really sick or nothing. She just wants to lose weight. • It's not a danger to her. • She's not high risk, baby out of her, and not old. • After 6 to 8 weeks you can diet to lose baby fat. <p>Ask a doctor or pharmacist is NOT an acceptable response for this scenario.</p>
<p>Table I / Card M (Q24 / Q25)</p> <p>Not okay to use Orlistat while taking cyclosporine.</p> <p>Bob is overweight and is interested in trying Orlistat to lose weight. He has been taking cyclosporine.</p> <p>Q 24/Q25 Based on the package labeling, is it okay or not okay for Bob to use Orlistat?</p> <p><u>Note:</u> Since the label specifically states: "Do not use if you are taking cyclosporine . . ." the response "ask a doctor or healthcare professional" is NOT acceptable for this scenario.</p>	<p><u>Sponsor</u> Correct Acceptable Total</p> <p>% 91 5 96</p>	<p><u>Sponsor</u> Correct Acceptable Total</p> <p>% 89 1 90</p>	<p>Even though the label states under Warnings: Do not use if you are taking cyclosporine (a drug given after organ transplant), several respondents completely missed or misunderstood the warning, and 9 of those respondents said there was nothing on the package/label about cyclosporine. Examples of some incorrect responses:</p> <ul style="list-style-type: none"> • I can't find anything that says he cannot take it if he takes cyclosporine. • Not on package saying not to. • It doesn't say anything about cyclosporine that I can see. • Don't see anything on the package about this medication. • It didn't mention cyclosporine. • He doesn't have any kidney problems. • He has no problem with bladder or kidney stones. • It won't make any difference because he has been taking the other medicine for a while.

<p>Table J / Card Q (Q29 / Q30)</p> <p>Not okay to use Orlistat if allergic.</p> <p>Sharon is overweight and would like to use Orlistat for weight loss. She is allergic to Orlistat.</p> <p>Q 29/Q30 Based on the package labeling, is it okay for Sharon to use Orlistat?</p>	<table border="1"> <tr><td><u>Sponsor</u></td><td>%</td></tr> <tr><td>Correct</td><td>97</td></tr> <tr><td>Acceptable</td><td>2</td></tr> <tr><td>Total</td><td>99</td></tr> <tr><td><u>Reviewer</u></td><td>%</td></tr> <tr><td>Correct</td><td>97</td></tr> <tr><td>Acceptable</td><td>0</td></tr> <tr><td>Total</td><td>97</td></tr> </table>	<u>Sponsor</u>	%	Correct	97	Acceptable	2	Total	99	<u>Reviewer</u>	%	Correct	97	Acceptable	0	Total	97	<table border="1"> <tr><td><u>Sponsor</u></td><td>%</td></tr> <tr><td>Correct</td><td>94</td></tr> <tr><td>Acceptable</td><td>3</td></tr> <tr><td>Total</td><td>97</td></tr> <tr><td><u>Reviewer</u></td><td>%</td></tr> <tr><td>Correct</td><td>94</td></tr> <tr><td>Acceptable</td><td>0</td></tr> <tr><td>Total</td><td>94</td></tr> </table>	<u>Sponsor</u>	%	Correct	94	Acceptable	3	Total	97	<u>Reviewer</u>	%	Correct	94	Acceptable	0	Total	94	<p>The label states under Warnings: "Do not use if you are allergic to any of the ingredients in Orlistat capsules."</p> <p>Ask a doctor or pharmacist is NOT an acceptable response for this scenario.</p>																
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<p>Table K/Card G (Q11/Q12/Q13/Q14)</p> <p>Not okay to use Orlistat if had kidney stones in the past.</p> <p>Kate is overweight and has had kidney stones in the past. She would like to start taking Orlistat to help her lose weight.</p> <p>Q11/Q12/Q13/Q14 Based on the package labeling, is it okay or not okay for Kate to use the product?</p>	<table border="1"> <tr><td><u>Sponsor</u></td><td>%</td></tr> <tr><td>"Ask doctor"</td><td>53</td></tr> <tr><td>After probe 1</td><td>4</td></tr> <tr><td>After probe 2</td><td>2</td></tr> <tr><td>"Not okay"</td><td>38</td></tr> <tr><td>Total</td><td>97</td></tr> <tr><td><u>Reviewer</u></td><td>%</td></tr> <tr><td>Ask doctor</td><td>53</td></tr> <tr><td>After probe 1</td><td>4</td></tr> <tr><td>After probe 2</td><td>2</td></tr> <tr><td>Acceptable</td><td>38</td></tr> <tr><td>Total</td><td>97</td></tr> </table>	<u>Sponsor</u>	%	"Ask doctor"	53	After probe 1	4	After probe 2	2	"Not okay"	38	Total	97	<u>Reviewer</u>	%	Ask doctor	53	After probe 1	4	After probe 2	2	Acceptable	38	Total	97	<table border="1"> <tr><td><u>Sponsor</u></td><td>%</td></tr> <tr><td>"Ask doctor"</td><td>44</td></tr> <tr><td>After probe 1</td><td>2</td></tr> <tr><td>After probe 2</td><td>4</td></tr> <tr><td>"Not okay"</td><td>47</td></tr> <tr><td>Total</td><td>97</td></tr> <tr><td><u>Reviewer</u></td><td>%</td></tr> <tr><td>Ask doctor</td><td>44</td></tr> <tr><td>After probe 1</td><td>2</td></tr> <tr><td>After probe 2</td><td>4</td></tr> <tr><td>Acceptable</td><td>47</td></tr> <tr><td>Total</td><td>97</td></tr> </table>	<u>Sponsor</u>	%	"Ask doctor"	44	After probe 1	2	After probe 2	4	"Not okay"	47	Total	97	<u>Reviewer</u>	%	Ask doctor	44	After probe 1	2	After probe 2	4	Acceptable	47	Total	97	<p>The label specifically states: Ask a doctor before use if you have gallbladder problems or kidney stones, yet 5 respondents said that the package/label did not mention this point, and one respondent said it would be okay to take Orlistat because "She isn't really sick. She just has a kidney problem." Note: It is not acceptable to answer "ask a pharmacist first." The correct answer is "ask a doctor."</p> <p>Strictly speaking, it should not be acceptable to answer "Not okay," since that is not the information provided in the label. However, a large percentage of respondents (38% to 47%) answered strictly according to the wording of the question, rather than using the language from the Drug Facts label. For example, since the question specifically asked: "is it okay or not okay . . . ?" they responded either that it would be "okay" or "not okay" for Kate to use Orlistat, rather than answering according to the label, that she should "ask a doctor."</p>
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<p>Table L / Card Y (Q40 / Q41)</p> <p>Not okay to use Orlistat if having gallbladder problems.</p> <p>Ben is overweight and is considering using Orlistat. He has been having problems with his gallbladder.</p> <p>Q40/Q41 Based on the package labeling, is it okay or not okay for Ben to use Orlistat?</p>	<table border="1"> <tr><td><u>Sponsor</u></td><td>%</td></tr> <tr><td>"Ask doctor"</td><td>60</td></tr> <tr><td>After probe</td><td>1</td></tr> <tr><td>"Not okay"</td><td>38</td></tr> <tr><td>Total</td><td>99</td></tr> <tr><td><u>Reviewer</u></td><td>%</td></tr> <tr><td>Correct</td><td>60</td></tr> <tr><td>After Probe</td><td>1</td></tr> <tr><td>Acceptable</td><td>38</td></tr> <tr><td>Total</td><td>99</td></tr> </table>	<u>Sponsor</u>	%	"Ask doctor"	60	After probe	1	"Not okay"	38	Total	99	<u>Reviewer</u>	%	Correct	60	After Probe	1	Acceptable	38	Total	99	<table border="1"> <tr><td><u>Sponsor</u></td><td>%</td></tr> <tr><td>"Ask doctor"</td><td>45</td></tr> <tr><td>After probe</td><td>2</td></tr> <tr><td>"Not okay"</td><td>50</td></tr> <tr><td>Total</td><td>97</td></tr> <tr><td><u>Reviewer</u></td><td>%</td></tr> <tr><td>Correct</td><td>45</td></tr> <tr><td>After Probe</td><td>2</td></tr> <tr><td>Acceptable</td><td>50</td></tr> <tr><td>Total</td><td>97</td></tr> </table>	<u>Sponsor</u>	%	"Ask doctor"	45	After probe	2	"Not okay"	50	Total	97	<u>Reviewer</u>	%	Correct	45	After Probe	2	Acceptable	50	Total	97	<p>The label specifically states: Ask a doctor before use if you have gallbladder problems or kidney stones. It is not acceptable to answer "ask a pharmacist first." The answer should be "ask a doctor."</p> <p>Strictly speaking, it should not be acceptable to answer "Not okay," since that is not the information provided in the label. However, a large percentage of respondents (38% to 50%) answered strictly according to the wording of the question, rather than using the language from the Drug Facts label. For example, since the question specifically asked: "is it okay or not okay . . . ?" they responded either that it would be "okay" or "not okay" for Ben to use Orlistat, rather than answering according to the label, that he should "ask a doctor."</p>								
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Table M / Card B (Q2 / Q3)		Table N / Card S (Q32 / Q33)	
<p>Not okay to use Orlistat while taking Warfarin.</p> <p>Jim is overweight and suffered a mild heart attack. As a result, his doctor put him on Warfarin, a prescription blood thinning medication. Jim has just purchased Orlistat and would like to start taking it as a weight loss aid.</p> <p>Q2/Q3 Based on the package labeling, is it okay or not okay for Jim to start using Orlistat?</p>	<p>Sponsor</p> <p>"Ask dr/ph" "Not okay" After probe Total</p> <p>Reviewer</p> <p>"Ask dr/ph" "Not okay" After probe Total</p> <p>% 28 65 1 94</p>	<p>Sponsor</p> <p>"Ask dr/ph" "Not okay" After probe Total</p> <p>Reviewer</p> <p>"Ask dr/ph" "Not okay" After probe Total</p> <p>% 22 71 0 93</p>	<p>The label specifically states: Ask a doctor or pharmacist before use if you are taking Warfarin (blood thinning medicine), yet 13 respondents said there was nothing about this restriction/contraindication on the label/package; others missed the connection between a heart attack and taking Warfarin, and still others confused the warning about transplant medication with the Warfarin warning.</p> <p>Strictly speaking, it should not be acceptable to answer "Not okay," since that is not the information provided in the label. However, a large percentage of respondents (65% to 71%) answered strictly according to the wording of the question, rather than using the language from the Drug Facts label. For example, since the question specifically asked: "is it okay or not okay . . . ?" they responded either that it would be "okay" or "not okay" for Jim, to use Orlistat, rather than answering according to the label, that he should "ask a doctor or pharmacist."</p>
<p>Not okay to use Orlistat if currently taking medicine for diabetes.</p> <p>Charlie is overweight and would like to lose weight. He is diabetic and takes a prescription medicine to treat his condition.</p> <p>Q32/Q33 Based on the package labeling, is it okay or not okay for Charlie to use Orlistat?</p>	<p>Sponsor</p> <p>"Ask dr/ph" "Not okay" Acceptable Total</p> <p>% 45 50 2 97</p>	<p>Sponsor</p> <p>Ask dr/ph "Not okay" Acceptable Total</p> <p>% 39 56 2 96*</p> <p>* Percentages are rounded and do not always sum.</p>	<p>The label specifically states: Ask a doctor or pharmacist before use if you are taking medicine for diabetes. Your medication dose may need to be adjusted during weight loss. Yet 8 respondents missed this warning on the package label.</p> <p>Strictly speaking, it should not be acceptable to answer "Not okay," since that is not the information provided in the label. However, a large percentage of respondents (50% to 56%) answered strictly according to the wording of the question, rather than using the language from the Drug Facts label. For example, since the question specifically asked: "is it okay or not okay . . . ?" they responded either that it would be "okay" or "not okay" for Charlie to use Orlistat, rather than answering according to the label, that he should "ask a doctor or pharmacist."</p> <p>Acceptable responses after two probes included answers where subject said either "adjust diabetic medicine" or "ask a doctor/pharmacist first."</p>

<p>Table O / Card V (Q36 / Q37)</p> <p>Okay to use Orlistat if not currently taking any other medication for weight loss.</p> <p>Kevin is overweight and is interested in trying Orlistat to lose weight. Kevin has tried other weight loss products in the past, but is not using any other drugs for weight loss at this time.</p> <p>Q 36/Q37 Based on the package labeling, is it okay or not okay for Kevin to use Orlistat?</p>	<p><u>Sponsor</u> Correct 96 % Acceptable 2 2 Total 98</p> <p><u>Reviewer</u> Correct 96 % Acceptable 0 0 Total 96</p>	<p><u>Sponsor</u> Correct 94 % Acceptable 4 4 Total 98</p> <p><u>Reviewer</u> Correct 94 % Acceptable 0 0 Total 94</p>	<p>The label specifically states: “Ask a doctor or pharmacist before use if you are taking other weight loss drugs.”</p> <p>But notice that the scenario specifically states that Kevin is NOT using any other drugs for weight loss at this time. The correct response, then, is that it is “okay” for Kevin to take Orlistat.</p> <p>For this particular question, is it “acceptable” to respond “ask a doctor or pharmacist?” Probably not, given the specific wording of the scenario.</p>
<p>Table P / Card F (Q10)</p> <p>Maximum capsules of Orlistat in one day.</p> <p>Q10 Based on the package labeling, what is the most number of Orlistat capsules that you should take in one day?</p>	<p><u>Sponsor</u> Correct 84 % Acceptable 2 2 Total 86</p> <p><u>Reviewer</u> Correct 84 % Acceptable 2 2 Total 86</p>	<p><u>Sponsor</u> Correct 64 % Acceptable 3 3 Total 67</p> <p><u>Reviewer</u> Correct 64 % Acceptable 3 3 Total 67</p>	<p>Open-ended responses reveal that 72 respondents answered this question incorrectly, and 66 out of those 72 incorrect respondents apparently confused the per-meal maximum dose (1-2 tablets per meal) with the maximum daily dose of 6 tablets. It is disturbing that even simple numeric instructions are easily mixed up.</p> <p>These low percentages of correct responses are worrying considering the label specifically states: “do not exceed 6 capsules daily.”</p>
<p>Table Q / Card K (Q20)</p> <p>Recommended dosage to start taking Orlistat.</p> <p>Ellen is overweight and would like to start taking Orlistat.</p> <p>Q20 Based on the package labeling, what is the recommended dose for Ellen to start taking Orlistat?</p>	<p><u>Sponsor</u> Correct 93 % Acceptable 2 2 Total 95</p> <p><u>Reviewer</u> Start w/1 38 % 1-2 each meal 54 54 Acceptable 1 1 Total 93</p>	<p><u>Sponsor</u> Correct 87 % Acceptable 4 4 Total 91</p> <p><u>Reviewer</u> Start w/1 34 % 1-2 each meal 53 53 Acceptable 1 1 Total 90</p>	<p>The Drug Facts Label clearly states in the Directions: “start with 1 capsule. After you have gained experience with choosing meals that contain less than 30% fat you can increase to 2 capsules with each meal for maximum weight loss.”</p> <p>The question specifically asks about the starting dose. Therefore any other dose other than the starting dose, “start with 1 capsule,” is NOT a correct response.</p> <p>The general dose direction in the Drug Facts Label is: “1 to 2 capsules with each meal.” This is the dose that was referred to by more than half of all respondents. It is disturbing that several study participants mistook the general per-meal dose for the recommended starting dose.</p>

<p>Table R / Card O (Q27)</p> <p>Concern about vitamin absorption.</p> <p>Terry is overweight and would like to use Orlistat for weight loss. She is concerned that she will not be able to absorb the vitamins in the food if she starts taking Orlistat.</p> <p>Q 27 Based on the package labeling, what, if anything, should Terry do about this concern?</p>	<table border="1"> <tr> <td>Sponsor Correct</td> <td>% 69</td> <td>Sponsor Correct</td> <td>% 50</td> </tr> <tr> <td>Acceptable</td> <td>24</td> <td>Acceptable</td> <td>38</td> </tr> <tr> <td>Total</td> <td>93</td> <td>Total</td> <td>88</td> </tr> <tr> <td>Reviewer Correct</td> <td>% 47</td> <td>Reviewer Correct</td> <td>% 36</td> </tr> <tr> <td>Acceptable</td> <td>22</td> <td>Acceptable</td> <td>14</td> </tr> <tr> <td>Total</td> <td>69</td> <td>Total</td> <td>50</td> </tr> </table>	Sponsor Correct	% 69	Sponsor Correct	% 50	Acceptable	24	Acceptable	38	Total	93	Total	88	Reviewer Correct	% 47	Reviewer Correct	% 36	Acceptable	22	Acceptable	14	Total	69	Total	50		<p>The Drug Facts Label states in the Directions section: “to ensure adequate vitamin absorption, you should take a multivitamin once a day, 2 hours before or after taking Orlistat capsules.”</p> <p>It is crucial for consumers to understand not only the importance of taking a multivitamin each day, but also to realize that the multivitamin must be taken and digested 2 hours before or 2 hours after taking Orlistat (NOT any closer in time to taking Orlistat).</p> <ul style="list-style-type: none"> Per the label instructions, the only completely correct answer for this scenario and question is: “take a multivitamin once a day, 2 hours before or 2 hours after taking Orlistat.” While only 47% GP and 36% LL subjects gave that complete response, 22% of GP and 14% of LL subjects mentioned the need to take a multivitamin, but they did not include the directive about the timing of taking the multivitamin. These answers have been counted as “acceptable” but are not fully correct.
Sponsor Correct	% 69	Sponsor Correct	% 50																								
Acceptable	24	Acceptable	38																								
Total	93	Total	88																								
Reviewer Correct	% 47	Reviewer Correct	% 36																								
Acceptable	22	Acceptable	14																								
Total	69	Total	50																								
<p>Table S / Card P (Q28)</p> <p>Recommended timing for taking a multivitamin.</p> <p>Since 160 subjects in the General Population and 102 subjects in the Low Literacy group did not understand the proper timing for taking the multivitamin, they were given a second opportunity to provide the correct answer, and the scenario about Terry was repeated and a new question was posed to the study subjects. The new question was more specific than question 27, and specifically asked:</p> <p>Q28 “Based on the package labeling, what is the recommended timing for taking a multivitamin to ensure adequate vitamin absorption?”</p>	<table border="1"> <tr> <td>Sponsor Correct</td> <td>% 48</td> <td>Sponsor Correct</td> <td>% 34</td> </tr> <tr> <td>Acceptable</td> <td>31</td> <td>Acceptable</td> <td>31</td> </tr> <tr> <td>Total</td> <td>79</td> <td>Total</td> <td>66</td> </tr> <tr> <td>Reviewer Correct</td> <td>% 48</td> <td>Reviewer Correct</td> <td>% 34</td> </tr> <tr> <td>Acceptable</td> <td>0</td> <td>Acceptable</td> <td>0</td> </tr> <tr> <td>Total</td> <td>48</td> <td>Total</td> <td>34</td> </tr> </table>	Sponsor Correct	% 48	Sponsor Correct	% 34	Acceptable	31	Acceptable	31	Total	79	Total	66	Reviewer Correct	% 48	Reviewer Correct	% 34	Acceptable	0	Acceptable	0	Total	48	Total	34		<p>Per the label instructions, the only correct answer for this question is: “2 hours before or 2 hours after taking Orlistat.”</p> <p>It is crucial for consumers to understand not only the importance of taking a multivitamin each day, but to realize that the multivitamin must be taken and digested 2 hours before or 2 hours after taking Orlistat (NOT any closer in time to taking Orlistat).</p> <p>21% of GP and 16% of LL subjects gave partial responses – “2 hours before,” “2 hours after,” “once a day 2 hours before.” However, because they did not specify 2 hours before or after taking Orlistat, these responses could not be counted as “acceptable.”</p> <p>None of the Sponsor’s other so-called “correct” responses, nor any of the Sponsor’s other so-called “acceptable” answers, are valid. How could it possibly be “correct” to answer: “one to two hours before meals?” Similarly, how could it possibly be “acceptable” to answer the question with any of the following?</p> <ul style="list-style-type: none"> Daily for six months, once a day. Before a meal. Six months. After you eat.
Sponsor Correct	% 48	Sponsor Correct	% 34																								
Acceptable	31	Acceptable	31																								
Total	79	Total	66																								
Reviewer Correct	% 48	Reviewer Correct	% 34																								
Acceptable	0	Acceptable	0																								
Total	48	Total	34																								

<p>Table T / Card X (Q39)</p> <p>Weight loss goal not met after 6 months.</p> <p>Melissa has been using Orlistat for 6 months to reduce her weight. She has not yet reached her weight loss goal.</p> <p>Q 39 Based on the package labeling, what, if anything, should Melissa do now?</p>	<table border="1"> <tr> <td>Sponsor Correct</td> <td>% 75</td> </tr> <tr> <td>Acceptable Total</td> <td>3 78</td> </tr> <tr> <td>Reviewer Correct</td> <td>% 75</td> </tr> <tr> <td>Acceptable Total</td> <td>3 78</td> </tr> </table>	Sponsor Correct	% 75	Acceptable Total	3 78	Reviewer Correct	% 75	Acceptable Total	3 78	<table border="1"> <tr> <td>Sponsor Correct</td> <td>% 64</td> </tr> <tr> <td>Acceptable Total</td> <td>10 74</td> </tr> <tr> <td>Reviewer Correct</td> <td>% 64</td> </tr> <tr> <td>Acceptable Total</td> <td>10 74</td> </tr> </table>	Sponsor Correct	% 64	Acceptable Total	10 74	Reviewer Correct	% 64	Acceptable Total	10 74	<p>The correct response based on the label is “talk to your doctor.”</p> <p>An acceptable response would be to call the 1-800 phone number for advice.</p> <p>Given the very simple and straightforward nature of this instruction, it is hard to understand the relatively low correct response rates: 75% for GP and 64% for LL. I am inclined to think that the point may have been overlooked because of its positioning relatively far down in the drug facts label – many consumers simply don’t read all the way to the end of a set of instructions. However, it probably needs to stay where it is because other instructions may deserve greater weight and prominence in the list than this particular one.</p>
Sponsor Correct	% 75																		
Acceptable Total	3 78																		
Reviewer Correct	% 75																		
Acceptable Total	3 78																		
Sponsor Correct	% 64																		
Acceptable Total	10 74																		
Reviewer Correct	% 64																		
Acceptable Total	10 74																		
<p>Table U / Card AA (43)</p> <p>When to increase dosage from 1 capsule to 2.</p> <p>Valerie is overweight and would like to lose weight. She has been using 1 capsule of Orlistat with each meal for 3 weeks.</p> <p>Q43 Based on the package labeling, when could Valerie increase her dose from 1 capsule to 2 capsules with each meal?</p>	<table border="1"> <tr> <td>Sponsor Correct</td> <td>% 80</td> </tr> <tr> <td>Acceptable Total</td> <td>9 89</td> </tr> <tr> <td>Reviewer Correct</td> <td>% 76</td> </tr> <tr> <td>Acceptable Total</td> <td>13 89</td> </tr> </table>	Sponsor Correct	% 80	Acceptable Total	9 89	Reviewer Correct	% 76	Acceptable Total	13 89	<table border="1"> <tr> <td>Sponsor Correct</td> <td>% 61</td> </tr> <tr> <td>Acceptable Total</td> <td>19 80</td> </tr> <tr> <td>Reviewer Correct</td> <td>% 55</td> </tr> <tr> <td>Acceptable Total</td> <td>26 81</td> </tr> </table>	Sponsor Correct	% 61	Acceptable Total	19 80	Reviewer Correct	% 55	Acceptable Total	26 81	<p>The correct response according to the label is: “After gaining experience choosing meals that contain less than 30% fat.”</p> <p>Note: The label instructions are somewhat ambiguous in terms of a particular time frame, hence there was quite a lot of variation in the responses. Several responses coded as “correct” are not strictly correct per the label but may be moved into the “acceptable,” category or range.</p> <p>Again, given the relatively straightforward nature of this instruction, it is hard to understand why strictly “correct” response rates were fairly low: 76% for GP and 55% for LL. The nature of the question vis-à-vis the rather ambiguous time-frame in the instruction may have something to do with this. As mentioned, a large percentage of responses were very varied.</p>
Sponsor Correct	% 80																		
Acceptable Total	9 89																		
Reviewer Correct	% 76																		
Acceptable Total	13 89																		
Sponsor Correct	% 61																		
Acceptable Total	19 80																		
Reviewer Correct	% 55																		
Acceptable Total	26 81																		
<p>Table V / Card CC (Q46)</p> <p>Where to find information on using Orlistat.</p> <p>Ron has purchased Orlistat. He has read the labels on the package but still has some questions about this product.</p> <p>Q46 Based on the package labeling, where could Ron find information?</p>	<table border="1"> <tr> <td>Sponsor Correct</td> <td>% 81</td> </tr> <tr> <td>Acceptable Total</td> <td>15 96</td> </tr> <tr> <td>Reviewer Correct</td> <td>% 81</td> </tr> <tr> <td>Acceptable Total</td> <td>7 88</td> </tr> </table>	Sponsor Correct	% 81	Acceptable Total	15 96	Reviewer Correct	% 81	Acceptable Total	7 88	<table border="1"> <tr> <td>Sponsor Correct</td> <td>% 75</td> </tr> <tr> <td>Acceptable Total</td> <td>20 95</td> </tr> <tr> <td>Reviewer Correct</td> <td>% 75</td> </tr> <tr> <td>Acceptable Total</td> <td>10 85</td> </tr> </table>	Sponsor Correct	% 75	Acceptable Total	20 95	Reviewer Correct	% 75	Acceptable Total	10 85	<p>The Drug Facts Label specifically states in the Directions section: “before using this product, read the enclosed User’s Guide for complete directions and other important information.” The label also includes a toll free telephone number for “Questions or comments?”</p> <p>“Ask a doctor/pharmacist” (when it is not a specific label instruction) is simply a default response and is not acceptable. Several subjects used this response and were inappropriately coded as “acceptable.” Also, the scenario specifically states that Ron “has read the labels on the package” but still has questions. Why, then, would it be “acceptable” for the respondents to say that if Ron wants to find more information, he can find it on the back of the box or in the questions and comments section, which is what he has already read?</p>
Sponsor Correct	% 81																		
Acceptable Total	15 96																		
Reviewer Correct	% 81																		
Acceptable Total	7 88																		
Sponsor Correct	% 75																		
Acceptable Total	20 95																		
Reviewer Correct	% 75																		
Acceptable Total	10 85																		

<p>Table W / Card L (Q23)</p> <p><u>How to decrease likelihood of loose stool and bowel changes.</u></p> <p>Peggy is overweight and has been taking Orlistat for 1 week. She has noticed that she is having loose stool and bowel changes.</p> <p>Q23 Based on the package labeling, What, if anything, should Peggy do to decrease the likelihood of this happening?</p>	<p>Sponsor Correct Acceptable Total</p> <p>72 14 86</p> <p>% 14 86</p>	<p>Sponsor Correct Acceptable Total</p> <p>48 22 69*</p> <p>% 22 69*</p> <p>* Percentages are rounded and do not always sum.</p>	<p>The Warnings section of the Drug Facts Label specifically explains that: "You can decrease the likelihood [of loose stool and bowel changes] by reducing the fat in your diet." Based strictly on the label language, then, only a response that says Peggy should "reduce the fat in her diet" is the correct response. "Ask a doctor/pharmacist" is a weak default option and is not "acceptable."</p> <p>There were some interesting "incorrect" verbatim responses, for example:</p> <ul style="list-style-type: none"> • She should drink more fluids /Drink a lot of water /Increase water intake. • Take a multivitamin. • Eat less calories/ Eat less. • Take something to firm her up/ Take other medication to help with this problem. • She should take less fiber, not prune juice/ Cut back on fruit because it irritates your bowels.
<p>Table X / Card R (Q31)</p> <p><u>How Orlistat works to promote weight loss.</u></p> <p>Q31 Based on the package labeling, how do Orlistat capsules work to promote weight loss?</p>	<p>Sponsor Correct Acceptable Total</p> <p>82 3 84*</p> <p>% 3 84*</p>	<p>Sponsor Correct Acceptable Total</p> <p>61 3 64</p> <p>% 3 64</p> <p>* Percentages are rounded and do not always sum.</p>	<p>These are rather low "correct" and "acceptable" response rates, given that the question is based on fairly straightforward information.</p> <p>* Percentages are rounded and do not always sum.</p>
<p>Table Y / Card T (Q34)</p> <p><u>Changing your eating patterns before starting Orlistat.</u></p> <p>Normally Tim eats foods that are high in fat and calories. Tim realized that he is getting overweight and has decided to start using Orlistat to reduce his weight.</p> <p>Q34 What, if anything, should Tim do with his eating patterns before he begins taking Orlistat?</p>	<p>Sponsor Correct Acceptable Total</p> <p>55 41 96</p> <p>% 41 96</p>	<p>Sponsor Correct Acceptable Total</p> <p>34 58 93*</p> <p>% 58 93*</p> <p>* Percentages are rounded and do not always sum.</p>	<p>The question specifically calls for the response that is pulled from the Drug Facts Label and provides the following instructions: "you should follow a well-balanced diet that is reduced in calories and contains 30% or less. Try starting this diet before you begin taking Orlistat capsules. See enclosed User's Guide for information and tips on how to follow a well-balanced diet that it low in calories and fat." The response "ask a doctor/pharmacist" is NOT acceptable.</p> <p>Many of the responses coded by Sponsor as "acceptable" are not strictly in accordance with the label language, but are reasonably appropriate for that category, for example:</p> <ul style="list-style-type: none"> • Try a low fat diet • Follow diet plan / Guide for well balanced diet • Look in User's Guide / Manual / Directions on the label / Reference card • Eat better foods / more balanced diet / Watch diet

<p>Table Z / Card W (Q38)</p> <p><u>Timeframe of when to expect results when taking Orlistat.</u></p> <p>Gina is overweight and has started taking Orlistat today.</p> <p>Q38 Based on the package labeling, how soon can Gina expect to begin seeing weight loss?</p>	<p>Sponsor Correct Acceptable Total</p> <p>80 2 82</p> <p>% Correct Acceptable Total</p>	<p>Sponsor Correct Acceptable Total</p> <p>64 5 69</p> <p>% Correct Acceptable Total</p>	<p>The Drug Facts Label states: "you should start to lose weight within the first two weeks. How much weight you lose will depend on how closely you follow the recommended diet and the Orlistat program."</p> <p>Correct responses included: "Within the first two weeks" and "In two weeks."</p> <p>Acceptable responses included:</p> <ul style="list-style-type: none"> • Within a few weeks. • One week. • Two to three weeks. • A week or two. <p>The vast majority of "incorrect" responses were: "Six months," which is actually the directed maximum length of time that the product should be used as an OTC medicine. Participants confused the two time frames.</p>
<p>Table AA / Card Z (Q42)</p> <p><u>Why weight loss amount will vary per person.</u></p> <p>Diane and her friend Bev are both overweight and started taking Orlistat at the same time. After taking Orlistat for 4 weeks, Diane is frustrated since she has not lost the same amount of weight as Bev.</p> <p>Q42 Based on the package labeling, what, if anything, is the reason why Diane is not losing the same amount of weight as Bev?</p> <p>Note: "Didn't ask doctor/should ask doctor" is <u>not</u> an acceptable response.</p>	<p>Sponsor Correct Acceptable Total</p> <p>79 4 83</p> <p>% Correct Acceptable Total</p>	<p>Sponsor Correct Acceptable Total</p> <p>58 7 64*</p> <p>% Correct Acceptable Total</p> <p>* Percentages are rounded and do not always sum.</p>	<p>Correct responses include:</p> <ul style="list-style-type: none"> • Not closely following the program • Not following the recommended diet • Not reducing calories and fat • Not taking Orlistat with each meal • Not taking Orlistat as much • Eating more fat/Too much fat in diet • Taking in more fat and calories <p>Acceptable responses include:</p> <ul style="list-style-type: none"> • Not following User's Guide correctly • Eating too much • Not taking it correctly/not doing it right • Differences in diet and exercise • Different diets/eating habits <p>Incorrect responses include:</p> <ul style="list-style-type: none"> • Metabolism breaking down fat at different speed • Different body mass/weight • Not exercising/not as active • Need to take multivitamin • Label doesn't mention (1) • Every body/system is different • Different fat absorption • Bowel changes

<p>Table BB / Card J (Q19)</p> <p>Information on what to order when dining out.</p> <p>Steve is overweight. He has been using Orlistat. Steve is going out to dinner tonight but is not sure what would be best for him to order.</p>	<table border="1"> <tr> <td>Sponsor</td> <td>%</td> <td>Sponsor</td> <td>%</td> </tr> <tr> <td>Correct</td> <td>35</td> <td>Correct</td> <td>19</td> </tr> <tr> <td>Acceptable</td> <td>40</td> <td>Acceptable</td> <td>38</td> </tr> <tr> <td>Total</td> <td>75</td> <td>Total</td> <td>58*</td> </tr> </table> <p>* Percentages are rounded and do not always sum.</p>	Sponsor	%	Sponsor	%	Correct	35	Correct	19	Acceptable	40	Acceptable	38	Total	75	Total	58*	<p>The accurate response is: "Away from Home Guide" which clearly states that it covers "Dining Out" issues. Some variations are acceptable:</p> <ul style="list-style-type: none"> • Dining Out Guide. • In the little restaurant guide. • Calorie/fat counter/diet cards. <p>"Ask a doctor/pharmacist" is NOT an acceptable answer, nor are a number of other responses coded by Sponsor as "acceptable." The following are so general as to be no better than default answers:</p> <ul style="list-style-type: none"> • In the booklet • In the packet • Inside the box <p>Some examples of incorrect responses:</p> <p>42 respondents gave answers such as:</p> <ul style="list-style-type: none"> • Back of package/on back in drug facts / Directions on box/label/directions / On the label / box <p>4 respondents said:</p> <ul style="list-style-type: none"> • From restaurant/ ask the waiter / restaurant / consult the restaurant <p>Other respondents said Steve should look in the "When using this product" section of the label; or "In the inactive ingredients" section of the label; or in the "Activity tracker;" or at "The bottom of the label."</p>
Sponsor	%	Sponsor	%															
Correct	35	Correct	19															
Acceptable	40	Acceptable	38															
Total	75	Total	58*															
<p>Q19 Based on the package labeling, where could Steve find information?</p>	<table border="1"> <tr> <td>Reviewer</td> <td>%</td> <td>Reviewer</td> <td>%</td> </tr> <tr> <td>Correct</td> <td>35</td> <td>Correct</td> <td>19</td> </tr> <tr> <td>Acceptable</td> <td>2</td> <td>Acceptable</td> <td>4</td> </tr> <tr> <td>Total</td> <td>37</td> <td>Total</td> <td>23</td> </tr> </table>	Reviewer	%	Reviewer	%	Correct	35	Correct	19	Acceptable	2	Acceptable	4	Total	37	Total	23	<p>The accurate response is: "At Home Guide" which states that it covers "Food Preparation." Also correct is the response "Meal Planner / Balance Your Meal Plan" since these are relevant sections of the "At Home Guide."</p> <p>The following were coded by Sponsor as "acceptable" but are either incorrect or are so general as to be no better than default answers:</p> <ul style="list-style-type: none"> • User's Guide • Call the Toll Free 800 number • Inside the box/Guide inside box • Questions or Comments section. • Food chart • Diet book <p>Examples of incorrect responses include:</p> <ul style="list-style-type: none"> • Back of package/on back in drug facts / Directions on box/label/directions / On the label/box/bottom of box/label / On warning label • Questions or Comments section; Ingredients section • Ask a doctor/pharmacist
Reviewer	%	Reviewer	%															
Correct	35	Correct	19															
Acceptable	2	Acceptable	4															
Total	37	Total	23															
<p>Table CC / Card N (Q26)</p> <p>Information on preparing meals.</p> <p>Laura is overweight and has been using Orlistat. She would like to prepare meals for the week and wants to make sure she has the right ingredients on hand.</p>	<table border="1"> <tr> <td>Sponsor</td> <td>%</td> <td>Sponsor</td> <td>%</td> </tr> <tr> <td>Correct</td> <td>42</td> <td>Correct</td> <td>24</td> </tr> <tr> <td>Acceptable</td> <td>42</td> <td>Acceptable</td> <td>39</td> </tr> <tr> <td>Total</td> <td>84</td> <td>Total</td> <td>63</td> </tr> </table>	Sponsor	%	Sponsor	%	Correct	42	Correct	24	Acceptable	42	Acceptable	39	Total	84	Total	63	<p>The accurate response is: "At Home Guide" which states that it covers "Food Preparation." Also correct is the response "Meal Planner / Balance Your Meal Plan" since these are relevant sections of the "At Home Guide."</p> <p>The following were coded by Sponsor as "acceptable" but are either incorrect or are so general as to be no better than default answers:</p> <ul style="list-style-type: none"> • User's Guide • Call the Toll Free 800 number • Inside the box/Guide inside box • Questions or Comments section. • Food chart • Diet book <p>Examples of incorrect responses include:</p> <ul style="list-style-type: none"> • Back of package/on back in drug facts / Directions on box/label/directions / On the label/box/bottom of box/label / On warning label • Questions or Comments section; Ingredients section • Ask a doctor/pharmacist
Sponsor	%	Sponsor	%															
Correct	42	Correct	24															
Acceptable	42	Acceptable	39															
Total	84	Total	63															
<p>Q26 Based on the package labeling, where could Laura find information?</p> <p>Acceptable responses include: Call the toll free 800 number. Inside the box/Guide inside the box.</p>	<table border="1"> <tr> <td>Reviewer</td> <td>%</td> <td>Reviewer</td> <td>%</td> </tr> <tr> <td>Correct</td> <td>42</td> <td>Correct</td> <td>24</td> </tr> <tr> <td>Acceptable</td> <td>0</td> <td>Acceptable</td> <td>0</td> </tr> <tr> <td>Total</td> <td>42</td> <td>Total</td> <td>24</td> </tr> </table>	Reviewer	%	Reviewer	%	Correct	42	Correct	24	Acceptable	0	Acceptable	0	Total	42	Total	24	<p>The accurate response is: "At Home Guide" which states that it covers "Food Preparation." Also correct is the response "Meal Planner / Balance Your Meal Plan" since these are relevant sections of the "At Home Guide."</p> <p>The following were coded by Sponsor as "acceptable" but are either incorrect or are so general as to be no better than default answers:</p> <ul style="list-style-type: none"> • User's Guide • Call the Toll Free 800 number • Inside the box/Guide inside box • Questions or Comments section. • Food chart • Diet book <p>Examples of incorrect responses include:</p> <ul style="list-style-type: none"> • Back of package/on back in drug facts / Directions on box/label/directions / On the label/box/bottom of box/label / On warning label • Questions or Comments section; Ingredients section • Ask a doctor/pharmacist
Reviewer	%	Reviewer	%															
Correct	42	Correct	24															
Acceptable	0	Acceptable	0															
Total	42	Total	24															

<p>Table DD / Card U (Q35)</p> <p>Information on fat and calories.</p> <p>Tina is overweight and has been using Orlistat. She would like to eat lunch tomorrow at a fast food restaurant. Tina wants to find out how much fat and calories are in the meal she usually orders.</p> <p>Q35 Based on the package labeling, where could Tina find information?</p>	<p><u>Sponsor</u> Correct Acceptable Total</p> <p>% 42 32 74</p>	<p><u>Sponsor</u> Correct Acceptable Total</p> <p>% 23 34 57</p>	<p>The accurate response is: "Away from Home Guide" which clearly states that it covers "Fast Food Restaurants." The variations "Dining Out Guide" and "Calorie/fat counter/diet cards" are acceptable alternative response..</p> <p>A number of responses coded by Sponsor as "acceptable" are either incorrect or are so general as to be no better than default incorrect answers:</p> <ul style="list-style-type: none"> • User's Guide. • Call the toll free 800 number. • Inside the box/Guide inside box. • Meal planner/Balance Your Meal Plan. • Questions or Comments Section. • Activity Tracker. <p>Examples of incorrect responses include:</p> <ul style="list-style-type: none"> • Back of package/on back in drug facts; Directions on box/label/ directions; On the label/box; Bottom of box/label; Front of package • When using this product section; Ingredients section; Food packages • At the restaurant
<p>Table EE / Card DD (Q47)</p> <p>Information on snacking tips.</p> <p>Q47 Based on the materials in front of you, when using Orlistat where would you look to find information on snacking tips?</p>	<p><u>Sponsor</u> Correct Acceptable Total</p> <p>% 77 2 80*</p>	<p><u>Sponsor</u> Correct Acceptable Total</p> <p>% 69 1 69*</p>	<p>The accurate response is: "At Home Guide" which states that it covers "Snacking Tips." The variations "Balance Your Meal Plan" or "Meal Planner" are acceptable alternative responses.</p> <p>* Percentages are rounded and do not always sum.</p> <p>Responses coded by Sponsor as "acceptable" are so general as to be nothing more than default incorrect answers:</p> <ul style="list-style-type: none"> • Table of contents • Inside box/Guide inside box
<p>Table FF / Card EE (Q48)</p> <p>Information on fast food restaurants.</p> <p>Q48 Based on the materials in front of you, when using this product where would you look to find information on fast food restaurants?</p>	<p><u>Sponsor</u> Correct Reviewer Correct</p> <p>% 90 90</p>	<p><u>Sponsor</u> Correct Reviewer Correct</p> <p>% 90 90</p>	<p>The accurate response is: "Away from Home Guide" which clearly states that it covers "Fast Food Restaurants." The variation "Dining Out" is a correct alternative response.</p> <p>Sponsor listed "Table of Contents" as an acceptable answer which is NOT appropriate.</p>

<p>Table GG / Card FF (Q49)</p> <p>Information on setting realistic goals.</p> <p>Q49 Based on the materials in front of you, when using this product where would you look to find information on setting realistic goals?</p>	<p><u>Sponsor</u> Correct 89 Acceptable 0 Total 90*</p> <p><u>Reviewer</u> Correct 89 Acceptable 0 Total 90*</p>	<p><u>Sponsor</u> Correct 86 Acceptable 1 Total 86*</p> <p><u>Reviewer</u> Correct 86 Acceptable 1 Total 86*</p>	<p>The accurate response is: "User's Guide/ The Orlistat Approach to Weight Loss" which states in the Table of Contents under the subheading "Prepare for Success" that it includes information on how to set realistic goals. An alternative correct response is: "Prepare for Success."</p> <p>An acceptable response is: "Approach to Weight Loss."</p> <p>* Percentages are rounded and do not always sum.</p>
<p>Table HH / Card GG (Q50)</p> <p>Information on learning to navigate the grocery store.</p> <p>Q50 Based on the materials in front of you, when using this product where would you look to find information on learning to navigate the grocery store?</p>	<p><u>Sponsor</u> Correct 65 Acceptable 2 Total 67</p> <p><u>Reviewer</u> Correct 65 Acceptable 1 Total 66</p>	<p><u>Sponsor</u> Correct 64 Acceptable 1 Total 66*</p> <p><u>Reviewer</u> Correct 64 Acceptable 1 Total 65</p>	<p>The accurate response is: "At Home Guide" which contains a section titled "Learn to Navigate the Grocery Store." An alternative correct response is: "Take Charge" (the subheading in the Guide's table of contents).</p> <p>* Percentages are rounded and do not always sum.</p> <p>"Meal Plan and Food Preparation" is not a correct response.</p>
<p>Table II / Card HH (Q51)</p> <p>Information on understanding personal eating habits.</p> <p>Q51 Based on the materials in front of you, when using this product where would you look to find the information on understanding your eating habits?</p>	<p><u>Sponsor</u> Correct 81 Acceptable Total 82*</p> <p><u>Reviewer</u> Correct 81 Acceptable Total 82*</p>	<p><u>Sponsor</u> Correct 76 Acceptable Total 76</p> <p><u>Reviewer</u> Correct 76 Acceptable Total 76*</p>	<p>The correct response is "User's Guide/The Orlistat Approach to Weight Loss." An alternative correct response is: "Manage Your Eating Behavior" (the subheading in the Guide's table of contents).</p> <p>* Percentages are rounded and do not always sum.</p>
<p>Table JJ / Card II (Q52)</p> <p>Information on the food and activity tracker.</p> <p>Q52 Based on the materials in front of you, when using this product where would you look to find a food and activity tracker?</p>	<p><u>Sponsor</u> Correct 43 Acceptable 2 Total 45</p> <p><u>Reviewer</u> Correct 43 Acceptable 0 Total 43</p>	<p><u>Sponsor</u> Correct 41 Acceptable 3 Total 43*</p> <p><u>Reviewer</u> Correct 41 Acceptable 0 Total 41</p>	<p>The correct response is "Away From Home Guide."</p> <p>* Percentages are rounded and do not always sum.</p> <p>Contrary to Sponsor's coding, the response "Table of Contents" is NOT an acceptable answer.</p>

6 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Susanna Weiss
3/14/2006 03:09:00 PM
INTERDISCIPLINARY

Amended Orlistat LC Study Review -- Ready for your signature

Charles Ganley
3/14/2006 04:21:11 PM
MEDICAL OFFICER

Social Science Review

Date: 12/10/05

Is located at:

<http://www.fda.gov/ohrms/dockets/ac/cder06.html#EndocrinologicMetabolic>

**January 23, 2006 Joint Meeting with Nonprescription
Drugs Advisory Committee**

Briefing Information

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Section:

**7 Label Comprehension Review; Division of NonPrescription Clinical
Evaluation**



Social Scientist's Review
Division of Nonprescription Clinical Evaluation

NDA #: 21-887

Correspondence date: August 4, 2006

Document ID Number:

Review Date: December 18, 2006

Sponsor: GlaxoSmithKline Consumer Healthcare

Drug: Orlistat – proposed trade name Alli.

Dosage Form and Route of Administration: 60 mg capsules

Active Ingredient(s): Orlistat

Proposed Indication: For weight loss

BACKGROUND

This is a review of the Final Report for the second Orlistat Label Comprehension Study based on Protocol W2900425. Orlistat 60 mg (proposed trade name Alli) is a candidate for OTC approval as an aid to promote weight loss when taken with a low-fat, reduced calorie diet. Xenical® (orlistat) 120 mg capsules were approved for prescription marketing on April 23, 1999, under NDA 20-766. On June 14, 2001 Hoffmann-LaRoche submitted IND 62,758, to investigate the feasibility of an over-the-counter (OTC) version of orlistat, to be marketed as Xenical® 60 mg capsules. GlaxoSmithKline (GSK) subsequently acquired ownership of IND 62,758 from Hoffmann LaRoche and has pursued the OTC approval of orlistat 60 mg.

Brief Summary of the First Label Comprehension Study

As part of the review process for the proposed OTC approval of orlistat, Glaxo Smith Kline (GSK) was asked to conduct a full Label Comprehension Study of its proposed orlistat 60 mg labeling. A study of the entire Drug Facts panel, as well as other package labeling and the Tables of Contents for several additional materials enclosed inside the orlistat box, was conducted between January 31, 2005 and February 11, 2005 and involved 410 subjects. Key results were as follows:

- Overall comprehension of information in the Drug Facts label was generally positive

The ability of the Drug Facts label to transfer information to the reader was generally positive. Results indicated that the General Population (GP) scored above the 90th percentile on 15 out of the 27 scenarios/questions concerning the Drug Facts label, and between 82% to 89% on seven of the scenarios/questions. The Low Literacy (LL) group also scored above the 80th percentile on 17 of the 27 scenarios/questions associated with the Drug Facts label.

- Proper timing for taking a daily multivitamin was not well understood

On the first try, only 69% of the GP and 50% of the LL group responded correctly that a multivitamin should be taken once a day, and only 48% of the GP and 34% of the LL group understood that in order to ensure adequate vitamin absorption, the multivitamin must be taken 2 hours before or 2 hours after taking

orlistat. Even after two opportunities to review the label information and respond accurately, only 73% of the 304 GP subjects, and 58% of the 160 LL subjects understood the correct timing for taking the multivitamin. To increase the likelihood that consumers will read the instructions about taking a daily multivitamin, it was suggested that it might be better to move the instructions into the Warnings section of the Drug Facts panel that is sub-headed "When using this product."

➤ Issues concerning the cyclosporine warning

While 96% of the GP and 90% of the LL group gave correct or acceptable responses, several respondents missed or misunderstood the warning including nine respondents who said there was nothing on the package/label about cyclosporine. FDA indicated that, since the interaction between cyclosporine and orlistat can endanger an organ transplant, a virtually perfect correct response rate would be required when retesting the label. GSK has conducted a separate new study on this issue and it has been reviewed by Laura Shay, RN, MS, C-ANP.

➤ Need for clarification that Orlistat is intended for use only by overweight adults

Due to some ambiguity in the Drug Facts label, only 79% of the General Population and 78% of the Low Literate group responded correctly that it is "not okay" to use orlistat if a person is not overweight. GSK recognized this ambiguity shortly after completion of the label comprehension study, and added a new warning to the NDA Drug Facts Label. The revised label included the **Warning "Do not use . . . if you are not overweight."**

It was suggested to the Sponsor that some type of guidance, such as a "BMI chart," should be placed on the external packaging to help consumers determine what constitutes being "overweight" and make an accurate assessment of who is a candidate for taking orlistat, prior to purchasing the product. The supplementary educational materials, included inside the box, contained information about weight loss in general and described numerous ways to maintain a low fat, reduced calorie diet.

➤ Potential use by consumers younger than 18 years of age

To address concerns that teenagers under 18 years of age may use the drug, GSK ran a follow-up study using a population of 147 teenagers, 14 to 17 years of age (see the "Teenager Final Report" self-selection study submitted by GSK on January 24, 2006 and a review of that study entered in DFS on March 14, 2006). The results indicated that 59% (n=87) of teens made the correct self-selection decision and 41% (n=60) made the incorrect self-selection decision, primarily motivated by the urge to lose weight. While weight loss in teens is a very strong motivator, it does appear that the product's price has some influence on deterring teens from pursuing a purchase. After hearing the price of the product, the percentage of "incorrect self-selectors" who said they wished to purchase the product dropped from 72% to 28% and, overall, only 13% (n=19) of the entire study population said they would purchase the product "today" at a price of ~~————~~ for a 30-day supply. However, it should be noted that because the question about price referred to the subject's intent to purchase the product "today," other factors, such as availability of funds at the time of the interview may have influenced those results.

Further discussion on this issue among ONP medical officer reviewers and management led to the conclusion that although, at least initially, orlistat may be used by some teenagers, this would probably self-resolve because: (a) the price of the product would be a prohibitive factor for many teenagers; (b) there is no *rapid* weight loss, so the appeal may be greatly diminished, and (c) there are some unpleasant (though not risky) side effects associated with overuse or incorrect use of the product (e.g., soiled underwear) which may serve as deterrents.

Presentation to and Review by an Advisory Committee

The results of the label comprehension study described above (we can refer to it as “LC Study #1”), as well as the results of other studies that were included in GSK’s orlistat application (NDA 21-887), were presented to a Joint Meeting of the Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committee, held on January 23, 2006, in Bethesda, Maryland. Based on the outcome of the Advisory Committee meeting and FDA’s review process, an “Approvable” letter for the use of orlistat 60 mg Capsules (Alli™) as an over-the-counter weight loss aid was sent to GSK on April 6, 2006.

The “Approvable” Letter and Issues Discussed at the June 14, 2006 Sponsor Meeting

The April 6, 2006 action letter listed several items concerning various label revisions and label testing requirements that GSK needed to address prior to NDA approval. A truncated version of the items most relevant to the present review is as follows:

- (1) Emphasize in the Drug Facts label the concept that appropriate diet and exercise are the foundation of any weight loss program and must be tried before medication is considered.
- (2) There is a need for improved self-selection concerning the cyclosporine warning, including understanding of any self-selection failure.
- (3) It is important that you improve the labeling statement regarding vitamin use and test it in a label comprehension study.
- (4) Dosing limited to 60 mg three times a day is appropriate for introduction of orlistat into the over-the-counter market. Test this revised instruction in the next label comprehension study.
- (5) The proposed label should convey information that will help a consumer at the point of purchase determine whether they are overweight or provide information as to when to consider initiating drug therapy. It is also important that additional labeling information be provided, possibly inside the package with the educational materials, which allows consumers to determine their ideal body weight and a weight-loss goal, based on BMI.
- (6) It is important to provide educational materials with the OTC product in lieu of the consultation that otherwise may be provided by a health care provider in the prescription setting. Effective weight loss requires behavioral modification as well as drug therapy. The educational materials included with this application, which are the behavior modification component, should provide information on lifestyle modification that a consumer understands. You will need to test consumer understanding of these materials.

In response to the “Approvable” letter, GSK modified the proposed labeling and developed protocols to test specific labeling items that had been poorly understood in the initial label comprehension study, including a self-selection study concerning the revised cyclosporine (and transplant) warning. The separate self-selection study has been reviewed by Laura Shay, RN, MS, C-ANP.

SUMMARY OF ORLISTAT LABEL COMPREHENSION STUDY #2

Objectives

The study had three objectives:

1. To measure consumers' understanding of the dosing instructions contained in the Drug Facts label.
2. To measure consumers' understanding of the multivitamin instructions contained in the Drug Facts label.
3. To measure consumers' understanding of key lifestyle modification information included in the package insert called "*Keys to Successful Weight Loss*":
 - Change your behavior
 - Eat right
 - Write it down
 - Develop a routine
 - Get active
 - Stick to your program

Study Design and Population

This was an 18-site study using mall-intercept for General Population recruitment and pre-recruitment with site databases for designated Low Literacy sites. Screening for the study began on June 23, 2006 and interviewing ended on July 7, 2006. A total of 3,677 subjects were screened for the General Population at 15 sites and 526 subjects were screened for the Low Literacy population at 3 sites. Of the combined total of 4,203 subjects who were screened, 518 subjects completed an interview: 401 in the general population and 157 in the low-literacy group. All qualified subjects then completed the REALM test, read the Drug Facts label and "*Keys to Successful Weight Loss*" and completed the label comprehension interview.

Cohort Number	Cohort	Recruitment Method	Total
1	General Population	Mall Intercept	401
2	Low Literacy	Pre-Recruit	157

Note: Total interviews (N=518) are less than the sum of the cohorts because 40 subjects (10%) in the general population were also low-literate, based on the REALM test, and they count in both the General Population and Low Literacy cohorts.

Inclusion Criteria

Inclusion for this study was determined by cohort.

Cohort 1: General Population (N=401)

To be considered eligible for enrollment in the General Population, consumers had to:

- be male or female, of any race,
- at least 18 years of age, and
- express an interest in weight loss.

Cohort 2: Low Literacy (N=157)

For Low Literacy, consumers must have met all of the requirements for the General Population listed above, and read at a maximum 7th/8th grade equivalency level as determined by the REALM screening instrument.

Exclusion Criteria

Subjects were excluded from the study if they:

- or anyone in their household worked for a marketing research company, an ad agency/public relations firm, a pharmaceutical company, as a healthcare professional, or as part of a health care practice.
- did not express an interest in weight loss.
- normally wore corrective lenses, contacts or glasses to read and did not have them with them.
- could not read or speak English.

The following table indicates recruitment sites for the General Population and provides a summary of household income and educational data for the ZIP Codes corresponding to the 15 interview sites.

Recruitment Sites and Demographic Data for the General Population (Table Supplied by Sponsor)

City, State	Number of interviews	Household Income		Number of Years in School/College	
		Summary of Median Income	Summary of Mean Income	Summary of Median Education	Summary of Mean Education
Duluth, MN	25	\$ 36,453.00	\$ 44,660.00	14.0	13.3
Springfield, MO	25	\$ 39, 831.00	\$ 52,911.00	14.0	13.5
Ft. Smith, AR	25	\$ 31,826.00	\$48,637.00	12.0	12.4
Fredericksburg, VA	26	\$ 65,019.00	\$ 74,882.00	14.0	13.3
Salina, KS	36	\$ 40,614.00	\$ 51,398.00	14.0	13.3
Charleston, WV	26	\$ 34,165.00	\$ 44,326.00	12.0	12.5
South Bend, IN	26	\$ 44,143.00	\$ 56,902.00	12.0	13.0
Lakeland, FL	26	\$ 39,778.00	\$ 50,204.00	12.0	12.5
Wayne, NJ	25	\$ 67,882.00	\$ 83,974.00	14.0	13.4
Corpus Christi, TX	26	\$ 42,051.00	\$ 54,932.00	14.0	12.9
San Francisco, CA	29	\$ 61,934.00	\$ 76,270.00	14.0	12.9
Milwaukee, WI	28	\$ 51,601.00	\$ 66,724.00	14.0	13.4
Atlanta, GA	26	\$ 61,360.00	\$ 91,795.00	17.5	14.5
Boston, MA	26	\$ 50,986.00	\$ 79,091.00	14.0	13.7
Seattle, WA	26	\$ 45,080.00	\$ 61,481.00	14.0	13.5

Sponsor's Note: The Summary data represents the numerical averages/medians of the data from the individual ZIP codes that correspond to each site. No adjustments have been made to account for potential differences in the populations of different ZIP Codes.

Forty (40) of the General Population interviews involved low-literate individuals. These respondents were classified and counted in both cohorts. The remaining 117 Low-Literacy respondents were pre-recruited using the site databases and interviewed through designated Low Literacy sites in Baltimore, MD, Los Angeles, CA, and Louisville, KY. The following table provides a summary of household income and educational data for the ZIP Codes corresponding to the three sites.

Recruitment Sites and Demographic Data for the Low Literacy Population (Sponsor’s Table)

City, State	Number of interviews	Household Income		Number of Years in School/College	
		Summary of Median Income	Summary of Mean Income	Summary of Median Education	Summary of Mean Education
Baltimore, MD	34	\$ 46,706.00	\$ 59,198.00	12.0	12.8
Los Angeles, CA	73	\$ 51,196.00	\$ 75,440.00	14.0	13.5
Louisville, KY	10	\$ 39,928.00	\$ 52,647.00	12.0	12.8

Sponsor’s Note: The Summary data represents the numerical averages/medians of the data from the individual ZIP Codes that correspond to each site. No adjustments have been made to account for potential differences in the populations of different ZIP Codes.

Population Demographics

Sponsor’s table below indicates demographic breakdowns with regard to gender, age, and race/ethnicity for the two study cohorts.

Demographic Breakdown	General Population (N=401)		Low Literacy Group (N=157)	
	N	%	n	%
Gender				
Male	133	33.2	54	34.4
Female	268	66.8	103	65.6
Age				
18-24	57	14.2	27	17.2
25-29	47	11.7	20	12.7
30-39	95	23.7	34	21.7
40-49	96	23.9	43	27.4
50-59	59	14.7	19	12.1
60+	47	11.7	14	8.9
Race/Ethnicity				
Caucasian (non-Hispanic)	284	70.8	85	54.1
African-American (non-Hispanic)	59	14.7	37	23.6
Hispanic	29	7.2	22	14.0
Asian	14	3.5	7	4.5
Native American (non-Hispanic)	3	0.7	2	1.3
Other (non-Hispanic)	11	2.7	4	2.5
Missing	1	0.2	0	0

Study Procedures

The Sponsor provided a mock orlistat Drug Facts label (*Appendix 2: Drug Facts Label*) and a 4-page insert, “*Keys to Successful Weight Loss*,” in the actual size and color of the anticipated final product (*Appendix 3: Keys to Successful Weight Loss*).

Drug Facts Label – Product Usage and Multivitamin

Subjects were asked to read the Drug Facts label. The label remained in front of the respondent at all times during the interview, but subjects were only told once (at the outset) that they could refer back to the label for assistance in answering questions. Baseline questions about product use and dosage were asked prior to testing comprehension of the multivitamin communication. This included 3 questions related to use and timing of the multivitamin in conjunction with orlistat.

Keys to Successful Weight Loss

Next, subjects were handed the package insert, “*Keys to Successful Weight Loss*,” and asked to read it. The interviewer stepped out of the room and continued the interview after the respondent indicated that he/she had finished reading the insert. Subjects were then asked a variety of scenario-based questions. In most cases, the questions asked the respondent to say whether or not the decision of the hypothetical character in the scenario would “follow or not follow the Keys to Successful Weight Loss,” although other questions were more open-ended (e.g., “what should Lilly do”). Responses, other than those that were correct, were followed by a probe question, “Why do you say that?” Question order and type were mixed to minimize subjects learning or detecting correct response patterns.

Data Management, Coding Process, Statistical Methods, and Analytical Plan

Coding Of “Correct,” “Acceptable” and “Incorrect” Responses

Since disagreement between GSK and FDA about these definitions had been the subject of considerable discussion in the review and analysis of Sponsor’s first label comprehension study (LC Study#1), further discussion of the definitions of “correct,” “acceptable,” and “incorrect” responses that would be acceptable to FDA took place during the June 14, 2006 meeting with GSK. FDA emphasized that an ACCEPTABLE response must capture all of the learning objectives of a particular label instruction that is being tested. Although a respondent’s own words can differ slightly from the precise label language, the response must reflect the complete instructional intent of the label language, and must be functionally equivalent in meaning to the label instruction that is being tested. FDA cited a specific example on page 106, card D, Protocol W2900425, concerning the way in which the response related to the timing for taking a multivitamin would be coded. FDA asked GSK how they would code a partial response that just said “once a day”. GSK explained that they would do a follow up probing question to try to obtain more information about the timing for take the multivitamin, and if the response was, for example “at bedtime” or “last thing at night,” those answers would be coded as acceptable.

Statistical Analysis and Data Reporting

Summary tables indicating the number and percentage of “correct,” “acceptable,” and “incorrect” responses were produced for each cohort and each question. “Correct” and “acceptable” responses were reported separately and then combined for a single summary of positive comprehension. In addition, tables listing verbatim responses to open-ended questions and the corresponding sub-net and net codes were provided, as were subject listings of incorrect responses were prepared.

Sample Size and Precision

Sponsor states that the study was designed to provide approximately 481 complete interviews: 385 interviews with general population adults (18 years of age or older) and 96 with low literacy adults. (About 14% of the general adult population was expected to qualify as low literacy and count towards both Cohort 1 and Cohort 2). For this study, precision was defined as the error range around the point estimate of the comprehension level. The “worst case” precision level for the general population cohort (with a comprehension level of 50%) would be $\pm 5\%$, and the “worst case” precision for the low literacy cohort would be $\pm 8\%$; however, as shown below, those precision levels would improve substantially at higher comprehension levels.

Cohort	Precision level if comprehension level is		
	50%	80%	95%
General Population (n = 385)	$\pm 5.0\%$	$\pm 4.0\%$	$\pm 2.2\%$
Low Literacy (n = 150)	$\pm 8.0\%$	$\pm 6.4\%$	$\pm 3.5\%$

Results

1. Drug Facts Label – Product Use

Reviewer Comment: Table 1 indicates that 99.8% of the General Population and 98.7% of the Low Literacy group understood that the product is used for weight loss.

Table 1: Product Use (Table Supplied by Sponsor)

Card A. Based on the label, what is this product used for? (Q1)		
	General population N=401 n (%)	Low literacy N=157 n (%)
Correct/Acceptable	400 (99.8)	155 (98.7)
Correct	375 (93.5)	145 (92.4)
For weight loss/to lose weight	140 (34.9)	98 (62.4)
For weight loss in overweight adults, 18 years and older, when used along with a reduced calorie and low fat diet	135 (33.7)	10 (6.4)
A weight loss aid	82 (20.4)	28 (17.8)
For weight loss in overweight adults	15 (3.7)	9 (5.7)
Weight loss and blocking fat absorption	2 (0.5)	0
For weight loss/to lose weight, for dieting	1 (0.2)	0
Acceptable	25 (6.2)	10 (6.4)
For dieting	17 (4.2)	8 (5.1)
To block/prevent/decrease fat absorption	8 (2.0)	2 (1.3)
Incorrect	1 (0.2)	2 (1.3)
Don't know	1 (0.2)	1 (0.6)
Fat burner	0	1 (0.6)

2. Drug Facts Label – Dose

Dosing instructions are located in the Directions section of the Drug Facts label, bullet items 3 and 4.

Directions

- take 1 capsule with each meal containing fat
- do not exceed 3 capsules daily

Table 2: Recommended Dose (Sponsor’s Table Amended by Reviewer)

Card B. Based on the label, what is the recommended dose when taking this product? (Q2)		
	General population N=401 n (%)	Low literacy N=157 n (%)
Correct/Acceptable	381 (95.0) 327n (81.5%)	146 (93.0) 109n (69.5%)
Correct	267 (66.6)	60 (38.2)
Take 1 capsule with each meal containing fat, but not more than 3 times a day	135 (33.7)	24 (15.3)
Take 1 capsule with each meal containing fat	117 (29.2)	33 (21.0)
Follow a well balanced diet reduced in calories and contains 30% fat or less, then take 1 capsule with each meal	15 (3.7)	3 (1.9)
Acceptable	114 (28.4)	86 (54.8)
Take 1 capsule with each meal	60 (15.0)	45 (28.7)
3 times a day [NOT an acceptable response]*	47 (11.7) [move to "Incorrect"]	34 (21.7) [move to "Incorrect"]
With meals [NOT an acceptable response]*	7 (1.7) [move to "Incorrect"]	3 (1.9) [move to "Incorrect"]
One with each meal	0	4 (2.5)
Incorrect	20 (5.0) 74n (18.5%)	11 (7.0) 48n (30.5%)
One per day	13 (3.2)	6 (3.8)
Don't know	5 (1.2)	3 (1.9)
Two per day	1 (0.2)	1 (0.6)
60 mg	1 (0.2)	0
Dose depends on height and weight	0	1 (0.6)

Move to "Incorrect"

* *Reviewer’s Note:* The partial responses “3 times a day” and “With meals,” as indicated in the table above, are not “acceptable” and should therefore be moved into the “incorrect” category of responses, thus altering the total number of combined “correct/acceptable” responses. A full explanation of the adjustments to Sponsor’s totals appears on the next page of this review.

Reviewer’s Comments:

Reviewer’s amendments to Sponsor’s Table (above) indicate that (after adjustment) 81.5% of the General Population and 69.5% of the Low Literacy group fully comprehended the dosing instructions to take 1 capsule with each meal containing fat and to not exceed 3 capsules daily.

In accordance with recommendations provided by FDA to GSK at the June 14, 2006 meeting, responses coded as “correct” must closely reflect the words of the Drug Facts label, and a “correct” answer should be a complete recitation of all the components of the educational message, i.e., cover all of the cognitive steps of the instruction. This is an especially reasonable expectation in view of the fact that respondents could refer back to the label whenever they wished while providing their answers.

“Acceptable” responses, while they do not necessarily need to be verbatim repetition of the Drug Facts language, must, either upon first response or upon follow-up probe, encompass all of the instructional components of the message. Partial phrases that fail to incorporate the full communication objectives of the particular label instruction are not acceptable.

*The instructional objectives of the label **Directions: “take 1 capsule with each meal containing fat” and “do not exceed 3 capsules daily”** are three-fold:*

- 1. The dose is **1 (ONE) capsule** with each meal containing fat (i.e., take only one capsule per meal, not more).*
- 2. The capsule must be taken **with a meal containing fat** (i.e., non-fat meals don’t call for orlistat).*
- 3. **Do not take more than 3 capsules per day***

The last instruction of course implies that you can take less but you must not take more than 3, total. If you eat only one meal on a given day that contains fat, then on that day you would only take one capsule.

Simply responding “3 times a day” is too general and completely misses two crucial components of the instructional message: (a) take only “1 (one) capsule” at a time, and (2) take orlistat with a meal that contains fat. A response of “3 times a day” leaves open the possibility that several capsules at a time can be taken, as long as they are taken three times a day, and the lack of acknowledgement that the capsules should be taken with meals containing fat leaves open the possibility that capsules could, for example, be taken first thing on waking, then around noon (regardless of food), and then last thing at night, which would not only be wrong in terms of dosing, but would also interfere with the multivitamin instruction, i.e., to take the multivitamin “at bedtime.”

Similarly, the partial response: “with meals” completely misses three crucial components of the instructional message: (a) the capsule must be taken with a meal containing fat; (b) only take 1 capsule (maximum) at a time, and (c) take no more than three capsules in a day. A response “with meals” leaves open the possibility that several capsules can be taken at one time, as long as they are taken with meals.

Note that, if the initial response had said: “three times a day” and then the follow-up probe had revealed the understanding “1 capsule per meal” and “with meals containing fat” then the combined responses would have been “acceptable.” Likewise, if an initial partial response had been: “take with meals” and then a follow-up probe had extracted the understanding that the meals must contain fat and no more than one capsule per meal should be taken, then, again, this combination of answers would lead to a total response code of “acceptable.” However, nothing in the Sponsor’s results table indicates that, even after follow-up probing, the subjects in question understood the full set (all components) of the key educational objectives of the product’s dosing instructions.

While it is true that in vernacular speech people often shorten their sentences and sometimes offer only partial thoughts, the study interviewers had every opportunity to ask a follow-up question to probe for complete information that would provide confirmation of understanding the full instructional message. However, the partial responses provided in Sponsor’s Table fail to show a complete and accurate grasp of all pieces of dosing information that need to be gleaned from the label. They are therefore not acceptable and have been moved from the “Acceptable” category and placed in the “Incorrect” section.

3. Drug Facts Label – Multivitamins

The multivitamin instruction is repeated twice in the Drug Facts label. The first time it occurs is in the **Warnings** section under the sub-heading “**When using this product.**” It is highlighted in yellow and is the first in a list of seven bulleted items. The second time the instruction occurs is in the **Directions** section. There it is in bold letters (not highlighted) and is number 8 in a list of 9 bulleted items.

Warnings

When using this product

- you need to take a multivitamin once daily, at bedtime. Orlistat can reduce the absorption of some vitamins.

Directions

- you need to take a multivitamin once daily, at bedtime, when using orlistat capsules

Reviewer’s Comments:

Results on the sequence of questions pertaining to multivitamin use were positive: 88.3% of the General Population and 79.0% of the Low Literacy group gave correct responses to the entire (three-part) sequence of questions concerning multivitamin use, showing that they fully understood the need to take a multivitamin, once a day, at bedtime.

Table 3: Multivitamin Use (Table Supplied by Sponsor)

Need a Multivitamin	Label Element		No. correct	General Population (N=401)		Low Literacy Group (N=157)	
	Take Multivitamin Daily	Take multivitamin at bedtime		N	%	n	%
C	C	C	3	354	88.3	124	79.0
C	C	I		12	3.0	6	3.8
C	I	C		3	0.7	2	1.3
I	C	C		22	5.5	20	12.7
			2	37	9.2	28	17.8
C	I	I		2	0.5	0	0
I	C	I		4	1.0	1	0.6
I	I	C		1	0.3	1	0.6
			1	7	1.7	2	1.3
I	I	I	0	3	0.7	3	1.9

Note: C=correct, I=incorrect.

Correct=correct initially, correct after probe, acceptable initially, or acceptable after probe

However, as the chart on the next page indicates, only the first question in the three-part sequence (Q3) was a completely non-leading question, since it contained no reference whatsoever to the word multivitamin. The subsequent questions (Q4 and Q5) educated the subjects to the fact that they were being asked about multivitamins, and likely prompted them to look at the label for specific information pertaining to multivitamin use. Their task was then made particularly easy by the fact that the relevant information in the label was highlighted in yellow.

Results summarized below show that, on Question 3 – where subjects had no prompting whatsoever that they were being asked about multivitamins – 22 people were unable to answer that they should take a multivitamin if taking Orlistat. On Questions 4 and 5, after the subjects were “clued into” the fact that they were being asked about multivitamin use, the numbers who were unable to state that they needed to take the multivitamin daily and needed to take the multivitamin at bedtime dropped to 3 and 12, respectively. The three elements of the multivitamin label instruction are presented below in conjunction with the actual question(s) asked in the study protocol.

Multivitamin Label Element	Corresponding Label Comprehension Question
need to take a multivitamin	Q.3 Based on the label, when using this product, what else, if anything, does a person taking this product need to take?
need to take it daily	Q.4 Based on the label, how often should a multivitamin be taken? Q4A. Could you be more specific and tell me how often that would be?
need to take it at bedtime	Q.5 Based on the label, what is the recommended timing for taking a multivitamin, that is, when should a person taking this product take a multivitamin? Q5A. Could you be more specific and tell me when that would be?

4. Educational Materials – Keys to Successful Weight Loss

Reviewer’s Comments:

An important aspect of the “approvable” letter was the message that additional labeling information must be provided, possibly inside the package, emphasizing that effective weight loss requires behavioral modification as well as drug therapy. The Sponsor acknowledges that long-term weight loss can only be accomplished with lifestyle and eating behavior changes, and that a healthy, low-fat, reduced-calorie diet and regular exercise are the cornerstones of any successful weight loss program. GSK plans to market Alli with several helpful educational components, including a pamphlet called “**Keys to Successful Weight Loss**” that introduces the consumer to the “Alli” weight loss program.

Twelve (12) scenario-based questions were used to test consumer understanding of six communication objectives contained in the package insert “**Keys to Successful Weight Loss.**” These communication objectives were:

- Change your behavior
- Eat right
- Write it down
- Develop a routine
- Get active
- Stick to your program

At the June 14, 2006 meeting, FDA indicated to GSK that the scenarios and questions designed to test consumer understanding of key educational messages in the “**Keys to Successful Weight Loss**” were too general and simplistic, and asked GSK to amend the scenarios and questions. The idea was to encourage meaningful educational testing by requiring the use of scenarios and questions that could be answered correctly only by gaining knowledge (extracting information) from the “**Keys to Successful Weight Loss**” pamphlet, rather than by using guesswork, basic common sense, or prior knowledge. The scenarios and questions as they were written in the protocol, followed by the amended versions used in the final study, are in **Appendix #1**.

According to the scores reported in Table 4, overall comprehension of the six communication objectives were above the 90th percentile on 10 of the 12 questions; 100% on one, and above the 80th percentile on one. However, these results should be viewed somewhat cautiously, given the simplistic nature of the scenarios and questions that were used to test consumer knowledge gain. It is possible that some correct answers were guesswork or basic common sense; others may have stemmed from prior knowledge of behavior modification weight-loss programs similar to the one described in the “**Keys to Successful Weight Loss**” pamphlet.

In hindsight, it would have been advisable to conduct a pre-test of consumer knowledge prior to exposure to the “**Keys to Successful Weight Loss**” material, then conduct a post-exposure test to assess the amount of knowledge gained from the material.

Table 4: Summary of Keys to Successful Weight Loss Understanding (Table Supplied by Sponsor)

Keys to Successful Weight Loss	Sponsor Scores	
	GP N=401 n (%)	LL N=157 n (%)
Change your behavior		
Card F	339 (84.5)	133 (84.7)
Card G	384 (95.8)	144 (91.7)
Card H	377 (94.0)	146 (93.0)
Eat right		
Card I	367 (91.5)	130 (82.8)
Card J	391 (97.5)	152 (96.8)
Card K	381 (95.0)	139 (88.5)
Write it down		
Card L	382 (95.3)	143 (91.1)
Develop a routine		
Card M	389 (97.0)	153 (97.5)
Get active		
Card N	397 (99.0)	153 (97.5)
Card O	381 (95.0)	145 (92.4)
Stick to your program		
Card P	401 (100.0)	157 (100.0)
Card Q	394 (98.3)	153 (97.5)

Conclusions

Results from the first Orlistat Label Comprehension Study, that were presented to an Advisory Committee in January 2006, indicated that the General Population (GP) scored above the 90th percentile on 15 out of the 27 scenarios/questions concerning the Drug Facts label, and between 82% to 89% on seven of the scenarios/questions. The Low Literacy (LL) group also scored above the 80th percentile on 17 out of the 27 scenarios/questions associated with the Drug Facts label.

Only four areas of labeling information needed to be re-tested in follow-up studies: (1) revised dosing instructions, (2) multivitamin instructions, (3) introductory behavior modification information contained in a pamphlet called "Keys to Successful Weight Loss," and (4) organ transplant/cyclosporine warnings, to be tested in a separate study. (The latter study has been reviewed by Laura Shay, RN, MS, C-ANP).

Results from the second Orlistat Label Comprehension Study (based on Protocol W2900425) indicate that, with regard to "product use," 99.8% of the General Population and 98.7% of the Low Literacy group understood that the product is used for weight loss. With regard to the "recommended dose," amended results indicate that 81.5% of the General Population and 69.5% of the Low Literacy group understood the instructions to take 1 capsule with each meal containing fat and to not exceed 3 capsules daily.

Results for the questions pertaining to multivitamin use indicate that 88.3% of the General Population and 79.0% of the Low Literacy group gave correct responses to the entire three-part sequence of questions concerning multivitamin use, showing that they fully understood the need to take a multivitamin, once a day, at bedtime. It should be noted that yellow highlighting was used to give added emphasis to the multivitamin information in the Drug Facts label that was tested, and the results may have depended on such highlighting. Therefore, future labeling of OTC orlistat should use the same highlighting.

With regard to comprehension of the information contained in the "Keys to Successful Weight Loss," the assessment is more mixed. Although comprehension of its six communication objectives was above the 90th percentile on 10 of the 12 questions; 100% on one, and above the 80th percentile on one, these results should be viewed somewhat cautiously, given the simplistic nature of the scenarios and questions that were used to test consumer knowledge gain.

Recommendation

The reviewer defers to supervisory and management recommendations.

Reviewer:

Susanna Weiss, Ph.D., J.D.
Social Science Analyst
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products

Team Leader:

Bindi Nikhar, M.D.
Medical Officer and Team Leader
Division of Nonprescription Clinical Evaluation
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 Deliberative Process

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Susanna Weiss
12/21/2006 04:59:36 PM
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Bindi Nikhar
12/22/2006 12:44:48 PM
MEDICAL OFFICER
Please also see Clinical Team Leader memo in DFS.



SOCIAL SCIENCE REVIEW

Food and Drugs Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

NDA: 21-887

Type of Submission: Self-Selection Study

Product/Ingredient Name: Alli™ (orlistat 60 mg)

Dosage Form Route of Administration: oral

Sponsor: GSKCH

Date Submitted: August 4, 2006

Date Received: August 7, 2006

Date Review Completed: November 21, 2006

Reviewer: Laura Shay, RN, MS, C-ANP

Introduction

This document is a review of the self-selection study conducted on a subpopulation of organ transplant recipients that was submitted in support of NDA 21-877.

Background

On June 6, 2005, GlaxoSmithKline Consumer Healthcare (GSKCH), submitted NDA 21-877 for Alli™ (orlistat) 60 mg capsules. Orlistat is a pancreatic lipase inhibitor that acts by inhibiting the absorption of dietary fat. When orlistat is taken within 2 hours of taking cyclosporine, the absorption of cyclosporine is decreased by 30%. Acute graft rejection has been reported in individuals taking cyclosporine and prescription orlistat (Xenical® 120 mg), therefore the proposed nonprescription product label contained a cyclosporine/organ transplant warning. In the actual use study submitted in support of this application, one out of two subjects who reported being on cyclosporine made an incorrect self-selection decision after reading the proposed label. In the label comprehension study, 96% of the general population subjects understood that cyclosporine users should not take orlistat, however in an online self-selection study with 46 cyclosporine users, only 89% made the correct self-selected decision.

On April 6, 2006 GSKCH received an approvable action letter. One of the deficiencies listed in the letter was to improve self-selection based on the cyclosporine warning including the understanding of any self-selection failures. On August 4, 2006, GSKCH submitted the results of a self-selection study conducted on a subpopulation of organ transplant recipients in response to this deficiency. The label tested had been changed from the original in that organ transplant warning was written to exclude all organ transplant patients regardless of which immunosuppressive drug they are on. In addition, the organ transplant warning was enhanced with a yellow highlight. Prior to initiating this study, GSKCH requested an end-of-review meeting to discuss their proposed label revisions. The issue of highlighting a specific warnings on the label was raised with the sponsor and is reflected in the June 14, 2006 meeting minutes: "We are not certain if yellow highlighting enhances comprehension of the highlighted text or whether highlighting positively or negatively affects comprehension of the remainder of the label. You may want to evaluate this in your label comprehension studies."

GSKCH chose to conduct their self-selection study using only a label containing a highlighted organ transplant warning on a group of organ transplant recipients.

Review

Study Title: Orlistat Self-Selection Study in Organ Transplant Recipients (W2900424)

Purpose: To test whether or not the revised organ transplant warning improved the correct selection rate among organ transplant recipients.

Objectives: The primary objective of this study was to evaluate whether organ transplant recipients who are interested in losing weight can correctly decide that OTC orlistat is not appropriate for them to use based on their understanding of the package label and their own medical history.

Study Design: One group descriptive study

Recruitment: Subjects who received an organ transplant were identified from 4 transplant centers in the U.S. These subjects were mailed flyers describing the nature of the survey and inviting them to participate.

Screening: When subjects called the phone number on the flyer, trained staff from individual market research sites screened subjects for an interest in weight loss using a standardized screening questionnaire. Subjects interested in weight loss were invited to participate in the study without being told the purpose of the study. No screening questions asked about organ transplant or use of immunosuppressive drugs. Verification of organ transplant was obtained on all subjects from the medical staff at the transplant centers.

Inclusion Criteria:

1. Interested in losing weight
2. 18 years of age
3. Reviewed and signed confidentiality agreement form
4. Able to speak, read, and understand English sufficiently to understand the nature of the study and was willing, able and likely to comply with all study procedures

Exclusion Criteria:

1. Employee of the Sponsor or CRO conducting the study, employee of other pharmaceutical companies, or a healthcare professional
2. Currently taking Xenical (Rx orlistat)
3. Participated in a web-based or marketing research survey in the past 6 months for a weight loss product
4. If wore or had any type of corrective lenses but did not have them with them

Sample Size: Sixty subjects participated in the study.

Study Sites: (Two out of the four study sites provided eligible subjects)

1. Transplant Division, Saint Barnabas Medical Center, New Jersey
2. The Clarian Transplant Center/Indiana University Hospital, Indiana

Data collection method: Data was collected on paper questionnaires. Site interviewers forwarded the questionnaires to [redacted] who forwarded the questionnaires to GSKCH where the data was entered into the database using double entry and other quality control standards.

Study Plan:

After verifying the subject's identity with the medical staff at the transplant centers, subjects were asked to review the Drug Facts label (Appendix 2). They were allowed as much time as needed to read the label and were then asked whether they considered the product to be appropriate for them to use and the reasons for their decision. Subjects who made an incorrect selection were asked additional questions asking them to clarify their understanding of the label instructions and reasoning. Subjects were also asked questions on demographics and subject confirmation of organ transplant. Subjects were compensated for their time and participation. A copy of the Screening Questionnaire and the On-Site Questionnaire used in the study were provided (Appendix 3 and 4).

Reviewer's Comments:

The sponsor did not describe why only two centers were able to provide eligible subjects. The screening questionnaire and the questions listed in the On-Site Questionnaire appear to be reasonable without language or the ordering of questions that would bias the subjects. Demographic data collected was limited to gender, age, race, and ethnicity. Data on level of education was not collected.

Informed Consent:

All subjects were required to sign a Confidentiality Agreement Form. A copy of the agreement was provided (Appendix 5).

Reviewer's Comments:

The confidentiality agreement does not appear to contain any biasing information. However, it is unclear how the sponsor was able to verify the subject's identity with the medical staff at the transplant center based on the Confidentiality Agreement which states: "All information will be kept confidential and your information will be linked only to your participant number and not directly to you. In all cases, your confidentiality will be maintained." It is also unclear how they were able to conduct this study without the required Health Insurance Portability and Accountability Act (HIPPA) release form that is required when any subject's medical information requested.

Data Analysis:

The primary endpoint was the number of eligible subjects who made a correct selection decision. Subjects were considered correct self-selectors if they stated that orlistat was not appropriate for them and subjects were considered incorrect self-selectors if they stated it was appropriate for them or if they were not sure if orlistat was appropriate for them to use. Eligible subjects were those subjects who met the inclusion/exclusion criteria and had medical confirmation of organ transplant.

Results:

The rate of correct selection was computed as the number of eligible subjects who made a correct selection decision divided by the number of eligible subjects. A one-tailed 95% confidence bound was computed for the true correct selection rate using exact methods.

A total of 100 subjects were screened, 39 were screening failures mostly (21) due to not being interested in losing weight. One subject was confirmed not to have had an organ transplant and 12 qualified but were not interested in participating. Sixty were eligible for analysis. The average age was 48.1 ± 12.02 years with an age range of 21-72 years. Fifty five percent were male, 51.7% Caucasian non-Hispanic, and 31.7% African-American. There were 5 Caucasian Hispanic subjects, 2 Asian subjects and 3 subjects of other races.

Of the 60 eligible subjects, 59 (98.3%) made a correct selection decision. One subject made an incorrect selection decision. The lower 95% confidence limit for the correct selection rate was 92.3%.

The sponsor states that having additional testing confirmed that the organ transplant alert highlighted in yellow was clear and understood by the population in that 56 subjects stated that they made a correct selection decision based on the transplant alert warning on the label or that they had had a transplant.

The one subject who made an incorrect self-selection decision when asked why he thought orlistat was appropriate for him stated "I would ask my doctor first. I can take almost any medication I want except for ibuprofen, according to my doctor."

Conclusion

This study demonstrates that individuals who have had an organ transplant are able to correctly determine that orlistat is not appropriate for them to use when a yellow highlight is added to the organ transplant warning.

Because this self-selection study only tested a label that contained a highlighted warning on a post-transplant population, it remains to be seen if the highlighting affects self-selection of other subpopulations. However, given that the concomitant use of cyclosporine is the only absolute contraindication for orlistat, it appears reasonable to approve this label without further testing.

Recommendations

None

Laura Shay, RN., MS, C-ANP, Social Science Analyst
Bindi Nikhar, MD, Medical Team Leader
Division of Nonprescription Clinical Evaluation
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/s/

Laura Shay
11/27/2006 12:30:05 PM
CSO

Bindi Nikhar
11/28/2006 08:24:46 AM
MEDICAL OFFICER



SOCIAL SCIENCE REVIEW

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

DATE: June 12, 2006

FROM: Susanna Weiss, Ph.D., J.D.
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products

THROUGH: Karen Feibus, M.D.
Acting Medical Team Leader, Office of Nonprescription Products

RE: **NDA 21-887**
GlaxoSmithKline Healthcare
Orlistat 60 mg capsules (for weight loss)

SUBJECT: **Review of Protocol #W2900425 for Orlistat Label Comprehension Study.**
See Briefing Package for June 14, 2006 meeting requested by GSK.
Submitted: May 17, 2006

INTRODUCTION

On May 17, 2006, GlaxoSmith Kline (GSK) submitted a Briefing Package as part of their request for a meeting with FDA to discuss the contents of the "Approvable" letter that was sent to GSK on April 6, 2006 concerning NDA 21-887 for the use of Orlistat 60 mg Capsules (Alli™) as an over-the-counter weight loss aid. (*A copy of the April 6, 2006 Approvable letter is provided in Appendix #1*). As part of the review process that led to the "Approvable" letter, GSK and FDA presented the new drug application to a Joint Meeting of the Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committee, held on January 23, 2006, in Bethesda, Maryland.

Included in the Briefing Package is the company's revised Orlistat labeling and plans for testing the revised labeling in accordance with the action letter. Specifically, at the meeting the sponsor wishes to:

- obtain agreement from the Agency as to the next steps required to obtain final approval of Orlistat
- discuss GSK's proposals to address the issues noted in the action letter
- obtain comments regarding the proposed labeling
- receive specific feedback related to the proposed label study protocols
- confirm the content and format of the proposed resubmission to facilitate review

Reviewer's comments in this document are limited to answering the sponsor's question concerning the proposed protocol and questionnaire for the label comprehension study (Protocol #W2900425).

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 Deliberative Process

GEMINI LABEL COMPREHENSION STUDY: PROTOCOL #W2900425

Objectives

There are two objectives for this study:

- To measure consumers' understanding of the multivitamin label communication,
- To measure consumers' understanding of key lifestyle modification information included in the *Keys to Successful Weight Loss* package insert.

Study Design

This will be a multi-site (15) study to learn if the population targeted for using this product understands the multivitamin label communication and in-pack *Keys to Successful Weight Loss*.

Two cohorts will be evaluated in this study: (1) adults representative of the general population who express an interest in weight loss, and (2) adult low-literate individuals who express an interest in weight loss. Participants will take the REALM test (Rapid Estimate of Adult Literacy in Medicine) to assess literacy in medicine and determine cohort placement. One label version will be tested.

Cohort 1 interviews will be completed using mall intercept recruitment (12 sites) and Cohort 2 interviews will be pre-recruited using site databases (3 sites). There will be an overlap in cohorts if a low-literate individual is found in the general population. This overlap is estimated to occur in approximately 14% of the interviews for Cohort 1.

Cohort	Population Target	Sample Size	Number of Sites
C 1	General Sample	n=385	12
C 2	Low-Literacy	n=150	3

Respondents will be recruited to represent a demographic mix of age and geographic areas throughout the United States, and approximate percentages of seventy (70%) female and thirty (30%) male will be attempted. All qualifying participants will be screened for general security and must express an interest (somewhat or very interested) in weight loss.

The interview will contain questions to test comprehension of the back panel Drug Facts multivitamin objective. The subject will then read the *Keys to Successful Weight Loss* and complete additional comprehension questions.

Inclusion Criteria

Inclusion for this study is determined by cohort:

Cohort 1

To be considered eligible for enrollment in the General Population, consumers must:

- Be male or female, of any race
- At least 18 years of age
- Express an interest (somewhat or very interested) in weight loss

Cohort 2

For Low Literacy, consumers must meet all of the requirements for the General Population listed above, and read at a maximum 7th to 8th grade equivalency as determined by the REALM screening instrument.

Exclusion Criteria

Subjects will be excluded from the study if:

- they or anyone in their household works for a marketing research company, an ad agency/public relations firm, a pharmaceutical company, as a healthcare professional, or as part of a health care practice.
- they do not express an interest in weight loss.
- Normally wear corrective lenses, contacts or glasses to read and do not have them with them.
- Can not read or speak English.

Procedures for Testing the Label and Keys to Successful Weight Loss

Qualified subjects will be asked to read the back panel Drug Facts label. The label will remain in front of the respondents at all times during the interview. Subjects will be told that they may refer back to the label for assistance in answering questions. Subjects will then be asked comprehension questions.

Subjects will then be asked to read the package insert, *Keys to Successful Weight Loss*. The interviewer will again step out of the room and continue the interview after the respondents indicate that they have finished reading the *Keys to Successful Weight Loss*. Subjects will be asked questions addressing understanding of key weight loss principals as described in the package insert.

Demographic information will be also collected during the course of the study. The respondents' age, gender, and race/ethnicity will be recorded at the time of screening.

Data Coding Process

Each scenario will be accompanied by a list of likely responses (not to be read to the subject). If a subject's answer does not match a pre-specified response, his or her verbatim response will be recorded. These verbatim responses will be coded using sub-net codes. Examples include "Call 1-800 number," "Ask a doctor or pharmacist," "Package does not specify."

All of the pre-specified responses and sub-net codes will be classified using the net codes "correct," "acceptable" or "incorrect." Correct responses are those that are initially correct, that is, correspond to the package instructions or those that are incomplete but, upon probing, are correct. Acceptable responses are those that do not correspond to the label, but do not indicate incorrect use of the product. Incorrect responses are those that do not conform to the label or do not indicate correct use of the product. Sub-net coding will be performed by two independent coders and discrepancies will be resolved by consensus. Classification of sub-net codes into net codes will be determined by GSK in conjunction with

Statistical Analysis

Subject characteristics (age, sex, race, literacy) will be summarized. Summary tables of number and percentage of "correct," "acceptable," and "incorrect" responses will be produced for each cohort and each question. "Correct" and "acceptable" responses will be reported separately and combined for a single summary of positive comprehension. A glossary of verbatim responses to open-ended questions and the corresponding sub-net and net codes will be prepared. In addition, subject listings of questions and responses will be prepared.

Sample Size and Precision

Approximately 481 unique interviews will be completed in this study: 385 interviews will be conducted with general population adults (18 years of age or older) and 96 with low literacy adults. (Approximately 14% of the general adult population [n=54] is expected to qualify as low literacy and count towards both Cohort 1 and Cohort 2).

For this study, precision is defined as the error range around the point estimate of the comprehension level. The “worst case” precision level for the general population cohort (with a comprehension level of 50%) would be $\pm 5\%$, and the “worst case” precision for the low literacy cohort would be $\pm 8\%$; however, as shown below, those precision levels would improve substantially at higher comprehension levels.

Cohort	Precision Level if Comprehension Level is...		
	50%	80%	95%
General Population (n = 385)	$\pm 5.0\%$	$\pm 4.0\%$	$\pm 2.2\%$
Low Literacy (n = 150)	$\pm 8.0\%$	$\pm 6.4\%$	$\pm 3.5\%$

CONCLUSIONS AND RECOMMENDATIONS

- The responses that GSK has provided to the April 6, 2006 “Approvable” letter, and the actions they have taken with regard to the new labeling and the new “*Keys to Successful Weight Loss*” pamphlet are clear, rational and appear to be appropriate for moving forward with the research. *(The Alli® label and the “Keys to Successful Weight Loss” pamphlet that were submitted for review on May 17, 2006 are attached in Appendix #2 and Appendix #3, respectively).*
- The new label that was submitted by GSK as part of the meeting package on May 17, 2006, is very nice – it is well written, well designed, and accommodates the issues raised in, and the changes requested in, the “Approvable” letter dated April 6, 2006. It appears to be appropriate for testing in the proposed label comprehension study.
- The pictures and instructions in the pamphlet titled “*Read Me First: Keys to Successful Weight Loss*” (submitted for review on May 17, 2006) is also very nice, and synthesizes well the main points of the behavior modification booklets and other materials that are enclosed inside the Alli® box. It appears to be appropriate for testing in the proposed label comprehension study.
- The overall design of the proposed label comprehension study is good, and the stated objectives of the study comply with the call of the “Approvable” letter. There are just a couple of changes and items of clarification that I would recommend regarding the coding of responses and the scenarios that will be used to test the “*Keys to Successful Weight Loss*” pamphlet.

Recommendations:

1. GSK needs to describe precisely which responses in the interviewers’ sheets will be coded as “correct” and which will be coded as “acceptable” so that we can determine if we are in agreement or not. For example, we want to be sure that consumers understand not only the need to take a multivitamin once a day, but also the correct timing for taking the multivitamin, i.e., at bedtime (or at least not at the same time nor close in time to taking Orlistat).

In order for a consumer's response to be counted as "correct," the response does not need to match the label language verbatim. However, it needs to resemble the label instruction sufficiently so that it captures the learning objective(s) of the particular instruction that is being tested. In short, a respondent's own words can be different from the precise label language, but they must adequately reflect the complete instructional intent of the label language. Similarly, an "acceptable" response may often not use the same wording that was used in the label, but it must be functionally equivalent in meaning to the label instruction that is being tested.

2. Some of the scenarios that are proposed for use in testing comprehension of the new package insert "*Read Me First: Keys to Successful Weight Loss*" are a little too general and simplistic. They may make it too easy for respondents to guess the correct answer ("FOLLOW" or "NOT FOLLOW"). I would suggest making the scenarios a little more complex, and perhaps also employ some direct questions, that require open-ended responses, in addition to using scenarios.

5 Page(s) Withheld

For APPENDIX #1: Approvable Letter

*(See Approvable Letter located after the
Approval Letter in the beginning of the
Approval Package)*

Withheld Track Number: Social Science-

4

11 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

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/s/

Susanna Weiss
6/22/2006 04:13:14 PM
INTERDISCIPLINARY

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