OTC MEDICAL OFFICER'S REVIEW

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

NDA # / Serial Number: 21-887
Type of Submission: Final study reports
Product/Ingredient Name: Alli/ orlistat
Proposed Indication: Overweight
Dosage Form/Route of Administration: Oral capsules
Sponsor: GlaxoSmithKline Consumer Healthcare, L.P.
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Reviewer: Karen B. Feibus, M.D.

Introduction

This document reviews two self-selection studies completed by GlaxoSmithKline Consumer Healthcare, L.P. (GSK) in the fall of 2005 to support NDA 21-887 for orlistat OTC. These studies were conducted in individuals using cyclosporine and individuals using warfarin, medicines that are absolute and relative contraindications respectively on the proposed orlistat OTC label. These data were submitted to enhance the consumer behavioral information provided on these populations from the actual use study (AUS) and label comprehension (LC) study. The actual use study review by Karen Feibus, M.D. and the label comprehension review by Susanna Weiss, Ph.D., J.D. may be found in the Document File System.

Background

Orlistat 120 mg (Xenical®) was approved for the prescription treatment of obesity and weight management in April 1999 with an unlimited duration of use. The sponsor was Roche, Inc. On June 6, 2005, GlaxoSmithKline (GSK) Consumer Healthcare, L.P., submitted NDA 21-887 for orlistat 60 mg capsules to promote weight loss in overweight adults, age 18 years and older, when used along with a reduced calorie, low-fat diet. The proposed dosing regimen is 1 – 2 capsules (60 – 120 mg) with each fat-containing meal, up to three times per day (TID).

During OTC drug development, LC studies are usually completed prior to the AUS. The best comprehended label is then used for the AUS to obtain the strongest AUS results. For this application, Roche performed the AUS submitted with NDA 21-887 for orlistat OTC, and GSK subsequently designed a new label and performed the LC Study and three self-selection studies

on cyclosporine users, warfarin users, and teenagers ages 14 – 17 years of age. The self-selection studies were completed using the proposed NDA label, which is attached as Appendix A. The label tested in the LC study was identical to the proposed NDA label except that a "Do not use if you are not overweight" warning was added following the study.

Orlistat, tetrahydrolipistatin, is a pancreatic lipase inhibitor that acts by inhibiting the absorption of approximately 30% of dietary fat. Three percent of the drug is systemically absorbed, and most of the absorbed drug is rapidly metabolized to inactive compounds. When co-administered with orlistat, cyclosporine absorption is decreased by 30%, and use of orlistat within two hours of cyclosporine dosing reduces serum levels of cyclosporine. The FDA Adverse Event Reporting System (AERS) has post-marketing reports of acute graft rejection in individuals using cyclosporine and prescription orlistat concomitantly. The current Xenical® (orlistat, 120 mg) prescription label states that cyclosporine should be taken at least two hours before or two hours after orlistat to reduce the risk of drug-drug interaction, but concomitant use is not contraindicated. For proposed use in the nonprescription setting, the orlistat OTC label and the labels used in the actual use and label comprehension studies all contain a warning that states:

Do not use if you are taking cyclosporine (a drug given after transplant surgery).

The actual use study enrolled two subjects using cyclosporine and one made an incorrect self-selection decision and said that orlistat was appropriate to use. In the label comprehension study, 96% of General Population subjects understood that cyclosporine users should not take orlistat.

Orlistat treatment produces a decrease in the absorption of vitamins A,D, E, and beta-carotene and has the potential to decrease the absorption of vitamin K. Based on clinical trial data, long term orlistat treatment does not appear to cause frank vitamin K deficiency as assessed with prothrombin time. However, prothrombin time is not a sensitive indicator of vitamin K deficiency and may remain normal with mild to moderate vitamin K deficiencies. (Eric Colman, M.D. medical officer review, NDA 20-766) Published literature suggests that fat malabsorption is associated with vitamin K deficiency.[1] Drug-drug interaction studies have not demonstrated a pharmacokinetic or pharmacodynamic interaction between orlistat and warfarin, but AERS post-marketing reports document cases of increased bleeding in individuals using warfarin and orlistat.[2]

The actual use study enrolled 14 subjects using warfarin and 50% made incorrect self-selection decisions based on the *Do not use if you are taking warfarin (blood thinning medicine) warning* on the actual use study label. As with other OTC products that carry a warfarin warning, the proposed orlistat OTC label and the label tested in the LC study contained the following warning:

Ask a doctor or pharmacist before use if you are taking warfarin (blood thinning medicine).

Based on data from controlled clinical trials and from the actual use and label comprehension studies, GSK conducted a self-selection study on consumers using cyclosporine and consumers using warfarin.

Study 1:
A Targeted Self-Selection Study to Evaluate Self-Selection of a Weight Loss Product Among Individuals Taking Cyclosporine

Study Objective:

- Evaluate the self-selection decision for individuals taking cyclosporine following an organ transplant who were interested in losing weight.

Study Design:

- **Self-administered, internet-based self-selection study**
  This study population was recruited from an existing research panel maintained by an affiliate marketing program. Panel members are recruited through targeted e-mail campaigns and placement of internet banners and pop-up advertisements. Members of the on-line panel are 18 years of age or older and provide demographic information to the marketing program at enrollment. Members agree to participate in research studies conducted on-line or through telephone or mail.

  For the cyclosporine self-selection study, an initial sample of organ transplant recipients was identified from the research panel based on survey results from April 2004. The survey identified 1004 households reporting one or more adult household members with an organ transplant. E-mail invitations were sent to these 1004 households and invited an adult male/female household member to take part in an online survey. The invitation did not indicate that organ transplant recipients or cyclosporine users were targeted. The invitation did offer entry into a monthly drawing for monetary prizes. The enrollment period lasted seven days.

  It is important to note that in households with more than one adult, it is possible that the individual completing the survey was not the organ transplant recipient.

- **Inclusion Criteria**
  1. Taking cyclosporine
  2. Interested in losing weight

- **Exclusion Criteria**
  1. Less than 18 years of age
  2. Household member employed by a marketing department, marketing research company, or pharmaceutical company or trained as a healthcare professional.

- **Data Quality and Management**
  The research company performed minimal data quality assessment. Response ranges for open-ended questions were evaluated, but logistical discrepancies in responses were not followed up or investigated. For example, one male participant indicated that he was pregnant and breastfeeding, but he was included in the data analysis because he indicated current cyclosporine use. Two were cyclsporine users but were not transplant recipients.

- **Study Procedures**

  The complete study questionnaire is provided in Appendix B. The respondent was asked three screening questions that addressed inclusion and exclusion criteria. Respondents, who were interested in losing weight and met the other study criteria, were shown the proposed orlistat label and asked the following self-selection question:

  > *Based on the information provided on the package label, is this product appropriate for you to use or not?*
  >
  > ☐ *appropriate for use*
  > ☐ *not appropriate for use*
  > ☐ *not sure*

  This initial multiple choice question was followed by these open-ended questions:

  - What led you to say (answer to self-selection question)?
  - Are there any other reasons that led you to say (answer to self-selection question)?

  Respondents who made an incorrect self-selection decision were asked whether they would speak to their doctor before using orlistat and were then asked why or why not. Respondents were then shown a list of medicines relevant to orlistat label warnings and asked to identify which medicines they were taking. Cyclosporine users were asked what dosage form(s) and brand of cyclosporine they used. All respondents were asked questions about how often they speak to their doctor about the medications they use, and cyclosporine users were asked how often they have cyclosporine levels monitored. Respondents were asked medical history questions relevant to indications and contraindications present on the orlistat label and were asked whether they had ever had an organ transplant. Organ transplant recipients were asked about their current organ rejection prevention medicines.

  This initial series of questions was followed by further questions about the cyclosporine label warning. Respondents were asked whether they saw the warning. Those who made an incorrect self-selection decision were asked why they said that orlistat was appropriate for them to use. Respondents were shown the orlistat label again and asked to review the "Warnings" section. The following question was asked:

  > *Now that you have seen the statement about cyclosporine, is orlistat appropriate for you to use or not?*

  Some demographic information was then collected.

Reviewer comments:

1. *The research company did not follow-up on data inconsistencies or confirm that the person who completed the survey was the household member using cyclosporine. This may confound the accuracy of the self-selection decision rate among individuals using cyclosporine.*

2. *The self-selection portion of the questionnaire was generally well-constructed. Following label review, the self-selection question was asked first and was non-leading. The follow-up questions gathered open-ended information that could offer insight into participants' decision-making processes.*

3. *Some questions that appeared later in the questionnaire did not appear relevant to the study objective and/or were presented in an illogical order:*

    - *Question 3 asks about whether participants use medicines and dietary supplements that appear in the orlistat label warnings. Questions 3a and 3b then ask about cyclosporine dosage form and brand. Eight questions later, participants are asked about cyclosporine duration of use.*

    - *Question 6b asked participants about the duration of their cyclosporine use before question 6c asked about their organ rejection medicines in general.*

Results

Population disposition

From the 1004 contacted households, 462 adult household members accessed the online survey for a response rate of 46% (typical for on-line surveys). Thirty-six respondents did not meet study criteria, and 45 respondents did not complete the survey. Among the 381 respondents who completed the survey, 89 were taking cyclosporine and 46 of these individuals were interested in losing weight. The questionnaire responses from these 46 participants were included in study data analysis.

Population Demographics

Among the 46 cyclosporine users included in the analysis:

- 44 (96%) had an organ transplant
- 42 (91%) were Caucasian (4% African American, 4% Hispanic)
- 27 (59%) were 50 years of age or older
- 22 (48%) were female
- 34 (74%) had at least some formal education after graduating high school, and 17 (37%) graduated college or technical school.

Self-selection

Forty-one (89%) participants made a correct self-selection, stating that the product was not appropriate for their use. The main reasons for this decision were *using cyclosporine* (66%) and *had a transplant* (32%). One participant said he/she took too many drugs already and another said he/she disliked taking diet medication.

Five (11%) participants, including the two without organ transplant, made incorrect self-selection decisions and said that orlistat was appropriate for them to use. All were male and three provided no reason for their self-selection decision. One respondent said that the product would help him lower his weight, and one said that it would be easy to use. Three of these five participants did not see the cyclosporine warning when they read the label. When shown the

label and questioned again about appropriateness of orlistat for their use, two of the three men said that orlistat was not appropriate to use.

Both participants without a transplant indicated that they were using cyclosporine, warfarin (coumadin), diabetes medicine, a weight loss drug, and a daily multivitamin. All three participants who indicated use of another weight loss drug made an incorrect self-selection decision.

Reviewer comments:

1. *The correct self-selection rate of 89% is improved over the 50% seen in the Actual Use Study for orlistat OTC; however the actual use study only had a sample size of two cyclosporine users.*

2. *These results suggest that among the 5 participants who made an incorrect self-selection decision, two made an incorrect decision because they did not see the cyclosporine warning on the label (label comprehension issue), and three disregarded the warning. This suggests a label comprehension rate of 96%, which is consistent with the results seen in the Label Comprehension Study for orlistat OTC. It also suggests that strong label comprehension may not translate directly to equally strong compliance with the label.*

3. *The dataset for this study and specific information on the two non-transplant participants and the male participant who was" pregnant and breastfeeding"have been requested from GSK. If data from these individuals appears incomplete or implausible, the results of the study should be evaluated with their data excluded.*

Other information

Among the 46 cyclosporine users, 26% see or talk to their doctor at least once a month, and 63% at least every three months. Ninety-three percent (including all incorrect self-selectors) discuss their cyclosporine use with their doctors, and 85% have cyclosporine levels monitored at least every three months.

Summary/Conclusions

Among 46 cyclosporine users, 44 had an organ transplant. Overall, 89% made a correct self-selection decision and 92% of these individuals made their decision based on using cyclosporine or having an organ transplant. If the self-selection rate is calculated only for cyclosporine users with a transplant and the data on the participant who was "male, pregnant, and breastfeeding" is excluded, 40 out of 43 (93%) participants made a correct self-selection decision.

Three of the five participants who made an incorrect self-selection decision did not see the cyclosporine warning when they reviewed the orlistat label. When presented with the label and warning for a second time, two of the three stated that orlistat was not appropriate to use. It is not clear whether or not the participant who self-selected incorrectly the second time had an organ transplant. This information has been requested. As is true for all nonprescription drug

products, some individuals who read and understand the cyclosporine warning may choose to disregard it.

Recommendations (Cyclosporine study)

1. Strengthening labeling language and enhancing the appearance of the cyclosporine warning on the orlistat label may improve self-selection decisions among consumers.
   - The warning should contain information about possible increased risk of organ rejection.
   - The warning should be bolded.

2. The final NDA label should be tested with a label comprehension study that contains a self-selection component. To avoid some of the data collection uncertainties that occurred in this study, future studies should be designed with an in-person interview process.

3. Consideration should be given to additional cyclosporine warning information prominently placed in the packaged educational materials.

Study 2:
A Targeted Self-Selection Study to Evaluate Subject Self-Selection of a Weight Loss Product Among Individuals Using Warfarin

Study Objectives

- To determine if warfarin users made the correct self-selection decision regarding the use of orlistat, stating they "should ask a doctor before use" as stated in the label warning.

- To determine if warfarin users did not select the product when they also had a condition noted in the "Do Not Use" warning on the label.

Study Design

Recruitment

[———] recruited warfarin users from preexisting clinical databases belonging to [———] The sites identified known warfarin users and recruited them by telephone to participate in the study. During the telephone screening interview, potential participants were asked about their interest in a variety of personal care areas, including weight loss. If an individual expressed an interest in losing weight, he/she was invited to the study site but was not aware that the invitation was issued because of the interest in weight loss or their use of warfarin. Questions about medications were not asked during the screening process. Demographic information was collected.

Qualified subjects were invited to participate in evaluating a new healthcare product and were told they would be compensated for their time.

Inclusion Criteria

- Taking warfarin
- Interested in weight loss
- At least 18 years old
- Able to speak, read, and understand English to comply with study procedures.

Exclusion Criteria

- Did not bring corrective lenses, contacts, or glasses normally worn to read
- Previous participation in this study
- Participated in marketing or clinical research study or interview in the past three months.
- Worked for a physician's office, healthcare company, pharmaceutical manufacturer, or market research company; or worked in advertising, marketing, sales promotion, or public relations.

Study Procedures

At the study site, participants signed a Confidentiality Disclosure Agreement and completed the REALM test. Trained marketing research interviewers conducted the interviews. The product package remained within view throughout the interview process.

Participants read and reviewed the product package, taking as much time as needed. The interviewer then asked the following self-selection question:

> *Based on the information provided on the package label, is this product appropriate for you to use or not?*

After the participant answered this question, the interviewer asked:

> *What led you to make that decision?*

Interviewers asked participants a series of questions about:

- Contraindicated medicines the participant may or may not be taking
- The participant's interactions with his/her doctor
- Contraindicated conditions the participant may or may not have
- Frequency of blood work to monitor warfarin levels.

Participants who made incorrect self-selection decisions were asked additional questions about their medical history and self-selection decision to try and understand their decision-making processes. The complete questionnaire is included in Appendix C.

Definition of self-selection responses

The warfarin warning on the proposed orlistat OTC label, as with other OTC warfarin warnings, states:

> *Ask a doctor or pharmacist before use if you are taking warfarin (blood thinning medicine)*

The sponsor defined self-selection decision responses as follows:
For participants who had a "Do not use" condition in addition to taking warfarin:

- Correct: "This product is not appropriate for me to use."
- Incorrect: Any other answer.

For participants who did not have a "Do not use" label condition:

- Corrrect: Participant had to express the need to check with a doctor or pharmacist first.
- Acceptable: "This product is not appropriate for me to use."
- Incorrect: Any other answer including an "I don't know" if it was not qualified by "I need to check with my doctor or pharmacist."

Reviewer comment:

1. *Orlistat OTC is not a medically necessary drug. If a warfarin user reads the label and decides that this product is not appropriate to use, then that individual has not exposed himself to risk and has not foregone a necessary medicine. Therefore, this response is considered acceptable in this study.*

Data Management
Closed-ended responses were entered into a database using a double entry system to verify accuracy of input. The first 20% of open-ended responses were entered verbatim and then used to create response codes. The remainder of open-ended responses were coded to group similar responses together and entered into the database. New codes were created when needed to cover the range of verbatim responses. Coding principles defining correct selection decisions were agreed to by the sponsor and [———] prior to starting the classification process.

Results

Study population and disposition
The research centers contacted 107 warfarin users by telephone. Twenty-five refused to participate in the screening process, and 11 of those contacted were not interested in losing weight. Seven did not meet inclusion/exclusion criteria.

Sixty-four of the 107 warfarin users contacted qualified to participate in the study. One chose not to accept the invitation, and 9 failed to show up for the interview. Fifty-four warfarin users participated in the study.

Population demographics:
Among the 54 warfarin users who participated in the study:

- 56% were female
- 89% were ages 50 years and older and 52% were over 70 years of age
- 96% were Caucasian
- 29% had no formal education after completing high school and 2% did not complete high school
- 13% were of low literacy by the REALM test.

Self-selection

As shown in Table 1 below, 28 (52%) study participants had warfarin as their only labeled contraindication to orlistat use. The other 26 participants also had an absolute ("Do not use") label contraindication or another conditional ("Ask before use") contraindication.

Based on the entire orlistat label, 32 (59%) of 54 participants made correct or acceptable self-selection decisions. Among those with warfarin as their only label contraindication to orlistat use, 86% made absolutely correct self-selection decisions and 14% made incorrect decisions. Only 31% of warfarin users with additional label contraindications to orlistat use made correct or acceptable self-selection decisions. Only one out of ten warfarin users with a "Do not use" contraindication to orlistat use made a correct or acceptable self-selection decision. Of the 16 warfarin users with another "Ask before use" label contraindication, 7 (44%) made correct or acceptable self-selection decisions. Twelve participants said that orlistat was appropriate to use and did not mention warfarin in their open-ended explanation of their decision. Three of these individuals did not notice the warfarin warning (5.5% of the study population; 14% of those who self-selected incorrectly).

Table 1: Self-selection decisions by contraindications

Participant contraindications	N	Self-selection decision			
		Correct (C)	Acceptable (A)	C + A	Incorrect
Warfarin only	28	24	0	24	4
Warfarin and a "Do not use" condition	10	1	0	1 (10%)	9 (90%)
Warfarin and another "Ask before use" condition	16	5	2	7	9
Total	54	30 (56%)*	2 (4%)	32 (59%)	22 (41%)

*percentages may not add to 100% due to rounding

Among 14 study participants using warfarin and a diabetes medicine, seven (50%) made correct or acceptable self-selection decisions. One participant who reported a gallbladder problem self-selected correctly and three participants who reported kidney stones self-selected incorrectly. Forty-four of the 54 enrolled warfarin-users reported being overweight but 48 actually were overweight or obese by BMI. Among 6 normal-weight study participants, only one self-selected to use orlistat.

The sponsor stated that overall, 39 (72%) warfarin users in the study did not select the product. Seven of these participants heeded the "ask a doctor" warning, as expressed in verbatim answers to question 2a, but their self-selection decision was considered incorrect overall. Six of these seven participants specifically mentioned the warfarin warning as a reason to ask a doctor before using orlistat; however these individuals were not overweight and did not heed the "Do not use if you are not overweight" warning. The sponsor provided the verbatim responses to questions 2a/2b for all study participants. Two patients took their doctor's permission to participate in the study as permission to use orlistat, and this resulted in incorrect self-selection decisions.

Reviewer comments:

1. *While it is encouraging that 86% of warfarin users without other contraindications to orlistat use made correct self-selection decisions, it is concerning that only 31% of warfarin users with other labeled contraindications to product use made correct or acceptable self-selection decisions. It is possible that participants with contraindications in different parts of the drug facts label have difficulty integrating the information in order to make a correct decision.*

2. *Fourteen percent of those who self-selected incorrectly did not see the warfarin warning when they reviewed the label.*

3. *Warfarin users were able to self-diagnose overweight. There were no underweight individuals enrolled in the study. Only one of six normal weight participants self-selected to use orlistat.*

4. *The three participants who reported a history of kidney stones made incorrect self-selection decisions. This contrasts the label comprehension study results where 97% of subject understood the warning.*

5. *In the actual use study submitted to the orlistat OTC NDA, 14 subjects were using warfarin and 50% made correct self-selection decisions. On the label comprehension study, 94% of subjects comprehended the warfarin warning.*

Other information
All 54 enrolled warfarin users have blood work to monitor blood coagulation at least four times per year, and 49 have coagulation monitoring at least once a month. Fifty-three of 54 participants usually discuss their medications with their doctor, and 48 of 53 stated they specifically discussed warfarin use. Forty-two of the 54 study participants communicate with their doctor at least three times per year.

Summary

This was a well-designed self-selection study of 54 warfarin users. Based on the orlistat OTC label, 59% made a correct self-selection decision. Among warfarin users with no other labeled contraindications to orlistat use, self-selection decisions were correct 89% of the time. However, warfarin users with other labeled contraindications to use correctly self-selected only 31% of the time (10% for those with "Do not use" contraindication).

Fourteen percent of those who self-selected incorrectly did not notice the warfarin label warning when they reviewed the label. These results suggest that other participants saw the label warning and either chose to disregard it or did not know how to integrate all of their labeled contraindications into a correct selection decision. The verbatim responses provided by the sponsor suggest that some warfarin users justified that orlistat use was appropriate, because they were overweight, their doctor recommended losing weight, or they did not have other labeled conditions other than taking warfarin.

Warfarin users enrolled in the study were able to self-diagnose overweight. All reported having coagulation studies done at least four times per year and most reported having coagulation studies at least monthly. Given that orlistat may decrease vitamin K absorption over time and influence bleeding risk in warfarin users, the frequency of blood coagulation monitoring among study participants is reassuring.
In the Actual Use study (AUS) submitted to support the orlistat OTC NDA, only 14 subjects were warfarin users and 50% made correct self-selection decisions. In this study, 59% of warfarin users made correct self-selection decisions. It is difficult to compare this data, because the warfarin warning on the AUS label was a "Do not use" warning, and the warfarin warning on the proposed NDA label used in this study was an "Ask before use" warning. In the LC study, 94% of subjects demonstrated comprehension of the warfarin warning.

Conclusions

- Warfarin users with additional contraindications to orlistat use are most likely to make an incorrect self-selection decision.
- Some warfarin users make incorrect self-selection decisions because they do not see the warning when they read the label.
- The discrepancy between label comprehension of the warfarin warning and the correct self-selection suggests that some study participants may base their self-selection decision on things that, in their mind, outweigh a label warning (like their desire to lose weight).
- Warfarin users have frequent blood coagulation studies (49 of 54 monthly; all subjects at least every 3 months)

Recommendations (Warfarin study)

1. The warfarin warning on the orlistat OTC label should be bolded.

2. A statement should be added to the warfarin warning to inform warfarin users that they need frequent monitoring of blood clotting during weight loss.

3. The warfarin warning should be moved to the "Ask a doctor before use" section of the label.

4. The sponsor may want to explore ways to provide label information outside the Drug Facts box to help consumers with more than one label contraindications determine whether they should ask a doctor before use or not use the product at all.
   For example:

Follow these steps to see if orlistat OTC is right for you.			
STEP	**Questions**	**Answer**	**What to do**
1	▪ Are you overweight? (Use the chart on the package to help you decide)	**NO**	**Do not use orlistat OTC**
		YES	Go to Step 2
2	▪ Are you allergic to any orlistat OTC ingredients? ▪ Do you take cyclosporine (medicine to prevent rejection of organ transplant)? ▪ Do you have problems absorbing food? ▪ Are you pregnant or breastfeeding?	**YES to any question**	**Do not use orlistat OTC**
		NO for all questions	Go to Step 3
3	▪ Do you have kidney stones? ▪ Do you have problems with your gall bladder? ▪ Do you take any of these medicines/drugs: Warfarin or coumadin (blood thinner) Diabetes medicine Weight loss drugs?	**YES to any question**	You need to **speak to your doctor** to find out if using orlistat OTC is right for you.
		NO For all questions	You may use orlistat OTC with a low-fat, reduced calorie diet to help you lose weight.

Please see page 7 for recommendations from cyclosporine study.

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1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

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Withheld Track Number: Medical-3

Appendix B: On-line Study Questionnaire for Cyclosporine Self-Selection Study

Cyclosporine Study (Job #3B65)
– Main Questionnaire –

Now I would like to show you the back label for a new weight loss product and then get your opinions about it. Take as much time as you need to review it and when you are through, click the "next" button. Please do not try to guess the answers to the questions, instead refer back to the package label.

1 - Based on the information provided on the package label, is this product appropriate for you to use
or not?
PLEASE SELECT ONE

Product is appropriate for me to use
Product is not appropriate for me to use
Not sure

2a - What led you to say [INSERT RESPONSE FROM QU.1]?
PLEASE BE SPECIFIC

2b - Are there any other reasons that led you to say [INSERT RESPONSE FROM QU.1]?
PLEASE BE SPECIFIC

2c - Would you talk to your doctor before using Orlistat?
PLEASE SELECT ONE

Yes
No

2d - Why did you say "[INSERT RESPONSE FROM QU.2C]" to talking to your doctor before using Orlistat?
PLEASE BE SPECIFIC

Thank you for answering these questions. The remaining questions are for classification purposes only and will be kept strictly confidential.

3 - Are you taking any of the following medications?
PLEASE SELECT ONE FOR EACH

Scale:
Yes
No

Medicine:
Any medications to treat diabetes
Any weight loss drugs
Cyclosporine (a drug given after an organ transplant)
Daily multi-vitamin
Warfarin, a blood thinning medication

3a - Is the cyclosporine you take a capsule, oral solution, or both?
PLEASE SELECT ONE

Capsule
Oral Solution
Both

3b - And, is the name of the capsule product Sandimmune, Neoral, Gengraf, or is it simply called Cyclosporine? If you are not sure, please refer to the name on your prescription package (if available).
PLEASE SELECT ONE

Cyclosporine
Gengraf
Neoral
Sandimmune
Not sure

4 - How often do you see or talk to your doctor?
PLEASE TYPE IN

Once a week or more
Once every 2 or 3 weeks
Once a month/every 4 weeks
Once every 2 or 3 months
Once every 4 to 6 months
Once or twice a year
Less often than once a year
Never

4a - Do you usually discuss the medications you are taking with your doctor?
PLEASE SELECT ONE

Yes
No

4b - Specifically, do you discuss your Cyclosporine medication with your doctor?
PLEASE SELECT ONE

Yes
No

5 - How often do you get blood work done to monitor your Cyclosporine levels?
PLEASE TYPE IN

Once a week or more
Once every 2 or 3 weeks
Once a month/every 4 weeks
Once every 2 or 3 months
Once every 4 to 6 months
Once or twice a year
Less often than once a year
Never
Not sure

6 - Do any of the following apply to you?
PLEASE SELECT ALL THAT APPLY

Scale:
Yes
No
Not Applicable

Questions:
Are you allergic to Orlistat?
Are you breastfeeding?
Are you pregnant?
Do you consider yourself to be overweight?
Do you have gallbladder problems?
Do you have kidney stones?
Have you ever been diagnosed with problems absorbing food?
Have you had an organ transplant?

6a - How long ago did you have the organ transplant?
PLEASE SELECT ONE

Within the past year
1-2 years ago
3-5 years ago
More than 5 years ago

6b - How long have you been taking Cyclosporine?
PLEASE SELECT ONE

Less than 1 year
1-2 years
3-5 years
More than 5 years

6c - What organ rejection medication(s) are you currently taking?
PLEASE BE SPECIFIC

7A - WHEN YOU FIRST READ THE LABEL FOR THIS WEIGHT LOSS PRODUCT, DID YOU NOTICE THE STATEMENT ABOUT CYCLOSPORINE?

Please select one

YES

NO

7B - EARLIER YOU MENTIONED THAT YOU ARE CURRENTLY TAKING CYCLOSPORINE AND THAT THE WEIGHT LOSS PRODUCT IS APPROPRIATE FOR YOU TO USE. CAN YOU EXPLAIN WHY YOU SAID THIS?

please be specific

Please review the "Warnings" section in the label shown below:

7c - Now that you have seen the statement about Cyclosporine, is Orlistat appropriate for you to use or not?
PLEASE SELECT ONE

Yes, it is appropriate for me to use
No, it is not appropriate for me to use

8a - About how tall are you without shoes?
PLEASE TYPE IN

_____ ft.
_____ inches
Prefer not to answer

8b - How much do you weigh without shoes?
PLEASE TYPE IN

_____ pounds
Prefer not to answer

9 - Are you of Hispanic origin?
PLEASE SELECT ONE

Yes
No
Prefer not to answer

10 - Which group do you consider yourself to be a part of?
PLEASE SELECT ONE

African American/Black
Asian
Caucasian/White
Native American
Other

Prefer not to answer

11 - What is the last year of school you completed?
PLEASE SELECT ONE

Less than High School
Completed High school
Some College/Technical School
Graduated College/Technical School or more
Prefer not to answer

12 - Which statement below best describes how you would rate the quality of the label image as it appears on your screen?
PLEASE SELECT ONE

Excellent
Good
Poor

13 - And how would you rate the ease of reading the words included in the label?
PLEASE SELECT ONE

Very easy to read
Somewhat easy to read
Somewhat difficult to read
Very difficult to read

Appendix C: Study Questionnaire for Warfarin Self-Selection Study

Once again, thank you for agreeing to participate in our survey. Your opinions are very important and we appreciate your time.

HAND RESPONDENT THE PRODUCT PACKAGE.

Here is the package for a new product. Please read the entire package, front and back, taking as much time as you want.

When you are ready, I will ask you a few questions about what you have read.

Take as much time as you need and when you are through, we will continue with the interview. I'm going to step out of the room and let you read the entire package. Please let me know when you are done.

LEAVE INTERVIEWING AREA AND WAIT FOR THE RESPONDENT TO TELL YOU WHEN THEY HAVE FINISHED READING THE PACKAGE.

> **IF RESPONDENT ASKS ANY QUESTIONS, RESPOND WITH:** To make sure that each person is interviewed under the same rules, I can't give you any information other than what is on my script.

INTERVIEWER RETURNS TO ROOM.

Please note that while going through the survey you will be able to refer to the package as often as you would like. Please do not try to guess the answers to the questions, instead refer back to the package label.

1. Based on the information provided on the package label, is this product appropriate for you to use or not?

PRODUCT IS APPROPRIATE FOR ME TO USE	1
PRODUCT IS NOT APPROPRIATE FOR ME TO USE	2
ASK A DOCTOR	3
ASK A PHARMACIST	4
DON'T KNOW	5

2a. What led you to make that decision? **CLARIFY COMMENTS – "PLEASE EXPLAIN", TELL ME MORE ABOUT THAT", ETC.)**

_____

_____

_____

ASK Q2B. ONLY IF "WARFARIN USE" IS NOT MENTIONED AT Q2A, OTHERWISE SKIP TO Q3.

2b. Is there any other reason for your decision?

_____

_____

_____

3. Are you taking any of the following medications? **READ LIST.**

		CIRCLE "YES" OR "NO"	
A	Cyclosporine, specifically used after an organ transplant?	YES	NO
B	Warfarin or Coumadin, a blood thinning medication?	YES	NO
C	Any medications to treat diabetes?	YES	NO
D	Any other weight loss drugs?	YES	NO
E	Daily multi-vitamin?	YES	NO

IF Q3B = NO, TERMINATE, OTHERWISE CONTINUE.
NOTE: IF TERMINATED, THIS PERSON DOES NOT QUALIFY FOR THIS COHORT AND THE INTERVIEW WILL NEED TO BE REPLACED.

4a. How often do you see or talk to your doctor?

_____ TIME(S) PER _____
(NUMBER OF TIMES) **(WEEK, MONTH, YEAR, ETC.)**

4b. Do you usually discuss the medications you are taking with your doctor?

CONTINUE TO Q4C → YES..... 1
SKIP TO Q5 → NO..... 2

4c. Do you usually discuss your warfarin, Coumadin, or blood thinning medication with your doctor?

YES..... 1
NO..... 2

5. How often do you get blood work done to monitor your warfarin levels?

_____ TIME(S) PER _____
(NUMBER OF TIMES) **(WEEK, MONTH, YEAR, ETC.)**

6. Do any of the following apply to you? **READ LIST.**

		CIRCLE "YES" OR "NO"	
A	Are you pregnant?	YES	NO
B	Are you breastfeeding?	YES	NO
C	Do you have gallbladder problems?	YES	NO
D	Do you have kidney stones?	YES	NO
E	Have you ever been diagnosed with problems absorbing food?	YES	NO
F	Are you allergic to Orlistat?	YES	NO
G	Do you consider yourself to be overweight?	YES	NO

IF Q1 = 1, ASK Q7 OTHERWISE TO GO END

7a. You said you are currently taking warfarin or Coumadin and also said this product is appropriate for you to use. Can you explain why you said this?

PROBE AND CLARIFY. MAKE SURE THE QUESTION IS ANSWERED.

_____

_____

_____

IF AT Q7A, RESPONDENT DOES NOT MENTION THE "WARFARIN LABEL WARNING", PROBE FURTHER BY SAYING THE FOLLOWING:

7b. The label says "Ask a Doctor or Pharmacist before use if you are taking warfarin". Can you explain why you said this product is appropriate for you to use?

_____

_____

_____

7c. When you first read the label, did you notice the statement about warfarin, Coumadin, or blood thinning medication?

YES	1
NO	2

END:

Those are all of my questions. Thank you so much for your time today. The last thing we would like to do is collect your height and weight.

8. **RECORD HEIGHT (WITHOUT SHOES) AND WEIGHT OF RESPONDENT HERE**

HEIGHT: _____ feet _____ inches

WEIGHT: _____ pounds

Thank you again for your time.

INTERVIEWER:
CHECK TO BE SURE THE RESPONDENT NAME, ADDRESS AND TELEPHONE NUMBER ARE RECORDED ON THE FRONT OF THIS QUESTIONNAIRE.

Those are all of my questions. Thank you so much for your time today.

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

/s/

Karen Feibus
3/22/2006 02:23:08 PM
MEDICAL OFFICER

Daiva Shetty
3/23/2006 06:30:55 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-887
Submission Code	000
Letter Date	June 6, 2005
Stamp Date	June 7, 2005
PDUFA Goal Date	April 7, 2006
Reviewer Name	Julie Golden, M.D.
Review Completion Date	March 8, 2006
Established Name	Orlistat
(Proposed) Trade Name	Alli
Therapeutic Class	Lipase inhibitor
Applicant	GlaxoSmithKline
Priority Designation	S
Formulation	Capsule
Dosing Regimen	60 mg, 1-2 capsules TID
Indication	Weight loss
Intended Population	Overweight

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Not approvable.

Orlistat 60-120 mg TID has been demonstrated in controlled clinical trials to be safe and efficacious in the treatment of individuals with a BMI $\geq$ 28 kg/m^2 under a physician's care. In this setting, the use of orlistat results in a 2-3% weight loss over placebo after six months of treatment and contributes to weight maintenance and prevention of weight regain when taken chronically. The prescription product (Xenical 120 mg TID, Hoffman-La Roche)[1] was approved based on achievement of an efficacy criterion defined as a statistically greater percentage of subjects on orlistat losing greater than or equal to 5% of their baseline weight as compared to those on placebo.[2]

GlaxoSmithKline Consumer Healthcare is proposing that orlistat 60 mg be available as a nonprescription weight loss aid for overweight adults. There are several issues that concern this reviewer with regard to this application in particular and the approval of a nonprescription weight loss agent in general.

1. Defining the population

The National Institutes of Health's *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*[3] defines normal weight as a body mass index (BMI) of 18.5 – 24.9 kg/m^2, overweight as a BMI of 25 – 29.9 kg/m^2, and obese as a BMI $\geq$ 30 kg/m^2. The guidelines recommend weight loss through a combination of diet modification, increased physical activity, and behavior therapy for obese patients, and for patients who are overweight or have a high-risk waist circumference, when accompanied by two or more risk factors. In the event that lifestyle changes do not promote weight loss after six months, drugs should be considered as adjunctive therapy for select patients who have a BMI $\geq$ 30 kg/m^2, or a BMI $\geq$ 27 kg/m^2 if concomitant obesity-related risk factors or disease exist. This mirrors FDA's current approach to the evaluation and approval of prescription weight-loss drugs.

The recommendation to limit the use of weight-loss drugs to individuals with a BMI $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 if accompanied by obesity-related risk factors, represents an attempt to maximize the therapeutic risk-benefit profile by targeting drug therapy to those individuals whose risk for weight-related disease is high and is likely to outweigh the risks associated with any given

1 NDA 20-766
2 Guidance for the Clinical Evaluation of Weight-Control Drugs; Sept. 1996. http://www.fda.gov/cder/guidance/index.htm
3 *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.* NIH Publication Number 98-4083; September 1998. (*Practical Guide.* NIH Publication Number 00-4084; October 2000) U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute

pharmacological agent. As is emphasized in the guidelines: *In those patients with a lower level of obesity risk, nonpharmacological therapy is the treatment of choice.*[3]

A risk-benefit analysis cannot be done when the benefit aspect of the equation (or the risk of having a particular condition) is not quantifiable. Thus, this reviewer cannot quantify the benefit of drug-induced cosmetic weight loss in a healthy overweight population.

2. Determining the duration

Obesity and overweight tend to be chronic conditions.[4] Successful drug treatment is therefore expected to be chronic. To assess the long-term efficacy and safety of prescription weight-loss drugs, FDA currently recommends that pre-approval trials be at least one year in duration.

It is well-known that once treatment with a weight-loss drug is stopped, lost weight is regained and improvement in co-morbidities reversed.[5] Furthermore, two-year data from the prescription NDA suggest that if orlistat is continued but salutary lifestyle changes are modified or stopped, lost weight is regained. This underscores the critical role lifestyle modification plays in determining the efficacy of orlistat, as is discussed further, below.

It is unclear to this reviewer what the proposed six-month duration of therapy will achieve in terms of durable weight loss. However, weight loss drugs previously considered appropriate for nonprescription use were imposed with an even stricter duration limitation than six months. The Advanced Notice of Proposed Rulemaking (ANPR) for Weight Control Products for Over-the-Counter Human Use published on February 26, 1982,[6] stated that:

Attempts at weight reduction which involve the use of this product should be limited to periods not exceeding 3 months, because that should be enough time to establish new eating habits.

In the last 10 years or so, the medical community has shifted its thinking on this issue such that overweight and obesity are now considered to be chronic conditions, as stated above. Therefore, although a tentative monograph for nonprescription weight loss aids currently exists, a three-month limitation on a weight-control therapy no longer seems to make medical or scientific sense. There are *no* data to suggest that a three-month treatment duration allows for the establishment of new eating habits. This reviewer would even go so far as to posit that such establishment of new eating habits is a lifelong undertaking, and one in which the addition of a drug is unlikely to impact. Of some concern is that the opposite of the desired effect may occur such that an individual may abandon healthful lifestyle changes with the promise of a weight-loss pill.

4 Yanovski SZ, et al. N Engl J Med. 2002 Feb 21;346(8):591-602.
5 Davidson M, et al. JAMA. 1999. Jan 20;281(3):235-242.
6 47 FR 8466

3. Concomitant lifestyle modification

Because the standard of care is to administer orlistat, as is the case with all obesity drugs, in conjunction with lifestyle modification, the efficacy of orlistat without some degree of lifestyle intervention has not been studied. We do know that lifestyle modification is critical both for weight loss and maintenance. This concept has been highlighted in a recent study that demonstrated greater successes with sibutramine – a centrally-acting obesity drug approved for long-term weight loss – in combination with health care provider visits.[7] Sibutramine plus intensive behavioral modification was the most successful treatment, followed by intensive behavioral modification alone and sibutramine plus brief visits with the primary care physician. Least successful was the group randomized to sibutramine therapy alone. Similar success of lifestyle therapy as compared to drug has been demonstrated in other studies of disease prevention. For example, the Diabetes Prevention Program demonstrated that intensive lifestyle modification was significantly more efficacious than metformin therapy in the prevention of type 2 diabetes in individuals at risk for the disease.[8]

All placebo-controlled clinical trials for orlistat utilized some form of dietary/lifestyle intervention along the spectrum of brief physician visits to intensive dietary intervention. The actual use trial, a three-month pilot study that utilized written materials similar to those planned for labeling of the nonprescription product, did not employ a control group; therefore, a reliable assessment of efficacy in this setting cannot be made.

An additional concern, which illustrates this reviewer's discomfort with the entire concept of a nonprescription weight loss product, is that a consumer may actually *replace* a healthful lifestyle with the use of a drug. The development of overweight and obesity occurs because of an imbalance in energy intake *vs.* expenditure. Resetting this balance often involves changing one's relationship with food and physical activity, and is frequently accompanied by psychological, behavioral, emotional, and social disruption. This reviewer feels strongly that the attainment of durable weight loss cannot be accomplished solely by the available weight-loss drug treatments. The decision to be treated for obesity with a medication, including orlistat, is one that the health care provider and the patient should make together, only after a conversation about the patient's commitment to making the appropriate lifestyle changes. Current recommendations state that that pharmacotherapy for obesity is to be initiated only after six months of attempted weight loss with diet and other lifestyle intervention has been inadequate.[3]

4. Efficacy issues

Given the sponsor's proposal to market nonprescription orlistat for short-term use, the six-month time point was chosen as the efficacy endpoint of interest from the two prescription NDA clinical studies (BMI 28 - 43 kg/m^2). In these studies, which were pooled due to similar study designs and patient populations, 42% of subjects treated with orlistat 60 mg, 45% of subjects treated with orlistat 120 mg, and 23% of those treated with placebo achieved a weight loss of $\geq$

7 Wadden TA, et al. N Engl J Med. 2005 Nov 17;353(20):2111-20.
8 Knowler WC, et al. N Engl J Med. 2002 Feb 7;346(6):393-403.

5% at six months ($p < 0.001$, orlistat *vs.* placebo). Placebo-subtracted mean weight loss in the two prescription NDA clinical studies at six months was 2.3 kg (~2.4%) in subjects on the 60 mg dose and 2.9 kg (~3.1%) in those on the 120 mg dose.

By contrast, in the nonprescription NDA clinical study (BMI 25 - 28 kg/m^2), 36% of orlistat 60 mg-treated subjects *vs.* 28% of placebo-treated subjects lost at least 5% of their baseline body weight at four months (between-group difference non-significant, $p = 0.104$). In the nonprescription NDA clinical study, after four months of treatment with orlistat 60 mg, the placebo-subtracted mean weight loss was 1.2 kg (~1.6%).

These findings raise the possibility that orlistat may be less effective in mildly overweight individuals (i.e., BMI*s* 25 - 28 kg/m^2) than in obese subjects. However, because the sponsor has not studied the effects of six months of orlistat therapy in mildly overweight subjects, we can only make assumptions about the six-month efficacy in this group.

Because the two prescription studies in subjects with BMI 28 - 43 kg/m^2 had differing degrees of lifestyle intervention (one study utilized dieticians and regular collection of food records were used to provide feedback, and the other occurred in the primary care physicians' offices where subjects were provided general encouragement, but no specialized counseling), the differential findings help inform efficacy issues related to dietary compliance. For example, there was less of a treatment and dose effect in the study with intensive lifestyle modification, although overall, weight loss (and weight maintenance over two years) was greater in this study.

5. Safety issues

Due to its low bioavailability, orlistat is considered a relatively safe drug in the prescription setting. The most common adverse events are gastrointestinal (GI) in nature, such as fatty and oily stool. Although these drug-related side effects are likely to be important to consumers, from a clinical perspective, this reviewer considers the GI side effects to be primarily tolerability rather than safety concerns.

On the other hand, fat-soluble vitamin and drug malabsorption are clearly important safety concerns with this drug, particularly in a nonprescription setting. The prolonged use of orlistat without appropriate vitamin supplementation may lead to clinically relevant fat-soluble nutrient malabsorption. Vitamin D may especially be a concern because deficiency of this nutrient is common in the United States, particularly among females, the elderly, and minorities,[9] and is associated with the risk for osteoporosis and other chronic diseases.[10] Furthermore, vitamin K malabsorption may put individuals taking warfarin at risk for development of supratherapeutic prothrombin time and consequently, bleeding.

9 Zadshir A, et al. Ethn Dis. 2005 Autumn;15(4 Suppl 5):S5-97-101.
10 Holick MF. J Nutr. 2005 Nov;135(11):2739S-48S.

Decreased concentrations of cyclosporine with concomitant use of orlistat have been documented,[11] and may, in the worst case scenario, result in transplanted organ rejection. Although there were very few subjects on either warfarin or cyclosporine in the actual use study, the preliminary findings, in which 50% of individuals on these drugs made an inappropriate purchase decision, raise concern that the messages regarding these drug interactions may not be effectively communicated.

In conclusion, GlaxoSmithKline (or previously, Roche) has shown in randomized, placebo-controlled clinical trials that: 1) subjects with BMIs $\geq$ 28 kg/m^2 lose a clinically significantly (as defined by the efficacy criteria of the 1996 FDA Draft Guidance on the Clinical Evaluation of Weight Control Drugs[2]) greater amount of weight loss on orlistat as compared to those on placebo when receiving lifestyle intervention under the supervision of a health care provider; 2) subjects with BMIs $\geq$ 25 kg/m^2 lose a statistically, but not necessarily a clinically, significantly greater amount of weight with orlistat than placebo when receiving lifestyle intervention under the supervision of a health care provider; 3) changes in co-morbidities are what one would expect with the observed changes in body weight; and 4) under health care provider supervision, when orlistat is discontinued, weight is regained, irrespective of the concomitant lifestyle intervention received.

GlaxoSmithKline has *not* shown: 1) that consumers are able to lose more weight (either clinically or statistically) on orlistat *vs.* placebo under "actual use" conditions; 2) that consumers are able to maintain weight loss beyond the duration of orlistat use in the actual use setting; 3) that subjects with a BMI in the 25 - 28 kg/m^2 range lose a clinically significant amount of weight with orlistat than placebo; 4) that having access to a weight loss drug has any impact on motivation, dietary or exercise compliance, or long-term health or weight loss outcomes; 5) that individuals derive a health benefit from having orlistat, or any other weight loss drug, as a nonprescription agent; and 6) that any cosmetic benefit achieved with orlistat being available as a weight loss drug outweighs actual or theoretical risks of orlistat; in particular, interactions with fat-soluble nutrients and drugs.

Although the answers to deficiencies 1, 2, and 3, above, could be achieved with further study, such as a well-designed, placebo-controlled, year-long actual use study, this reviewer does not believe that further study will satisfy the inherent deficiencies outlined in 4, 5, and 6. Therefore, this reviewer is recommending a Not Approvable action.

1.2 Recommendation on Post-Marketing Actions

1.2.1 Risk Management Activity

Risk management recommendations are being deferred at this time. However, in the event of nonprescription orlistat approval, the sponsor should be required to demonstrate that subjects on

---

11 Xenical package insert.

cyclosporine (or, more preferably, status post an organ transplant) have 100% compliance, or as close as possible, with the labeled cyclosporine/organ transplant warning.

1.2.2 Required Phase 4 Commitments

[redacted]

1.2.3 Other Phase 4 Requests

This reviewer has no recommendations for other phase 4 requests at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Orlistat is a lipase inhibitor; it acts by blocking hydrolysis of triglyceride in the stomach and small intestine, thereby inhibiting absorption of dietary fat. Orlistat (Xenical®, Hoffman-La Roche) is currently marketed as a prescription-only product in the United States at a dose of 120 mg TID for long-term weight loss in patients with BMIs ≥ 30 kg/m^2 or ≥ 27 kg/m^2 if accompanied by co-morbid conditions. The applicant of this new drug application (NDA), GlaxoSmithKline Consumer Healthcare (GSK), seeks to market nonprescription orlistat 60 mg for weight loss in overweight adults ≥ 18 years old for use up to six months, and the submitted NDA only supports a six-month limitation of use.

The sponsor submitted three studies in support of efficacy of the 60 mg dose. Studies BM14149 and NM14161 were conducted in support of the prescription NDA in a primarily obese population. Study NM17247 was a four-month study in low overweight subjects conducted specifically for the nonprescription NDA. Longer-term data available from these and other Roche-sponsored orlistat trials provided additional information regarding weight maintenance and regain that was not presented in the nonprescription NDA submission.

The primary data that the sponsor provided in support of safety were those studies that included an orlistat 60 mg arm, including three studies from the original prescription NDA, which the sponsor pooled, study NM17247, and supportive studies (phase 2 and uncontrolled). Other safety data reviewed in support of this application included post-marketing data in the FDA adverse event reporting system (AERS), published literature, and the FDA review of the original prescription orlistat NDA.

1.3.2 Efficacy

The weight-loss efficacy of the 60 mg TID dose of orlistat was studied in the first year of two 2-year trials from the original prescription NDA in subjects with BMIs ranging from 30 - 43 kg/m^2 in one study and 28 - 43 kg/m^2 in the other, and in a four-month trial designed specifically for the nonprescription NDA in subjects with BMIs of 25 - 28 kg/m^2.

Given the sponsor's proposal to market nonprescription orlistat for short-term use, the six-month time point was chosen as the efficacy endpoint of interest from the two prescription NDA clinical studies. In these studies, which were pooled due to similar study designs and patient populations, 42% of subjects treated with orlistat 60 mg, 45% of subjects treated with orlistat 120 mg, and 23% of those treated with placebo achieved a weight loss of $\geq$ 5% at six months ($p < 0.001$, both orlistat groups *vs.* placebo).

By contrast, in the nonprescription NDA clinical study, 36% of orlistat 60 mg-treated subjects *vs.* 28% of placebo-treated subjects lost at least 5% of their baseline body weight at four months ($p = 0.104$). In an analysis proposed by the sponsor, the percent of orlistat-treated subjects achieving a 3% weight loss was statistically significantly greater compared to placebo after four months of treatment (57% *vs.* 42%, $p = 0.004$).

Placebo-subtracted mean weight loss in the two prescription NDA clinical studies at six months was 2.3 kg (~2.4%) in subjects on the 60 mg dose and 2.9 kg (~3.1%) in those on the 120 mg dose (Table 1.3.2.A, below). In the nonprescription NDA clinical study, after four months of treatment with orlistat 60 mg, the placebo-subtracted mean weight loss was 1.2 kg (~1.6%).

These findings raise the possibility that orlistat may be less effective in mildly overweight individuals (i.e., BMIs 25 - 28 kg/m^2) than in obese subjects. However, since the sponsor has not studied the effects of six months of orlistat therapy in mildly overweight subjects, this is speculation on the part of this reviewer.

Table 1.3.2.A. Summary of Weight Loss (Kg) From Two Six-Month Studies and One Four-Month Study

			Difference From Placebo		
Study	**Treatment Group**	**Adjusted Mean Change from BL +/- SE**	**Adjusted Mean +/- SE**	**95% Confidence Interval**	**P-Value**
Pooled Six-Month Studies in Patients with BMIs of 28 – 43 kg/m^2					
Pooled 6-Month Studies	Placebo	-1.88 ± 0.223			
	Orlistat 60 mg	-4.14 ± 0.218	-2.29 ± 0.308	(-2.89, -1.68)	<0.001
	Orlistat 120 mg	-4.71 ± 0.221	-2.88 ± 0.309	(-3.49, -2.28)	<0.001
Four-Month Study in Patients with BMIs of 25 – 28 kg/m^2					
4-Month Study	Placebo	-1.90			
	Orlistat 60 mg	-3.05	-1.15 ± 0.31	(-1.76, -0.54)	<0.001

LOCF data, ITT Population, all sites

Orlistat-induced weight loss was associated with small favorable changes in lipids, fasting glucose, and blood pressure; however, it is well-known that once treatment with any weight-loss

drug is stopped, lost weight tends to be regained and improvement in co-morbidities reversed. This pattern of weight change has been observed in long-term trials with orlistat.[5]

1.3.3 Safety

Most of the identified adverse events due to orlistat, both in the clinical studies submitted in the NDA as well as in the literature, are related to its pharmacologic effect and are gastrointestinal in nature. Gastrointestinal adverse events impact the tolerability of orlistat, and may be modifiable by dietary adjustment (i.e., adherence to a low-fat diet). It should be noted that the incidence of serious adverse events, both overall and gastrointestinal, was similar between orlistat- and placebo-treated groups in all studies.

Drug-drug interactions

A reduction in the serum concentration of cyclosporine has been seen with co-administration with orlistat. Because weight gain is fairly common after organ transplantation,[12] the concomitant use of cyclosporine and orlistat is more than a theoretical possibility, and may lead to sub-therapeutic immunosuppression.[13] Fourteen unique cases of interactions between the two drugs were reported in the AERS database. Moreover, two cases of acute rejection episodes have been reported.[14, 15] In the case report of organ rejection from the literature[14], the decrease from and subsequent re-establishment of an adequate trough cyclosporine level was temporally associated with the starting and stopping of orlistat, respectively. The prescription labeling states in its Warnings section that in order to reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 2 hours before or after orlistat in patients taking both drugs and that more frequent monitoring of cyclosporine levels should be considered.

Warfarin is another drug that may be affected by concomitant orlistat use. Because warfarin blocks the activity of vitamin K, and therefore impairs coagulation, the impact of orlistat on prothrombin time in individuals who are on warfarin is considered to be a clinical consequence of vitamin K malabsorption. Clinical pharmacology studies conducted by Roche demonstrate that orlistat does not alter warfarin pharmacokinetics. However, there are post-marketing reports of both prolonged prothrombin time and bleeding with concomitant drug use. The prescription label instructs individuals who are on warfarin to have their coagulation parameters measured frequently.

Given the lack of a learned intermediary in the nonprescription setting, it is vital that labeling of nonprescription orlistat adequately communicate risk information. However, preliminary evidence suggests that nonprescription labeling may not effectively direct the safe use of orlistat. In a pilot actual use study, after reading the Drug Facts sheet for nonprescription orlistat, only

12 Van den Ham EC, et al. Transpl Int. 2003 May;16(5):300-6.
13 Colman E, et al. N Engl J Med. 2000 Apr 13;342(15):1141-2.
14 Schnetzler B, et al. Transplantation. 2000 Nov;70(10):1540-1.
15 FDA AERS data

50% of patients on cyclosporine or warfarin failed to realize that they should not take orlistat while on these medications.

Fat-soluble vitamins

In studies conducted under the prescription NDA, mean plasma concentrations of vitamins D and E and beta-carotene were shown to be statistically significantly lower after one and two years of treatment with either orlistat 60 or 120 mg compared to placebo. Furthermore, orlistat groups had a higher proportion of subjects with two consecutive low vitamin concentrations than the placebo groups. Vitamin D may especially be a concern because deficiency of this nutrient is common in the United States, particularly in females, the elderly, and minorities,[9] and is associated with the risk for osteoporosis and other chronic diseases.[10]

Based on data from the 14-day interview from the actual use study, 74% of orlistat users took a multivitamin regularly; however only 54% of these subjects timed the multivitamin administration correctly as instructed by the label (40% of total orlistat users).[16] Information regarding multivitamin use behavior beyond this 14-day interview was not provided.

Other safety issues

Other potential safety issues with orlistat include nephrolithiasis, cholelithiasis, hepatitis, and pancreatitis, although the causative role of orlistat in these conditions remains inconclusive. Rare, idiosyncratic hypertension of unknown etiology has even been raised as a post-marketing concern. Several published case reports document the use of orlistat as a purgative in women with bulimia nervosa.[17, 18, 19] The off-label use or misuse of orlistat would obviously take on greater significance in the nonprescription marketplace due to ease of access to the drug.

1.3.4 Dosing Regimen and Administration

The prescription dose of orlistat is 120 mg TID. GSK is proposing the nonprescription sale of a 60 mg dose, to be administered 1-2 capsules TID. The pharmacological effect (fecal fat excretion) describes the mechanism of action of orlistat's weight loss effect, that is, caloric deficit, as well as the biological plausibility for the increase in gastrointestinal (GI) side effects. Given that orlistat 60 mg is associated with approximately 25% fecal fat excretion, and orlistat 120 mg is associated with approximately 30% fecal fat excretion, it is expected that the 60 mg dose would be slightly less efficacious and cause fewer GI side effects than the 120 mg dose. This is supported by clinical data.

The pharmacological effect of orlistat also predicts that the more fat there is in the diet, the greater the drug effect. An individual who consumes a diet of 40% fat will experience a higher

16 Feibus K., review of actual use study NM17285.
17 Fernandez-Aranda F, et al. Int J Eat Disord. 2001 Dec;30(4):458-61.
18 Malhotra S, et al. Am J Psychiatry. 2002 Mar;159(3):492-3.
19 Cochrane C, et al. Eat Behav. 2002 Summer;3(2):167-9.

proportion of daily calories being excreted than someone consuming 20% fat if both individuals have the same amount of daily caloric intake.

However, not all of the weight loss achieved with orlistat may be directly attributable to its pharmacology. Some have suggested that individuals taking orlistat may reduce their dietary fat intake to levels below the recommended 30% of total calories in an effort to reduce or eliminate adverse GI side effects. A dramatic reduction in dietary fat intake may in and of itself reduce weight, but only if individuals do not compensate for the reduction in fat calories by increasing intake of carbohydrate or protein.

One might also conjecture that some individuals will avoid taking orlistat when they know they will be eating out in a social situation, or eating a high-fat meal, in order to avoid embarrassing GI side effects. We know that 3 - 5% of subjects in the first 4 - 6 months of treatment discontinue orlistat due to GI side effects as compared to 1% of placebo-treated subjects.

1.3.5 Drug-Drug Interactions

Because drug-drug interactions are a major determinant of the safety profile of orlistat, this was discussed under a subsection of Section 1.3.3 (summary of safety), above. Orlistat acts locally in the gastrointestinal tract and interferes with the absorption of some concomitantly-administered lipid-soluble drugs and vitamins.

Drug-drug interaction studies conducted as part of the prescription orlistat NDA indicated that orlistat has no effect on pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release tablets), oral contraceptives, phenytoin, pravastatin, or warfarin. In addition, alcohol does not affect the pharmacodynamics of orlistat.[11]

1.3.6 Special Populations

Special populations that require medical supervision with weight loss in general, and orlistat use specifically, include: 1) the adolescent population, for whom the drug will not be indicated, but who may purchase it nonetheless assuming adequate resources; and 2) the elderly population, who are more at risk from the drug than younger individuals due to nutrition-related consequences and polypharmacy.

Because of issues related to growth and development, the potential for syndromic and endocrine etiologies of obesity that require medical evaluation, as well as complex behavioral, emotional, and psychosocial concerns in the pediatric population, this reviewer is against approval of nonprescription orlistat for individuals under the age of 18 years.

Because the elderly population is at risk for weight-related co-morbidities and altered body composition, as well as morbidity due to weight *loss*, particularly related to nutritional complications and decreased lean body and bone mass, this reviewer believes that intentional weight loss in the elderly should generally be under a physician's supervision. However, the proposed label does not restrict use of orlistat in the elderly population. Clinical studies have

been inadequate to assess the safety in this group (approximately 2.4% of subjects in the pooled studies were ≥ 65 years).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Orlistat, or tetrahydrolipstatin, is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. Its molecular weight is 495.7.

Orlistat's pharmacologic class is lipase inhibitor; it acts by blocking hydrolysis of triglyceride in the stomach and small intestine, thereby inhibiting absorption of dietary fat. Orlistat (Xenical®, Hoffman-La Roche) is currently marketed as a prescription-only product in the United States at a dose of 120 mg TID for long-term weight loss in patients with BMIs ≥ 30 kg/m^2 or ≥ 27 kg/m^2 if accompanied by co-morbid conditions. The applicant of this new drug application (NDA), GlaxoSmithKline Consumer Healthcare (GSK), seeks to market nonprescription orlistat 60 mg for weight loss in overweight adults ≥ 18 years old for use up to six months.

2.2 Currently Available Treatments for Weight Loss

2.2.1 Prescription Drugs

All prescription drugs currently approved for weight loss are anorectic agents, with the exception of orlistat.

FDA-approved prescription medications for long-term weight loss are the following:
- Orlistat (Xenical)
- Sibutramine (Meridia)

FDA-approved prescription medications for short-term weight loss (i.e., a few weeks use) are the following:
- Phentermine (Ionamin)
- Diethylproprion (Tenuate)
- Phendimetrazine
- Benzphetamine (Didrex)

2.2.2 Nonprescription Drugs

Benzocaine is currently category III for weight control efficacy under the draft weight loss monograph. Category III means that the drug has not been determined to be GRAS/GRAE

(Generally Recognized as Safe/Effective). Benzocaine is not currently marketed in the US for a weight loss indication.

Phenylpropanolamine (PPA)-containing nonprescription drugs such as Dexatrim® were removed from the market in 2000 due to concern that PPA increased the risk for hemorrhagic stroke. Prior to its withdrawal, the extended release formulation was marketed as a nonprescription weight loss drug for short-term use (up to 12 weeks). Its demonstration of efficacy was based on four studies, 6-12 weeks in duration, which demonstrated statistically significant weight loss from placebo in overweight and obese subjects on a hypocaloric diet.[20] Unlike the current regulatory requirements for approval of prescription drugs for weight loss, at that time the Agency's criterion for a weight control ingredient to be considered effective was that it had to demonstrate statistically significant weight reduction in double-blind, placebo-controlled studies lasting six to 12 weeks. In the referenced studies, 75 mg daily of extended-release PPA was shown to affect a placebo-subtracted weight loss of 0.14 to 0.25 kg/week. [It should be noted that the adjusted mean placebo-subtracted weight loss in overweight subjects taking orlistat 60 mg (-1.2 kg over 16 weeks in study NM17247) is equivalent to a weight loss of only 0.075 kg/week. Even in the obese population, the adjusted mean placebo-subtracted weight loss of -2.3 kg over 24 weeks (pooled studies) is equivalent to 0.096 kg/week.]

The safety issues surrounding PPA are beyond the scope of this review. However, it is instructive to consider some of the discussion of the Nonprescription Drugs Advisory Committee Meeting in October 2000 (the safety of PPA used in nonprescription weight control and nasal decongestant drug products).[21] Committee members were concerned about the risk-benefit profile of PPA, noting that when a drug is only *marginally useful*, risk is much less tolerable. Another concern was raised that a high proportion of subjects in one PPA study, the design of which mimicked an actual use study, were hypertensive and taking PPA, suggesting that labeling alone could not be relied upon to adequately communicate warnings.

2.2.3 Non-Pharmacological Therapies

Surgical treatment of patients with morbid obesity (BMI $\geq$ 40 kg/m^2 or $\geq$ 35 kg/m^2 with co-morbidities) includes gastric bypass and laparoscopic banding.

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20 The following studies were described in a letter from FDA to Nonprescription Drug Manufacturers Association, May 1994:
(1)Weintraub M, et al. "Phenylpropanolamine OROS (Acutrim) vs. placebo in combination with caloric restriction and physician-managed behavior modification," Clinical Pharmacology and Therapeutics, 1986 May;39(5):501-9.
(2)Schteingart D. "A Double Blind Clinical Evaluation of the Anorectic Activity Of Phenylpropanolamine (75mg) Compared with Placebo in the Treatment of Exogenous Obesity," unpublished study in Comment No. CP11, Docket No. 81N-0022, Dockets Management Branch.
(3)Greenway F. "A Double Blind Clinical Evaluation of the Anorectic Activity Of Phenylpropanolamine (75mg) Compared with Placebo in the Treatment of Exogenous Obesity," unpublished study in Comment No. CP11, Docket No. 81N-0022, Dockets Management Branch.
(4)Atkinson R. "A Double Blind Clinical Evaluation of the Anorectic Activity of Phenylpropanolamine (75 mg) Compared with Placebo In the Treatment of Exogenous Obesity," unpublished study in Comment No. CP14, Docket No. 81N-0022, Dockets Management Branch.
21 http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3647t1.doc

Hypocaloric diet and increased physical activity are recommended for all overweight and obese individuals who are attempting weight loss. These lifestyle measures are not considered to be replacement for drug therapy, but rather, as an important foundation to drug therapy. However, it is unknown how many individuals will attempt to use an available drug as a replacement for such changes in the nonprescription setting.

2.3 Availability of Proposed Active Ingredient in the United States

Orlistat (Xenical) capsules are currently marketed by Hoffman La-Roche as a prescription medication for long-term weight-loss at a dose of 120 mg TID. An investigational new drug (IND) application was first submitted to the Division May 12, 1988, and orlistat was subsequently approved for marketing on April 23, 1999, under NDA 20-766. Xenical 120 mg is currently indicated for patients with an initial body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia) for:

- Obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet.
- Reduction of the risk for weight regain after prior weight loss.

Important labeling distinctions between orlistat and other approved weight-loss medications include: 1) the inclusion of clinical data from a study conducted in children, aged 12-16 years, and 2) the inclusion of results of the XENDOS trial, which suggest that orlistat-related weight loss delays the onset of type 2 diabetes in individuals with impaired oral glucose tolerance at baseline.

2.4 Important Issues with Pharmacologically Related Products

Orlistat is the only member of its pharmacologic class currently approved for marketing.

[redacted]. Gastrointestinal reactions have been the most common adverse events reported to date in drugs of this class, with significant decreases in vitamins D and E and beta-carotene noted. Please see Section 7, the Integrated Review of Safety, for further discussion of these issues.

2.5 Presubmission Regulatory Activity

Hoffman-La Roche (Roche) is the sponsor of the prescription orlistat (Xenical) product, which was approved for sale in the United States in 1999 (NDA 20-766). Roche initiated IND 62,758 June 14, 2001 to investigate the feasibility of a nonprescription dose of 60 mg orlistat for an overweight (but not obese) population. An End-of-Phase 2 (EOP2) meeting took place to discuss orlistat 60 mg as a potential nonprescription product between the Divisions of Metabolic and Endocrine Drug Products and Over-the-Counter Drug Products and Roche on July 17, 2002. Important discussions that took place during this meeting included:

1. The difficulty of distinguishing obese from non-obese overweight patients by self-selection.
2. A request that the company provide justification for proposing the marketing of orlistat 60 mg TID, rather than the approved prescription regimen of 120 mg TID.
3. A need to demonstrate that the nonprescription product could be used safely by the population for whom it confers benefit. Furthermore, a label comprehension study would have to be done to show that consumers who have co-morbidities contraindicated on the label, such as gallbladder disease, would know not to use the product.
4. A need to demonstrate that the 60 mg dose works in the target nonprescription population. Clinical trial data available at the time of the EOP2 meeting existed in patients with a BMI $\geq$ 28 kg/m^2 but not in patients with a BMI < 28 kg/m^2. It was discussed that ideally, effectiveness should be demonstrated in a proposed target population unless plausible justification is provided as to why such data are not needed.
5. A need for an actual use study that can demonstrate: a) the consumer's ability to understand and follow a reduced calorie diet without the intervention of a dietician, and b) the outcomes on safety and effectiveness for orlistat patients who do not make appropriate diet and exercise modifications.
6. The issue of fat-soluble vitamin and drug-drug interactions was addressed.

The following discussion regarding duration of use and weight regain was captured in the meeting minutes, which are excerpted verbatim here:

The Agency recommended that the sponsor provide data showing that patients understand the benefit of taking orlistat for 6 months and then discontinuing therapy. The firm responded that few patients take orlistat chronically, that the maximal effect of orlistat is seen at between 3 and 6 months' of use, and that the weight loss goal is for a 5% reduction of body weight.

The Agency questioned what a person should do if they re-gain weight after stopping orlistat. Roche explained that the safety data support consumers taking the medication for greater than 4 years, so that safety should not be an issue. However, Roche repeated that they would hope to direct consumers to proper diet and exercise habits within the first 6 months so that further treatment regimens would not be needed.

Subsequent to the EOP2 meeting, GlaxoSmithKline (GSK, the sponsor) acquired ownership of IND 62,758 from Roche, and participated with the Agency in a pre-NDA meeting December 8, 2004 in which the following issues were discussed:

1. The Agency asserted that the standards used to evaluate and label effectiveness of nonprescription weight loss products should be the same as those used for prescription weight loss products (1996 draft guidance).
2. When responding to further questioning about the marketing of orlistat 60 mg rather than the 120 mg dose over-the-counter, GSK noted that they continued to see a clinical importance in maintaining the prescription 120 mg product for long term use in obesity management, pediatric use, and as guidance to physicians on benefits of long term use on co-morbidities based on the XENDOS study data.

3. The level of dietary counseling in the clinical trials was raised and how it would apply to the nonprescription setting.
4. In discussing the "target" population, GSK stated that nonprescription weight loss use with orlistat will be intended to cover a wide range of BMIs from slightly overweight to obese.
5. Other issues covered during the meeting included the duration of use, multivitamin use, pediatric use, and abuse/misuse.

The following request was documented in the meeting minutes of the pre-NDA meeting:

A 12-month Actual Use Study should be conducted that compares active treatment to placebo. All subjects would use only labeled support information regarding proper product use and recommended dietary and activity changes. This study could provide additional efficacy and safety data for orlistat in an actual OTC-use environment with an all-comers population. A low literacy population should be enrolled. We encourage you to submit a draft protocol for review.

2.6 Other Relevant Background Information

Xenical (orlistat 120 mg) has been reclassified as a Pharmacy-Only Medicine (POM) in the Australian and New Zealand markets. The sponsor claims that this experience provides some perspective on the drug's safety profile in a consumer-driven nonprescription environment, although this POM designation in these countries affords some level of pharmacist intervention at the initial point of sale. The classification of a drug as a POM indicates that the medication is available without a doctor's prescription, but cannot be obtained via general sale on 'open' shelves. Orlistat can be obtained directly from a pharmacist following consultation.

In association with professional pharmacy/pharmaceutical societies, Roche developed a pharmacy protocol to be used by the consulted pharmacist in the dispensing of orlistat as a POM. Key steps of the dispensing protocol include: conducting a face-to-face consultation to clarify customer's needs (considering factors such as BMI, age and co-morbidities); confirming the appropriateness of orlistat (i.e., review of warnings); and providing counseling on important points such as the drug's mode of action and dosage, side effects, and vitamin supplementation.

For both markets, introduction to the marketplace and availability of orlistat capsules as a POM immediately followed regulatory approval. In Australia, consumers had access to orlistat on May 1, 2004, and in New Zealand, on March 11, 2005.

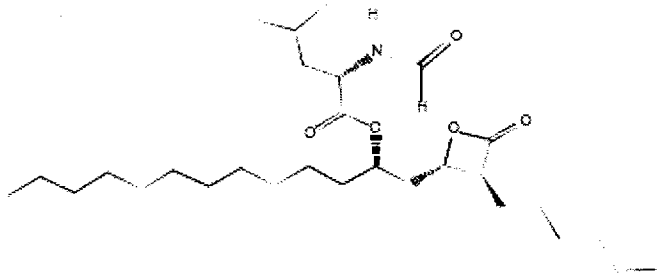
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

The orlistat prescription label states:

Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight

is 495.7. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529 nm. The structure is:



Orlistat is a white to off- white crystalline powder. Orlistat is practically insoluble in water, freely soluble in chloroform, and very soluble in methanol and ethanol. Orlistat has no pK_a within the physiological pH range.

XENICAL is available for oral administration in dark-blue, hard-gelatin capsules, with light-blue imprinting. Each capsule contains 120 mg of the active ingredient, orlistat. The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc. Each capsule shell contains gelatin, titanium dioxide, and FD&C Blue No.1, with printing of pharmaceutical glaze NF, titanium dioxide, and FD&C Blue No.1 aluminum lake.

Please see the chemistry review for specific chemistry issues regarding this application.

3.2 Animal Pharmacology/Toxicology

No new pharmacology or toxicology data were submitted with this application. Therefore, this reviewer will summarize the key findings from the pharmacology/toxicology and medical officer reviews of the original NDA 20-766.

3.2.1 Pharmacology

Orlistat is a reversible inhibitor of the gastrointestinal lipases, including pancreatic lipase, gastric/lingual lipase, and carboxylester lipase. Orlistat also inhibits lipoprotein lipase, hepatic lipase, hormone-sensitive lipase, and diacylglycerol lipase; however, because of the extremely low bioavailability of orlistat (see Section 3.2.2, below) these systemic lipases are not significantly affected in the clinical setting.

3.2.2 ADME

Please also refer to Section 5.1.1, ADME in the pharmacokinetics section of this review. In animals at high doses, orlistat is systemically absorbed in a greater than dose-proportional fashion and absorption increases at a given dose with chronic exposure. At clinical exposure concentrations, however, only a small amount of orlistat is absorbed and the increase in

absorption with chronic exposure does not occur. Systemically-absorbed orlistat is highly metabolized and bound to plasma proteins. The metabolic profile is similar in all species tested.

3.2.3 Toxicology

Findings in rats included:

- Increased fecal fat excretion, leading to loose or soft stools, unkemptness, and oily fur.
- Increases in food intake as body weights decreased, although increased food intake did not fully compensate for lost body weight.
- Hypertriglyceridemia, hyperbilirubinemia, and increased plasma cholesterol, amylase, and BUN.
- Decreased liver concentrations of vitamins E and A, sometimes accompanied by decreased plasma concentrations. These findings were not fully compensated for by dietary vitamin supplementation.

In dogs, findings were similar to those of rats; additional findings included decreased plasma cholesterol and vitamin D concentrations.

The effects of orlistat on the gastrointestinal (GI) tract were studied in a number of models with concomitant administration of a high fat and low or normal calcium diet. Although no GI neoplasia or hyperplasia was observed, a reversible increase in colonic proliferation was observed. In rats fed a high fat, normal calcium diet for nine months, there was a treatment-related increase in the number of colonic aberrant crypt foci observed. Of note, this finding was not detected in humans.

3.2.4 Mutagenicity

The Ames bacterial mutagenesis assay, V79/HGPRT mammalian mutagenesis assay, *in vitro* clastogenicity assay in peripheral human lymphocytes, *in vivo* mouse micronucleus assay, and UDS assay were all negative for mutagenic potential.

3.2.5 Carcinogenicity

Rat studies performed at doses > 29 times the human exposure (based on surface area) did not demonstrate any carcinogenic potential. Mouse studies performed at doses > 22 times the human exposure (based on surface area) demonstrated a statistically significant finding of liver hemangiosarcomas (2 tumors, high-dose female group; 0 tumors, any other group; $p = 0.025$). According to the pharmacology/toxicology reviewer, this finding was significant because of the rarity of the tumor in this strain. When the statistical analysis was repeated combining the incidence of hemangiomas and hemangiosarcomas, the finding was no longer statistically significant. No statistically significant findings of GI tract tumors were noted.

3.2.6 Reproductive Toxicology

Exposures were 23 and 47 times the clinical dose (high-dose) for rat and rabbit, respectively. There were no teratogenic findings in rabbits. In one rat study, an increase in dilated cerebral vesicles in pups from the mid- and high-dose groups was noted; this was statistically significant in the high-dose group only. Two other rat studies did not demonstrate this finding.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

As the sponsor noted in their background package for the Advisory Committee meeting January 23, 2006, orlistat has been studied in over 100 clinical trials, including four 2-year and one 4-year double-blind, placebo-controlled studies. The sponsor further noted that the 120 mg dose was approved for marketing in the US in 1999 and has been approved and marketed in over 145 countries, with over 22 million patients treated. Therefore, there is a considerable amount of data available on the safety and efficacy of this drug.

For efficacy, this reviewer focused on studies submitted to the NDA by the sponsor; in particular, the efficacy of the 60 mg dose. Studies BM14149 and NM14161 were conducted in support of the prescription NDA in a prescription population, as described above. Study NM17247 was a four-month study in low overweight subjects conducted specifically for the nonprescription NDA. Longer-term data available in these and other Roche-sponsored orlistat trials provided additional information regarding weight maintenance and regain that was not presented in the nonprescription orlistat NDA submission.

The primary data that the sponsor provided in support of safety were those studies that included an orlistat 60 mg arm, including three studies from the original prescription NDA, which the sponsor pooled, study NM17247, and supportive studies (phase 2 and uncontrolled). Other safety data reviewed in support of this application included post-marketing data in the FDA adverse event reporting system (AERS), published literature, and the FDA review of the original prescription orlistat NDA.

4.2 Tables of Clinical Studies

Table 4.2.A. Listing of Studies Included in Nonprescription NDA for Orlistat

Study No. / Study Completion Date / NDA	Type of Study	Role in OTC NDA	Duration	BMI	Dose	N†
BM14149 February 1996 N20-766	Weight loss study	Safety & Efficacy	2 yrs	28-43	Placebo 60 mg 120 mg	237 239 242
NM14161 February 1995 N20-766	Weight loss study using primary care providers	Safety & Efficacy	2 yrs	30-43	Placebo 60 mg 120 mg	212 213 210
NM17247 October 2003 N21-887	Weight loss study in a primary care setting	Safety & Efficacy	4 mos	25-28	Placebo 60 mg	195 196
BM14150 May 1995 N20-766	Dose-ranging study	Safety & Efficacy (Supportive)	6 mos	28-43	Placebo 30 mg 60 mg 120 mg 240 mg	124 122 123 120 117
NM14302 March 1996 N20-766	Weight maintenance effect of orlistat after 6 month period of weight loss by diet alone	Safety	18 mos*	28-38	Placebo 30 mg 60 mg 120 mg	185 186 171 180
RCH-ORL-002 December 2001 N21-887	Evaluation of orlistat in a naturalistic setting	Supportive	4 wks	≥ 27‡	60 mg	162
NM17285 October 2003 N21-887	Pilot actual use study	Supportive	3 mos	**	60-120 mg	284

† Safety population
*12 months of drug treatment
‡ Based on self-report
** This study was intended to simulate an OTC environment; no BMI restrictions were imposed

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4.3 Review Strategy

This reviewer's general approach to the review was described in Section 4.1, Sources of Clinical Data. This review describes and analyzes the data supporting safety and efficacy of nonprescription orlistat. Reviewers from the Division of Nonprescription Clinical Evaluation in the Office of Nonprescription Products conducted the primary reviews of the actual use and label comprehension studies.

4.4 Data Quality and Integrity

The Division of Scientific Investigation (DSI) was not consulted to audit the applicant's data or analyses. This reviewer reviewed the case report forms and did not discover any important discrepancies.

4.5 Compliance with Good Clinical Practices

Studies BM14150, BM14149, NM14161, and NM14302 (studies supporting the prescription NDA 20-766) were conducted and sponsored by Roche in compliance with Good Clinical Practices (GCP) requirements in effect at the time. As certified in NDA 20-766, no debarred investigators were used in the conduct of these studies. Roche and/or a contract organization continually monitored the progress of these clinical investigations in order to evaluate trial conduct and compliance with protocol, GCP, and with applicable regulatory requirements.

NM17247, NM17285, and RCH-ORL-002 (studies supporting the nonprescription NDA 21-887) were conducted under Roche IND 62,758, which was subsequently transferred to GSK (the sponsor). GSK reviewed the study documentation included in IND 62,758, and concluded that these studies were conducted in compliance with the current requirements of Institutional Review Board (21 CFR Part 56) and Informed Consent (21 CFR Part 50) regulations.

4.6 Financial Disclosures

An FDA Form 3455 was submitted for [redacted] investigator in study [redacted] earned $29,750 in honoraria from Roche (sponsor of the original orlistat NDA, [redacted]). In response to this reviewer's request, the sponsor provided a reanalysis of weight change and common adverse events without the inclusion of Dr. [redacted] site. There were no differences in these efficacy and safety measures, implying maintenance of the blind.

According to the company, steps taken to minimize bias include the following: 1) this was a randomized, double-blind, placebo-controlled study with [redacted] clinical sites and objective measures; 2) there was independent monitoring and auditing; and 3) patient enrollment was balanced by site.

No other investigators from studies NM17247 or RCH-ORL-002 had any financial disclosures. Financial information on two investigators (out of 18) from study NM17285 was originally omitted but provided upon request.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

5.1.1 ADME

5.1.1.1 Absorption

Systemic exposure to orlistat is low. In clinical studies monitoring plasma concentrations, detection of intact orlistat in plasma is sporadic and concentrations are < 10 ng/mL without evidence of accumulation. This is consistent with minimal absorption of the drug.

5.1.1.2 Distribution

Because of the limit of quantification, binding data could only be obtained at drug concentrations approximately twenty thousand times higher than those obtained at therapeutic doses. Orlistat is extensively bound (99%) to plasma proteins for all species tested (humans, dogs, and rats). Serum albumin appears to be a binding protein in human plasma. Orlistat is also strongly bound to plasma lipoproteins.

5.1.1.3 Metabolism

Animal data suggest that that the metabolism of orlistat occurs mainly within the gastrointestinal wall. The two major metabolites in humans are M1 (Ro 42-3988) and M3 (Ro 42-2556); these metabolites account for approximately 42% of total radioactivity in plasma. Both have very weak lipase inhibitory activity.

5.1.1.4 Elimination

Fecal excretion of the unabsorbed drug is the major route of elimination. Orlistat and its M1 and M3 metabolites are also subject to biliary excretion. Mean renal elimination is < 2% of the 360 mg dose. The time to reach complete excretion (fecal plus urinary) is 3 to 5 days. The half-life of absorbed orlistat is in the range of 1 to 2 hours. The disposition appears to be similar between normal weight and obese subjects.

5.1.2 Drug-Drug Interactions

Drug-drug interaction studies conducted as part of the prescription orlistat NDA indicated that orlistat has no effect on pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release tablets), oral contraceptives, phenytoin, pravastatin, or warfarin. In addition, alcohol does not affect the pharmacodynamics of orlistat.[11]

Studies conducted under the original prescription NDA also assessed the absorption of lipid-soluble vitamins and analogues. These studies found that the absorption of single doses of β-carotene and vitamin E acetate were reduced by 33% and 43%, respectively, with concomitant orlistat administration. Although it was reported that no effects were observed on vitamin A acetate or on vitamin K nutritional status, a published study in adolescents did find a non-significant decrease in serum vitamin K levels with concomitant orlistat and multivitamin (25 μg vitamin K/day) use.[22] Vitamin K in the context of warfarin is discussed further in Section 8.2.2. Other issues related to fat-soluble vitamins are discussed in Section 7.1.7.3.1.

In terms of lipophilic drug-drug interactions (inhibition of absorption), Roche conducted an orlistat and cyclosporine drug interaction study that indicated there was a reduction in cyclosporine plasma concentrations when orlistat was co-administered with cyclosporine.[11] In addition, the impact of orlistat on the pharmacokinetics of three highly lipophilic drugs, amiodarone, fluoxetine, and simvastatin, was recently studied.[23] Although the pharmacokinetic parameters, C_{max} and $AUC_{0-\infty}$, of fluoxetine and simvastatin were not significantly affected by orlistat, the absorption of amiodarone, an antiarrhythmic drug, was reduced by approximately 20-25%. The clinical impact of the cyclosporine and amiodarone findings is discussed in Section 8.2.

5.2 Pharmacodynamics

The pharmacodynamic effect of orlistat was thoroughly reviewed for the approval of the prescription orlistat NDA. This section will briefly discuss the pharmacodynamic effect of orlistat, namely, fecal fat excretion, for the 60 mg dose. Fecal fat was measured in the dose-ranging study BM14150 (see Section 7.2.1.1 for the study description). After 24 weeks of TID treatment, the subjects receiving 60 mg had a mean increase in fecal fat content of 15.4 g/day and those receiving 120 mg had a mean increase of fecal fat content of 18.5 g/day (Table 5.2.A). There was no appreciable change in the amount of fecal fat excreted by the placebo-treated groups after 24 weeks (-0.1 g/day). Therefore, approximately 25% of dietary fat absorption was inhibited by orlistat 60 mg and approximately 30% by orlistat 120 mg. This suggests the pharmacodynamic effect is less than dose-proportional at doses greater than 60 mg. It is noted that a single dose of two 60 mg capsules is bioequivalent to one 120 mg capsule.

22 McDuffie, et al. Pharmacotherapy. 2002 Jul;22(7):814-22.
23 Zhi J, et al. J Clin Pharmacol. 2003 Apr;43(4):428-35.

Table 5.2.A. Summary Statistics of Daily Fecal Fat Excretion (grams/24 hours) Over Time (Observed Data; 72 hour Fecal Fat Collection) Intent-to-Treat Population; Study BM14150

Treatment Group	Scheduled Visit	Value at Scheduled Visit N	Mean	SD	Median	Change from Start of Double-Blind Treatment N	Mean	SD	Median
Placebo	Lead-in	72	2.74	3.07	1.85				
	Week 24	72	2.53	1.82	2.15	71	-0.10	3.27	0.20
30 mg tid	Lead-in	76	2.31	2.32	1.85				
	Week 24	77	13.69	8.73	12.60	75	11.49	9.26	10.70
60 mg tid	Lead-in	70	2.34	2.57	1.70				
	Week 24	73	17.48	10.70	16.50	70	15.37	10.72	15.15
120 mg tid	Lead-in	76	1.97	1.69	1.55				
	Week 24	77	20.64	15.81	19.20	76	18.53	15.62	16.10
240 mg tid	Lead-in	78	2.25	1.88	1.95				
	Week 24	77	25.75	19.09	21.80	77	23.50	19.09	19.30

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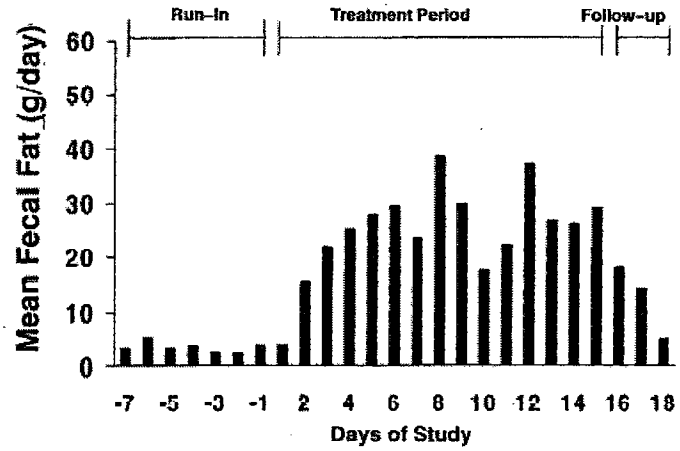
These findings are corroborated by fecal fat results obtained in the phase 3 study NM14161 (see Section 6.1.3 for the study description), in which mean fecal fat excretion was increased from the start of double-blind treatment by approximately 16 g/day in the orlistat 60 mg group and by 21 g/day in the orlistat 120 mg group after 52 and 104 weeks. The amount of fecal fat excreted by placebo-treated patients at these time points changed little. These results indicate that the pharmacologic effect of orlistat is maintained over two years.

The prescription label for orlistat states that the pharmacologic effect of the drug is observed within 24 - 48 hours. Following discontinuation of the drug, fecal fat excretion returns to normal within 48 - 72 hours. This is illustrated in the figure below.

Figure 5.2.A. Time Course of the Pharmacological Effect of Orlistat



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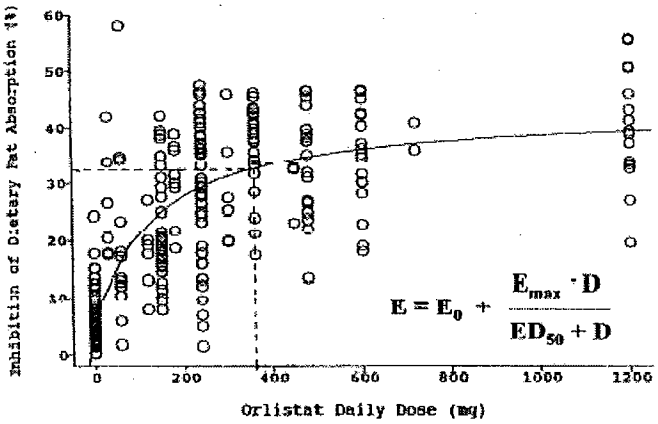
5.3 Exposure-Response Relationships

The exposure-response of orlistat is based on its pharmacologic effect and is discussed above in Section 5.2, and is further illustrated in the dose-response curve in Figure 5.3.A, below. Dose-dependent fecal fat excretion impacts the tolerability and efficacy of the drug and will be further discussed in the reviews of efficacy and safety (Sections 6 and 7). Dietary fat ingestion also affects the response of the drug. The higher the percentage of daily dietary fat for a given caloric intake, the greater the daily caloric excretion, and, assuming the diet is hypocaloric, the more negative the energy balance.

Figure 5.3.A. Dose-Response Curve



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6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Promotion of Weight Loss

6.1.1 Methods

To support the efficacy of the orlistat 60 mg dose, data from the first year (weight loss phase) of the prescription orlistat NDA phase 3 two-year studies BM14149 and NM14161 were analyzed pooled together (hereafter referred to as 'pooled studies' in the efficacy portion of this document) as well as individually, with an emphasis on the six-month time point. The efficacy data from study NM17247 were presented separately.

6.1.2 General Discussion of Endpoints

'Weight' is the primary variable when assessing efficacy of weight loss drugs, and the FDA Draft Guidance for the Clinical Evaluation of [Prescription] Weight-Control Drugs (September 24, 1996)[2] discusses this as excerpted here:

Actual weight loss should be reported, and, also, it is helpful to express weight loss in relative terms such as percent of body weight or percent of excess over ideal body weight or change in body mass index. Measurement of change in central obesity is also useful.

At least two weight-loss demonstrations are possible:

1) *demonstration that the drug effect is significantly greater than the placebo effect and the mean drug-associated weight loss exceeds the mean placebo weight loss by at least 5%.*
2) *demonstration that the proportion of subjects who reach and maintain a loss of at least 5% of their initial body weight is significantly greater in subjects on drug than in those on placebo.*

Measurement of obesity-associated cardiovascular risk factors (lipids, blood pressure and glucose tolerance) during drug administration is encouraged, as they may have a place in determining the balance of benefit vs risk for the drug.

The efficacy benchmark of 5% used for prescription weight-loss drugs is based on evidence that, in obese individuals, clinically meaningful improvements in blood pressure, cholesterol, glycemic control, and other metabolic and cardiovascular risk factors can be achieved with as little as a 5% reduction in body weight.[24]

Obesity is considered a chronic condition,[4] and it is assumed that in order to reap clinical benefit from drug-induced weight loss, drug treatment must be maintained long-term or chronically. As such, it is difficult to define the clinical benefits of short-term treatment with orlistat. This issue is further complicated by the fact that no data exist to support the clinical benefits of weight loss in subjects who are mildly overweight (i.e., BMI range of 25 - 27 kg/m^2). In fact, some evidence suggests that the overweight BMI range of 25 - < 30 kg/m^2 is not associated with increased mortality, and that those with a BMI of 25 kg/m^2 have a lower mortality risk than individuals with BMIs below or above this value.[25] Moreover, there is some suggestion that the positive relationship with BMI and risk of death decreases with age. In fact, weight loss is generally not recommended in the aging population without a concerted effort by the health practitioner to rule out concomitant disease; manage medications; address nutritional issues such as adequate protein, vitamin D, and calcium; and minimize loss of lean body mass and bone mass.[26] Issues related to orlistat in the aging population are further discussed in Section 8.3.2.

Ultimately, the benefits of weight loss are considered to be due to the reduction of risk for co-morbidities. However, in addressing the purported clinical benefits of weight loss the sponsor

24 Goldstein DJ, et al. Am J Clin Nutr. 1994 Nov;60(5):647-57.
25 Flegal KM, et al. JAMA. 2005 Apr 20;293(15):1861-7.
26 Villareal DT, et al. Am J Clin Nutr. 2005 Nov;82(5):923-34.

states in the NDA that, "serum lipid concentrations and blood pressure are not included in the integrated summary of efficacy [section in the nonprescription NDA]. This is mainly because the [nonprescription] indication is to promote weight loss and all other benefits achieved from orlistat would be most appropriately handled under the supervision of a physician."

GlaxoSmithKline appears to be saying that overweight individuals with weight-related co-morbidities such as type 2 diabetes, hypertension, or dyslipidemia are inappropriate candidates for nonprescription orlistat because weight loss in such patients will require management by a physician to ensure that such changes will favorably alter overall cardiovascular risks. It is difficult to imagine the proposed dichotomization of the target population into mildly-to-moderately overweight adults with and without weight-related co-morbidities, with the former appropriate, and the latter inappropriate for nonprescription orlistat, succeeding in the real-world setting. Nevertheless, this reviewer agrees that individuals with weight-related co-morbidities would be best treated under the care of a physician, given that weight loss in this setting is medically-indicated and requires adjustment of medications and other clinical follow-up. Indeed, the 2005 Dietary Guidelines for Americans recommends that overweight adults with chronic diseases and/or on medication should "consult a healthcare provider about weight loss strategies prior to starting a weight-reduction program to ensure appropriate management of other health conditions."[27]

The data on lipids, blood pressure, and carbohydrate metabolism were provided by the sponsor in the Integrated Summary of Safety rather than the Efficacy section of their NDA. This reviewer is therefore including these findings in Section 7 of this document, the Integrated Review of Safety.

6.1.3 Study Design

6.1.3.1 Screening

All efficacy studies included screening assessments performed within 21 or 28 days prior to entry into the study. Screening included the subjects' medical history, physical examination (including body weight), electrocardiogram, measurement of laboratory and safety parameters (vital signs), and a pregnancy test (when appropriate). Tables 6.1.3.1.A and 6.1.3.1.B outline the inclusion and exclusion criteria for the efficacy studies (BM14149, NM14161, and NM17247).

27 HHS-USDA Dietary Guidelines for Americans 2005. http://www.healthierus.gov/dietaryguidelines/

Table 6.1.3.1.A. Inclusion Criteria for 60 mg Phase III Studies			
	NM14161	BM14149	NM17247
Age: ≥ 18 years	X	X	X
Gender: men and non-pregnant women	X	X	X
BMI (kg/m^2):			
28-43		X	
30-43	X		
25-28			X

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Table 6.1.3.1.B. Exclusion Criteria for 60 mg Phase III Studies			
	NM14161	BM14149	NM17247
Weight loss > 4 kg 3 months prior to screening	X	X	
Weight loss ≥ 3 kg 3 months prior to screening			X
GI surgery for weight reduction	X	X	X
Myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty within 6 months prior to screening	X	X	X
Uncontrolled hypertension	X	X	
Chronically treated psychiatric/neurologic disorders	X	X	X
Lactating females	X	X	X
Excessive alcohol intake; use of substances of abuse	X	X	X
Change in smoking habit / cessation 6 months prior	X	X	X
Drug treated diabetes	X	X	X
Clinically significant abnormal lab results	X	X	X
Inability to comply with protocol requirements	X	X	X
Recent clinical trial participation, any orlistat trial	X	X	X
History/presence of significant:			
GI disorders	X	X	X
Cardiac, renal, hepatic, endocrine disorders	X	X	
Recurrent nephrolithiasis	X	X	
Symptomatic cholelithiasis	X	X	X
Post surgical adhesions	X	X	
Active peptic ulcer disease or malabsorption syndromes	X	X	X
Pancreatic enzyme deficiency or pancreatitis	X	X	X
Cancer except resected basal cell carcinoma of skin	X	X	
Bulimia or laxative abuse	X	X	X
Hypo/Hyperthyroidism unless euthyroid and controlled on stable dose of medication for at least 6 months			X
Drugs administered for the first time or withdrawn during the past 6 months which have significant impact on body weight			X
Use of certain medications, including appetite suppressants and lipid lowering drugs			X
Use of certain medications during 8 weeks before the screening period, including appetite suppressants and lipid soluble vitamin supplements	X	X	

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6.1.3.2 Randomization

In studies BM14149 and NM14161, subjects were stratified by amount of weight lost during the lead-in phase in order to balance the placebo and drug-treated groups in terms of probable

success in weight loss with diet alone. Subjects who lost 2 kg or less were assigned randomization codes sequentially within stratum 1; subjects who lost greater than 2 kg were assigned randomization codes sequentially within stratum 2. In these studies, regardless of stratification, subjects were randomized to treatment groups through the sequential assignment of randomization codes.

In study NM17247, there was no stratification. Subjects were randomized to either placebo or orlistat 60 mg.

6.1.3.3 Design

The original objectives of study BM14149 were to determine the long-term weight control effect of 60 mg orlistat, 120 mg orlistat, or placebo, all administered TID in combination with dietary counseling for two years, and to determine the long-term tolerability of orlistat. Subjects with a BMI 28 - 43 kg/m^2 were placed on a hypocaloric diet [(basal metabolic rate x 1.3) - 600 kcal/d] with 30% calories as fat during a four-week placebo lead-in period. Subjects were not provided a multivitamin. On day 1, subjects were randomized to placebo or orlistat in a 1:1:1 ratio. The minimum allowable prescribed caloric level was 1200 kcal/d. If at any time during the study a subject achieved a BMI $\leq$ 22 kg/m^2 on two consecutive visits, the caloric intake was increased to achieve weight stability by recalculating the diet based on the formula 1.3 x BMR minus 10% kcal/d. Dietary adjustments were made at the end of 24 weeks (i.e., -300 additional kcal/day or 1000 kcal/d for those prescribed 1200 kcal/d at screening). At the end of 52 weeks, subjects were placed on a eucaloric diet and maintained on the same drug treatment regimen for the next 52 weeks of the study. If during therapy a subject's BMI was $\leq$ 20 on two sequential visits, the visit at which the second BMI was determined would be considered the final visit.

The original objectives of study NM14161 were to determine the long-term weight control effect of 60 mg orlistat, 120 mg orlistat, or placebo, all administered TID for two years, and to determine the long-term tolerability of orlistat. Obese subjects (BMI 30 - 43 kg/m^2) were placed on a hypocaloric diet (1200 kcal/d if screening weight was < 90 kg, 1500 kcal/d if screening weight was $\geq$ 90 kg) with 30% calories as fat during a four-week placebo lead-in period. Subjects were not provided with a multivitamin. On day 1, subjects were randomized to placebo or orlistat in a 1:1:1 ratio. At the end of 52 weeks, the daily prescribed caloric intake was increased by 300 kcal/d for those subjects who lost more than 3 kg between weeks 48 and 52. Subjects who lost < 3 kg during this period were considered relatively weight stable and had no dietary adjustment. If any subject lost sufficient weight that his or her BMI became $\leq$ 18 kg/m^2, the visit at which that BMI was determined was considered the final visit, and the study would be considered complete for that subject.

Study NM17247 was a multi-center, double-blind, randomized, placebo-controlled trial conducted under the nonprescription orlistat IND. The objectives were to determine the weight loss effect of orlistat 60 mg or placebo administered TID in combination with a hypocaloric diet over a four-month duration and to determine the safety and tolerability of orlistat 60 mg TID over four months. This study consisted of two periods:

1. A 16-week double-blind treatment period; subjects were randomized to 60 mg orlistat TID or placebo TID. All treatment groups were prescribed a reduced-calorie diet.
2. An additional follow-up period that consisted of a final telephone contact 14 days after the last dose of study medication to assess the general health of the subject and possible closure of adverse events.

The caloric intake assignment was as follows:

- < 90 kg = 1200 kcal daily for females, 1400 kcal daily for males;
- ≥ 90 kg = 1400 kcal daily for females, 1600 kcal daily for males.

At the baseline visit, patients were counseled by the physician/staff on the desired caloric intake for the study. The study diet contained approximately 30% of calories as fat, 50% as carbohydrate, and 20% as protein. Cholesterol was limited to 300 mg/day and alcohol intake was limited to 150 grams (approximately 10 drinks) per week. The diet included three main meals and, if desired, a low-fat snack. The subject remained on the prescribed diet for the entire duration of the study. All subjects were provided with a Centrum® multivitamin to take daily.

If the subject's BMI fell below 20 kg/m^2 then the visit at which the BMI was determined was considered the final visit, and the study would be considered complete for that subject.

6.1.3.4 Lifestyle Intervention

In all studies, a hypocaloric diet containing approximately 30% of calories from fat was prescribed for the weight loss portions of the studies. However, lifestyle intervention differed somewhat between studies BM14149, NM14161, and NM17247 (Table 6.1.3.4.A), such that studies NM14161 and NM17247 were considered by GSK to have 'minimal' intervention. Nevertheless, the amount of intervention described below involves some degree of contact with health professionals, including multiple visits for measurement of body weight, and returning completed food records.

Table 6.1.3.4.A. Diet, Behavior Modification, and Exercise across all Controlled Double-Blind Studies						
Study	**Dose (mg)**	**Study Duration**	**Study Design**	**Dietary Instruction and Intervention**	**Behavioral Modification**	**Exercise**
BM14149 (non-US)	PLA, 60, 120	52 weeks for weight loss	Randomized, double-blind, placebo-controlled Specialized weight management sites	Dietitians on site Dietary counseling 12 times during 1 yr treatment period Multiple calorie levels assigned	No formal behavioral modification Dietary counseling by dietitian	No formal exercise counseling
NM14161	PLA, 60, 120	52 weeks for weight loss	Randomized, double-blind, placebo-controlled Outpatient Primary Care sites	No dietitians on site No specific staff training in nutrition or weight management techniques Assignment to only one of 2 calorie levels	Subjects viewed 4 videos on their own during the 52 weeks No group meetings or counseling sessions held.	No formal exercise counseling; subjects encouraged to increase physical activity by walking
NM17247	PLA, 60	16 weeks	Randomized, double-blind, placebo-controlled Outpatient Primary Care sites	No dietitians on site No specific staff training in nutrition or weight Assignment to only one of 2 calorie levels (M/F) Self-instructional materials	No group meetings or counseling sessions held Self-instructional materials	Self-instructional
PLA=placebo						

Study BM14149 was designed to incorporate an overall weight management program during the first year along with intensive dietary counseling. This study used academic research centers with weight management specialists and required a registered dietitian on site. In this study, a four-day comprehensive diary of food and beverage intake was completed to help subjects monitor food intake. At week -4, subjects received brief instructions on how to complete the food intake records accurately. Subjects recorded all food and beverages consumed for a period of four consecutive days, including two weekdays and two weekend days during the week preceding each clinic visit. The contents of the diaries were analyzed by a dietitian and used for counseling patients. The energy requirements were individualized based on calculated basal metabolic rate and a correction factor for level of activity. All subjects met with a registered dietitian at the start of the study and were personally instructed on their prescribed diet and accurate completion of the diet diaries. Subjects then met regularly throughout the study with the study dietitian for continued dietary counseling and diary review. Subjects were counseled on attaining their dietary goals and adherence to the prescribed diet. Diaries were completed 15 times during the one-year treatment period.

Study NM14161 was designed to mimic the primary care setting. At week -4, subjects received brief instructions on how to complete the food intake records accurately, and they subsequently viewed a video on food records to reinforce the skills learned. Subjects recorded all food and beverages consumed for a period of three consecutive days (which included two weekdays and one weekend day). The diaries were completed at seven time points in the first year (as

compared with 15 time points in study BM14149). Food intake records were analyzed by food analysis software. No feedback based on these dietary records were given to the subjects, nor were the results of the food record analyses communicated to the physicians or staff until the subjects had completed the study. Although no group meetings or counseling sessions were held, at four points during the first year, subjects viewed on their own one of four videos, which were based on a behavioral support program *Wise Weighs* (developed by the University of Minnesota) and covered topics such as goal-setting, exercise, identifying 'food cues' and characteristics of successful weight maintainers. During the first year, subjects met with physicians during brief visits at weeks 1, 2, 8, 16, 24, 32, and 44. Subjects met with the study coordinator or nurse every two weeks for the first month, and then every four weeks until week 52, at which time body weight was measured on a calibrated balance scale. Throughout the study, study staff encouraged subjects to increase physical activity by walking briskly for 20 to 30 minutes 3 to 5 times per week.

In study NM17247, the principal investigators were primary care practitioners and the clinic was commonly in the physician's office. The staff was not required to have special training in obesity, dietary, or behavior modification counseling. Subjects received brief instructions on how to complete food intake records from the physicians and staff at the initial visit.

The sponsor claims that the staff encouraged subjects to complete their food intake records at each visit but that no formal counseling was provided and the food intake records were not collected at the end of the study. The staff was instructed not to counsel subjects but rather to briefly reinforce some of the topics that subjects had been instructed to review in the information binder. The site's staff did not receive any special training or nutritional instruction, and that no group meetings or counseling sessions were held.

However, the original sponsor of this study, Roche, states in the NM17247 study report that: "Dietary instruction was provided at each treatment visit and dietary compliance was checked with the use of food diaries." Investigators were instructed in the use of diaries in the Study Procedures and Administrative Manual of study NM17247 as follows:

As part of the dietary instruction procedures required for this study, study staff will review a patient's food intake diary with them at each visit discussing how well the patient is following the required diet regimen. The diary is being used as a patient behavioral tool and will not be analyzed. Patients should complete two weeks initially and thereafter, one week prior to the next visit.

A table of assessments in study NM17247 was provided in the Roche study report (emphasis added):

Table 6.1.3.4.B. Schedule of Study Assessments and Procedures								
	Screening	Baseline			Treatment Period			Follow-up
Visit Number	1	2	3	4	5	6	7 or Premature Termination	8[d]
Study Day	-28 to -1	1	15	29	57	85	113	127
Informed Consent	X							
Eligibility Screening	X							
Medical History and	X							
Demographics								
Pregnancy Test[a]	X							
Thyroid Function Test	X							
Physical Examination	X						X	
Vital Signs and Physical Measurements[b]	X	X[c]	X	X	X	X	X	
Brief Physician Consultation	X						X	
Dietary Instructions		**X[c]**	**X**	**X**	**X**	**X**		
Dispensing of Medication		X[c]		X	X	X		
Dispensing of Multivitamin		X[c]						
Drug Compliance Evaluation				**X**	**X**	**X**	**X**	
Hematology	X	X[c]		X	X	X	X	
Blood Chemistry/Lipids	X	X[c]		X	X	X	X	
ECG	X							
Treatment Satisfaction Assessment				X	X		X	
Food Diary Dispensed		**X[c]**		**X**	**X**	**X**		
Food Diary Returned				**X**	**X**	**X**	**X**	
Concomitant Medication		X[c]	X	X	X	X	X	X
Adverse Events		X[c]	X	X	X	X	X	X

a A serum pregnancy test was performed at screening.
b All assessments were taken at each visit, except height, which was taken only at screening.
c Baseline assessments at Visit 2 were completed before the first dose of double-blind treatment.
d Follow-up consisted of a final telephone contact 14 days after the last dose of study medication to assess general health of the patient and possible closure of adverse events.

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At the beginning of study NM17247, each subject received a Dietary/Lifestyle Information Binder. These materials were initially developed for use with orlistat as part of the XeniCare® Program, the behavioral support program used in conjunction with the prescription drug. The original XeniCare® materials were revised for the study to reflect the 60 mg dosage. These revisions were described as providing a more consumer-friendly, self-instructional approach. The purpose of these materials was to reinforce dietary compliance while the subject was participating in the study. They were incorporated into the Dietary/Lifestyle Information Binder with the following tabbed sections and topics, which were then discussed with subjects at selected visits as shown in Table 6.1.3.4.C (from the Roche study report).

- **Get Started With Orlistat**: Orlistat and How It Works; Setting Your Calorie Levels; Reducing Dietary Fat; Achieving your Goal

- **Plan for Success**: Set Realistic Goals; Keep It Interesting; Snacking: Taking Control; Avoid the Pitfalls and Dealing with Unexpected Situations
- **Diet Basics**: Food Basics; How to Read a Nutrition Label; Why Calories Matter? and How Many Calories Do I Need?; Sample Menus; Food Exchange List
- **Exercise Your Options**: Benefits of Physical Activity; Formal vs. Informal Exercise; Develop an Action Plan
- **Food Preparation and Dining**: What to Buy; How is It Cooked; Substitution Lists; Stocking your Kitchen; Reading the Menu; Be Prepared - Know the Cooking Terms; Healthy Menu Choices
- **Stay Motivated**: Slipups Happen; Recognize your Accomplishments; Reward your Efforts; Use your Support System

Table 6.1.3.4.C. Schedule of Dietary/Lifestyle Topics for Discussion

Visit Day **Topics to be reinforced at visit**	2 Baseline • Getting Started • Setting goals	3 Day 15 • Food Basics • Balancing Your Diet	4 Day 29 • Eating behavior • Physical Activity	5 Day 57 • Food Preparation & Dining Out	6 Day 85 • Stay Motivated
Assessment: Wt status Compliance with diet Rx Compliance with study drug	Current weight Caloric requirement	Current weight Review food diary -Total calories -Fat per meal -Compare to diet Rx Drug Compliance	Current weight Review food diary -Total calories -Fat per meal -Compare to diet Rx Drug compliance	Current weight Review food diary -Total calories -Fat per meal -Compare to diet Rx Drug compliance	Current weight Review food diary -Total calories -Fat per meal -Compare to diet Rx Drug compliance
Educational Component Review and reinforce previous goals	Orlistat and how it works	Reinforce " a healthy" Weight loss is 1-2 pounds per week. -Focus on things you can change or control.	Go over daily fat intake and total calories -Review portions of food eaten (how big was the burger, what was on it?)	Review activity and food diary. Discuss any positive changes that have been made. What could they have done differently.	Review a typical day's meal pattern and physical activity. -Compare to a day at the start of the program?
Material/ Discussion points	• Discuss limiting calories to promote weight loss. • Set calorie limit • Go over recommended fat intake and how to divide total fat grams into 3 meals • Set realistic goals	• Calories count • Eat a balanced diet • Use food groups: dairy, meat, fruits and veg., starch and fat. • Use portion sizes • Reading a food label • Focus on serving size, calories and fat per serving. • Make it personal: using food exchange list to adapt the meal plan to personal tastes.	• Meal management - focuses on habits rather than the food. • Identify triggers to eating and solutions • Anticipate problems, think of alternatives • Review the importance of physical activity • Pick something you enjoy • Develop a plan of action **check with physician before starting any new exercise*	• Making healthy choices • Preparation (how is it prepared) and moderation (portion control) • Look for restaurant that has low fat choices on the menu • Understand cooking terms. • Ask how food is prepared • Ask them to bake, poach or grill • Ask for appetizer size portions	• Are you rewarding your accomplishment? • Give suggestions for rewards. • Review slip ups and getting back on track • Discuss support systems

Table 6.1.3.4.C. Schedule of Dietary/Lifestyle Topics for Discussion, cont.

Handouts	• Patient educational binder (includes fat gram wheel and portion hint card) • Diet sheets • Food diary	• Diet Sheets (optional)	• Food diary • Diet Sheets (optional)	• Food diary	• Food diary
Action plan	• Start to pay attention to what you are eating • Take study medication tid.	• Track fat grams, calories and portions sizes in journal. • Use food labels to help you make choices. • Even if you slip up or eat more than you wanted to, write it down so you can learn from it.	• Plan ahead: Post it in the kitchen • Determined a level of activity that is enjoyable and track progress:	• Balance your meal by making choices • Ex. If you want to enjoy a dessert, cut back on the appetizers and choose a low fat entrée.	• Make a list of support persons • Restate plan of action for getting back on track after a slipup

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Additionally included in the binder was a fat gram wheel, a portion hint card and a one-month food activity diary. Subjects were instructed on use of the food diary, which was used as a subject behavioral tool as stated above, and was not analyzed. Subjects also were provided two-week menu plans based on their caloric intake and food preferences (American, Hispanic, and Southern Fare).

6.1.3.5 Compliance

For all efficacy studies, during specified clinic visits the subject returned his/her entire drug supply (including empty, full, and partially full blister cards/plates/bottles) to the clinic and a staff member counted the number of capsules returned by the subject and calculated the number of capsules consumed. A comment indicating the reason why all blister cards or bottles were not returned was added to the case report form. Compliance was assessed on the basis of number of capsules taken per day. Obviously, such drug compliance monitoring does not occur in a nonprescription setting, so this aspect of these clinical trials limits the applicability to the current application.

In studies BM14149 and NM14161, subjects were randomized if they completed the single-blind lead-in period and were at least 75% compliant with study medication. Importantly, during the study subjects were counseled about remaining diligent to the treatment if compliance to drug treatment fell below 75% at any visit. The consumption of less than 70% of capsules was considered 'noncompliant'. Cumulative compliance was used to determine whether subjects were considered eligible for evaluation at the various study time points, and overall compliance was considered to determine whether subjects were evaluable for standard efficacy analysis at critical time points. As is discussed in Section 6.1.4.3.1, the intent-to-treat (ITT) population comprised all randomized subjects who received at least one dose of study medication and had body weight measurements before and after randomization, and therefore, did not appear to take medication compliance into account. Given that this drug will be used in a nonprescription

setting, the ITT analysis (i.e., analysis of subjects all levels of treatment compliance) is more appropriate for understanding efficacy in the 'real-world'.

Study NM17247 did not specify a percentage of missed orlistat capsules that designated the subject as 'noncompliant'. Moreover, a summary of subjects' compliance to the multivitamin administration was not assessed.

6.1.3.6 Body weight measurement

In all three studies, body weight was recorded at every visit with subjects wearing light indoor clothing, and no shoes, outerwear, or accessories. Body weight was measured in kilograms and recorded to one decimal place, using the same calibrated scale every time to ensure consistent weight measurements of the individual subjects. Two or more body weight measurements were performed at each visit and if the two weights differed by ≤ 0.5 kg, the average of the two measurements was recorded. If they differed by > 0.5 kg, however, the body weight measurements were repeated until two consecutive body weight measurements were within 0.5 kg of each other, and the average of those weights was taken. The converted weights were checked for proximity to each other and the average was recorded.

6.1.4 Efficacy Findings

6.1.4.1 Subject Enumeration

Table 6.1.4.1.A enumerates subjects in the various efficacy analysis populations by study and treatment group. The percentage of subjects completing the six-month time point in the pooled studies was similar between orlistat 60 mg- and 120 mg-treated groups (~81%). The orlistat groups in the pooled studies had a slightly higher rate of completion than the placebo group (~75%).

Completion rates were slightly higher in the orlistat 60 mg treatment group as compared to placebo in study NM17247 (78% versus 72%, respectively).

Table 6.1.4.1.A. Overview of Analysis Populations: Weight Loss in Overweight and Obese Subjects during 4-6 Months of Treatment				
Population	**Pooled Studies (NM14161 and BM14149)**	**Study BM14149**	**Study NM14161**	**Study NM17247**
Enrolled	1579	783	796	498
Randomized	1371	729	642	391
Intent to Treat				
Placebo	448	236	212	184
60 mg TID	452	239	213	194
120 mg TID	451	241	210	N/A
Completers*				
Placebo	341 (74.6%)	185 (76.1%)	156 (72.9%)	140 (71.8%)
60 mg TID	367 (80.5%)	198 (81.8%)	169 (79.0%)	152 (77.6%)
120 mg TID	373 (81.4%)	202 (82.8%)	171 (79.9%)	N/A
*Completers were defined as all subjects who did not have any protocol violations thought to affect efficacy and completed at least 22 weeks of treatment and had efficacy measurements between 154 and 182 days in the pooled studies and as all subjects who were randomized and completed 113 days of treatment in study NM17247.				

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6.1.4.2 Demographics

The majority of subjects in the studies were female (Tables 6.1.4.2.A and 6.1.4.2.B). In the pooled studies as well as study NM17247, a slightly higher proportion of subjects in the 60 mg group than in the placebo or 120 mg groups were male. Most subjects were White and had a mean age of 43 years in the pooled studies and 46 years in study NM17247. Very few randomized subjects were ≥ 65 years old. The mean initial weight in the pooled studies (weight before the lead-in period), mean baseline weight in study NM17247, and mean baseline BMI were similar across all treatment groups in the pooled studies and in study NM17247, although not between studies.

This reviewer has bolded the BMI groups 25 - 28 and 28 - 30 kg/m^2 in Table 6.1.4.2.A in order to highlight the number of overweight subjects in the pooled studies [approximately 50-60 subjects (10-12%) per group]. Therefore, the pooled studies are considered to be made up of a primarily obese population (and may be referred to as such), as compared to study NM17247, which is made up of subjects in the 25 - 28 kg/m^2 BMI range, a low-overweight range.

Table 6.1.4.2.A. Demographics and Baseline Characteristics – Studies BM14149 and NM14161						
	Placebo (N=448)		Orlistat 60 mg TID (N=452)		Orlistat 120 mg TID (N=451)	
	N	(%)	n	(%)	N	(%)
Sex						
Male	78	(17.4)	103	(22.8)	84	(18.6)
Female	370	(82.6)	349	(77.2)	367	(81.4)
Age Group						
< 65 years	438	(97.8)	442	(97.8)	439	(97.3)
≥ 65 years	10	(2.2)	10	(2.2)	12	(2.7)
Race						
Caucasian	428	(95.5)	436	(96.5)	423	(93.8)
Black	16	(3.6)	11	(2.4)	20	(4.4)
Hispanic	4	(0.9)	2	(0.4)	6	(1.3)
Other Race	0	(0.0)	3	(0.7)	2	(0.4)
BMI at Baseline (kg/m^2)						
≥ 25 to 28	**8**	**(1.8)**	**6**	**(1.3)**	**4**	**(0.9)**
≥ 28 to 30	**49**	**(10.9)**	**41**	**(9.1)**	**51**	**(11.3)**
≥ 30 to 35	178	(39.7)	211	(46.7)	198	(43.9)
≥ 35	213	(47.5)	194	(42.9)	198	(43.9)
Age (years)						
Mean SD	43.1 +/- 10.33		43.7 +/- 10.87		43.4 +/- 10.80	
(Min, Max)	(18, 71)		(20, 72)		(18, 78)	
Initial Weight (kg)						
Mean +/- SD	99.64 +/- 14.750		99.69 +/- 14.475		98.51 +/- 14.126	
(Min, Max)	(67.4, 155.5)		(68.9, 152.0)		(68.4, 147.3)	
BMI at Baseline (kg/m^2)						
Mean +/- SD	34.82 +/- 4.010		34.59 +/- 3.788		34.42 +/- 3.611	
(Min, Max)	(26.7, 45.9)		(26.7, 42.7)		(27.1, 42.8)	
ITT Population						

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Table 6.1.4.2.B. Demographics and Baseline Characteristics – Study NM17247				
	Placebo (N=184)		Orlistat 60 mg TID (N=194)	
	N	(%)	N	(%)
Sex				
Male	9	(4.9)	12	(6.2)
Female	175	(95.1)	182	(93.8)
Age Group				
< 65 years	176	(95.7)	182	(93.8)
≥ 65 years	8	(4.3)	12	(6.2)
Race				
Caucasian	165	(89.7)	172	(88.7)
Black	12	(6.5)	18	(9.3)
Hispanic	0	(0.0)	1	(0.5)
Other Race	7	(3.8)	3	(1.5)
BMI Group (kg/m^2)				
< 25	4	(2.2)	5	(2.6)
≥ 25 to 28	161	(87.5)	167	(86.1)
≥ 28 to 30	19	(10.3)	22	(11.3)
Age (years)				
Mean +/- SD	46.6 +/- 10.91		45.8 +/- 11.89	
Median	47.0		45.0	
(Min, Max)	(19, 72)		(20, 80)	
N	184		194	
Baseline Weight (kg)				
Mean +/- SD	72.76 +/- 6.61		72.76 +/- 6.97	
(Min, Max)	(56.2, 89.8)		(57.4, 102.5)	
BMI at Baseline (kg/m^2)				
Mean +/- SD	26.84 +/- 0.944		26.82 +/- 0.960	
(Min, Max)	(23.7, 28.6)		(24.5, 29.0)	
ITT Population				

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In addition to the above baseline demographics, collected baseline measurements, such as mean waist circumference, mean hip circumference, and mean waist-to-hip ratio, were similar among treatment groups in the pooled studies and study NM17247.

6.1.4.3 Statistical Considerations

6.1.4.3.1 Analysis populations

The sponsor analyzed the efficacy data using intent-to-treat (ITT) and completers populations. In the pooled studies, the ITT population comprised all randomized subjects who received at least one dose of study medication and had body weight measurements before and after randomization. The '6-month completers' population included randomized subjects who did not have any protocol violations that might affect the efficacy evaluation, completed at least 22 weeks of treatment, and had efficacy measurements between 154 and 182 days on treatment. The pooled studies were then analyzed for observed data for the ITT population, last observation carried forward (LOCF) data for the ITT population, and observed data for six-month

completers. In the pooled studies, the observed ITT population analysis was similar to a completer analysis, except that it included all subjects who reached the six-month time point, not just that of the 'completers' (those without important protocol violations).

In study NM17247, the ITT population comprised all randomized subjects who received at least one dose of study drug, had a baseline efficacy assessment and had at least one post-baseline efficacy assessment. The completers population was a subset of the ITT population that included subjects who completed 113 days of treatment. Study NM17247 was analyzed with observed data for the ITT population, LOCF data for the ITT population, and LOCF data for completers. To this reviewer's understanding, the LOCF for completers population was similar to the observed ITT population analyzed at study day 113, except the LOCF completers analysis also included data points that may have been collected after study day 113.

This reviewer will be presenting efficacy analyses using the ITT LOCF population unless stated otherwise, and with the exception of the presentation of body weight change over time (Section 6.1.4.4.1.2), which uses the ITT observed population. Although a LOCF analysis may provide more information than a completer or observed analysis, in a case where a greater number of subjects from the placebo group discontinued the study due to lack of efficacy and a greater number of subjects from the orlistat groups discontinued due to adverse events, a LOCF analysis could favorably bias orlistat. This reviewer evaluated all of the population analyses that were provided. In general, it appears that the different population analyses provided similar results; therefore, the impact of such bias appears minimal.

6.1.4.3.2 Study windows

The study time point windows were very broad, encompassing up to three months in the pooled studies and one month in study NM17247. The latest time point was used for analysis when there were multiple values in any one window. Given that there was differential discontinuation between treatment groups, systematic bias of the weight change estimates may have occurred.

6.1.4.3.3 Hypothesis testing

In the pooled studies, the primary efficacy analysis was the comparison of weight change from baseline to 24 weeks in the orlistat 60 mg TID treatment group to placebo using the ITT population. The pooled studies were originally designed to study the weight loss effect of orlistat plus a hypocaloric diet for one year, with a second year of orlistat or placebo plus a eucaloric diet to assess weight maintenance. Because the intent of this application is to market orlistat as a nonprescription product for a six-month treatment duration, the six-month time point was used as the primary efficacy time point in the nonprescription NDA.

Analysis of covariance (ANCOVA) was used to compare change in weight from baseline to six months among treatment groups. The factors in the model were study, site nested within study, category of lead-in period weight loss ($\leq$ 2 kg, >2 kg), baseline weight, and, in some cases, site by baseline weight interaction. Least squares means were computed for the treatment groups and each of the orlistat treatment groups was compared to the placebo group. Comparisons of 5% responder rates between each orlistat group and the placebo group were conducted using the Fisher's exact test.

In study NM17247, the primary statistical analysis used the ANCOVA method with change in body weight as the response variable. The model was: change = treatment center, with baseline body weight as the covariate. An analysis of the proportion of patients with at least 5% reduction from baseline in body weight was also performed using the Fisher's exact test. The same analysis was performed for the proportion of patients with at least 3% reduction from baseline.

Because the responder analysis is considered the primary analysis of interest, it will be presented first in the efficacy section of this document (Section 6.1.4.4.1.1).

6.1.4.3.4 Site outlier

The pooled analysis of adjusted mean weight loss presented in the sponsor's integrated summary of efficacy excluded site 12327 from study NM14161 because of a relatively large number of subjects failing to complete the study (only nine subjects completed the study at one year) and the study-site interaction was significant.

The orlistat 60 mg group at this site actually saw a mean weight gain, as presented in Figure 6.1.4.3.4.A below. (Although there is not a legend associated with this figure, it is presumed that the lines on the left represent orlistat 60 mg and lines on the right represent orlistat 120 mg.)

Figure 6.1.4.3.4.A. Study NM14161: 95% Confidence Intervals for Change in Body Weight at 52 Weeks; Difference from Placebo in LS Mean; Intent-to-Treat Population