CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-887

MEDICAL REVIEW(S)

Office Director NDA Memorandum

NDA #: 21-887
Drug Name: Alli (orlistat) 60 mg Capsules
Sponsor: GlaxoSmithKline (GSK)
Indication: Weight Loss
Date: Submitted August 7, 2007

Memo Date: February 7, 2007

From: Charles J. Ganley, M.D.
Director, Office of Nonprescription Products

Subject: Prescription to Over-the-Counter (OTC) Switch of Orlistat

Introduction

On April 6, 2006, FDA issued an approvable letter to GSK for the switch of orlistat from Rx to OTC marketing. On August 7, 2006, GSK submitted a complete response to the action letter. Also relevant to this action is a citizen petition submitted by Public Citizen on April 10, 2006. The petition requests the withdrawal from the market of prescription orlistat because of carcinogenicity concerns.

Recommended Action

The application should be approved. The sponsor has adequately addressed all of the deficiencies listed in the April 6, 2006 action letter. The citizen petition will be denied so it will not impact on the decision to allow marketing of orlistat OTC.

Deficiencies Listed in April 6, 2006 Action Letter

1. Adequate information has not been provided by the sponsor to support the limit on duration of use of up to 6 months. The data did not support that consumers adequately understood what to do after the 6 months. Instead, consideration should be given to long term treatment with appropriate labeling. If labeled for long term therapy, a 60 mg three times a day dose regimen without titration would be acceptable.
2. Cyclosporine users should not use the product in the OTC setting. The proposed label will not adequately alert them to the risk associated with concomitant use of cyclosporine and orlistat.
3. The Drug Facts label does not adequately emphasize the behavioral modification measures necessary to be considered prior to pharmacotherapy and in conjunction with pharmacotherapy.
4. A significant percentage of subjects did not understand the need for concomitant multivitamin use or the timing of dosing relative to orlistat dosing. The labeling should be improved to emphasize use and timing of dose of multivitamins.
5. The Drug Facts label should include information that allows consumers to calculate their body mass index (BMI) and understand its meaning. Additional information can be provided inside the package that will help a consumer determine a weight loss goal.
6. The gastrointestinal side effects are not adequately conveyed in the Drug Facts label.
7. A warning for continuous or severe abdominal pain should be added to the labeling to account for the possible occurrence of pancreatitis. Consumers with a history of pancreatitis should be instructed to talk to their doctor before use.
8. The educational materials included with the starter kit have not been adequately tested for comprehension. It would be helpful to know if the users would use the materials but it is not clear we can compel them to evaluate this.

Discussion

Duration of Use

GSK decided to remove the duration of use limitation and include information that allows the consumer to determine weight loss goals. This will allow the consumer to determine whether orlistat is beneficial in conjunction with diet and exercise and does not require a 6 month limit on use. The emphasis is placed on a weight loss goal and not on duration of use.

Cyclosporine Users

The sponsor conducted a labeling comprehension study in organ transplant recipients. The Organ Transplant Alert was understood by 59 of the 60 participants. The one who did not correctly answer the question clarified their answer by noting they would ask their doctor first. The Organ Transplant alert was found to adequately convey the message to organ transplant patients.

Behavioral Modifications Described in Drug Facts Label

The revised labeling emphasizes that diet and exercise are the starting points for any weight loss program and should be continued while taking Orlistat. The label comprehension study evaluated components of this label and the data suggest that participants understood it. The reviewer, however, had some concerns about the quality of the scenario questions used in the study in addressing this issue. These are valid concerns but I don't think that they warrant another study. The reviewer made no recommendation for another study. The concept of behavior modification will not be foreign to those who decide to purchase this drug. The labeling adequately conveys that orlistat alone is not going to be an effective weight loss therapy. The concepts of following a diet and exercise program, behavior modification, as a mainstay of a weight loss program, are emphasized in the new label. Consumers who don't follow a comprehensive weight loss program are unlikely to benefit from the therapy and likely will stop using the drug because of a lack of effect. The product contains an insert titled "Read Me First" that emphasizes dieting and behavioral measures as being necessary for successful weight loss. Companion guides that include more detailed information on diet are not being treated as labeling and are considered optional.

Understanding of Need for Concomitant Vitamin Use

The Directions section of labeling instructs the user to take a multivitamin at night. The label comprehension study suggests that consumers understood this direction.

Information in Label for Body Mass Index (BMI) Calculation

The sponsor has included a table in the Drug Facts label that allows the consumer to identify whether their BMI is greater than 27 kg/m^2. The Directions section includes the following: to see if orlistat capsules are right for you, find you height on the chart...You may consider starting a weight loss program with orlistat if your weight is the same or more than the weight shown for your height.

Description of Gastrointestinal Side Effects in Labeling

The sponsor has improved the labeling describing gastrointestinal side effects under the "When using this product" subsection of the warnings.

Pancreatitis Warning

Pancreatitis is included in the "Ask a doctor before use if you have ever had" subsection of the warnings.

Educational Materials

The orlistat package includes a "Read Me First" brochure plus enhanced Drug Facts labeling emphasizing diet and exercise in addition to establishing a weight loss goal. The sponsor proposed including additional material (e.g. Companion Guide, Daily Journal, QuickFacts Card, Healthy Eating Guide, Calorie & Fat Counter, and Welcome Guide) in the package [ ]. The sponsor has the option of including this information but it is not necessary for the safe and effective use of the drug.

As I noted in my memo of April 6, 2006, the prescription version of orlistat does not have specific recommendations for educational materials to be distributed by a doctor or pharmacist. The amount of information provided to the patients prescribed orlistat probably varies widely. The Drug Facts labeling for Alli is quite extensive, much more would probably detract from the message, and conveys the necessary information to understand the value of orlistat and how it fits into a weight loss program. It is not necessary that the sponsor conduct additional studies to evaluate the effect of any educational information provided.

Additional Pediatric Studies

As noted in my original review, orlistat should not be considered for OTC use by the adolescent population or younger. Children less than 18 years of age who are going to initiate pharmacologic therapy for weight loss should be evaluated by a health professional. There are no significant safety issues with the use of orlistat in this population. Consequently, there is no need for any type of restricted access. The sponsor should be given a waiver from conducting additional studies in children less than 18 years of age.

Safety Update

There were no significant safety issues identified in the safety update. There was one case of a possible drug interaction with a person receiving thyroxine therapy. The primary reviewer wanted to add this to the labeling. I have no objection to this.

Citizen Petition

Public Citizen submitted a Citizen Petition requesting that prescription orlistat be removed from the market because it can increase aberrant crypt foci in the colon, a possible predictor of increased risk for colon cancer. It also suggested that the possible relationship between orlistat use and breast cancer had not been resolved. Dr. Colman provided a rebuttal of the petition. The FDA response rebuts the grounds of the petition. The petition will be denied.

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/s/

Charles Ganley
2/7/2007 10:35:44 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Date: Tuesday, February 06, 2007
NDA: 21-887
Sponsor: GlaxoSmithKline Consumer Healthcare (GSK)
Proprietary Name: Alli (orlistat)
Author: Curtis J. Rosebraugh, MD, MPH, Deputy Director, ODE II

A. EXECUTIVE SUMMARY

This memorandum will discuss the complete response that was submitted by the sponsor on August 4, 2006, in response to the Approvable Letter dated April 6, 2006. The decisional authority for this application was delegated to me by Robert Meyer, MD, Director, Office of Drug Evaluation II. My determination is that the sponsor has successful remediated all the decencies identified in the Approvable Letter and that an **approval** action should be taken for application NDA 21-887 for Orlistat.

Also noted is that since the original review, Public Citizen filed a Citizen Petition on April 10, 2006 to remove prescription orlistat from the market due to safety concerns. Such an action would obviously also affect the potential of over-the-counter marketability of Orlistat. This Citizen Petition request will be denied and the issues surrounding the request are briefly discussed below.

Introduction:

The approvable letter identified several deficiencies summarized below:

1. Inadequate support for the labeled six-month duration limit on use of orlistat.
2. The Drug Facts label did not adequately convey that the foundation of any weight loss program included appropriate diet and exercise before consideration of medication.
3. Poor recognition by cyclosporine users to correctly determine that they should not use the product.
4. Poor understanding by subjects that multivitamins should be taken in conjunction with orlistat therapy.
5. The dosing regimen included use up to 120 mg three times a day. For introduction as an over-the-counter product, the Agency determined that the dosing regimen should be limited to 60 mg three times a day.
6. The labeling at the point of purchase needed to include information to consumers that would allow them to calculate their body mass index for informed purchase decisions.

7. The most common side effects should be prominently displayed in the Drug Facts labeling.
8. Labeling should include information regarding the potential of pancreatitis.
9. Labeling should include an educational component, that would be used in lieu of consultation with a health care provider, as part of a weight loss program.

In response to this action letter, the sponsor made several labeling changes and performed a further labeling comprehension study and self-selection study to evaluate how these changes would affect consumer choices at the point of purchase. Additionally, the sponsor deleted the six-month duration use limitation and decreased the dose to 60 mg three times a day, thereby successfully responding to deficiencies #1 and #5 listed above.

The label comprehension study was reviewed by Dr. Susanna Weiss (primary) and Dr. Andrea Leonard-Segal (secondary) and the self-selection study was reviewed by Captain Laura Shay, all from the Office of Non-prescription Products. I will briefly summarize the results of these studies and the reader is referred to their reviews for detailed discussion.

Label Comprehension Study:

The label comprehension study was performed to assess comprehension of the revised dosing instructions, multivitamin use instructions and the educational/behavioral components included in labeling. The results of the labeling comprehension studies demonstrated that the labeling changes incorporated by the sponsor adequately responded to deficiencies #2, 4, 6, 7, 8 and 9.

Self-Selection Study:

The sponsor modified the Drug Facts label to include a new "organ transplant alert" that is highlighted in yellow and includes a cyclosporine warning that appears in bold lettering. The self-selection study was conducted in a population of organ transplant recipients. The results indicate that this label change would remediate deficiency #3.

Safety Update:

The safety update was performed by Dr. Julie Golden, of the Division of Metabolic and Endocrine Products. There were not any new safety issues identified, with the exception of a potential drug-drug interaction between levothyroxine and orlistat as evidenced by a single case report. Although this report is not definitive signal for a drug-drug interaction, the sponsor has added labeling to address this issue. This interaction will also be added to prescription Orlistat and thyroid replacement labels.

Other Regulatory Issues:

The sponsor plans on marketing two package configurations. The first is a starter pack that will include additional references materials , including a "Welcome Guide" and "Companion Guide," in addition to the approved labeling of the "Read Me First" behavioral guide. The second configuration is a Refill Carton that will not have the additional reference materials. [redacted]

[redacted] These guides are not considered to be part of the required behavioral guide, but are a supplement that the sponsor is including to try to aid consumers in having the best result possible. As such, I do not consider them official labeling, though I find it acceptable that they are included within the carton. Because they are not approved labeling, they will not be reviewed as labeling.

Citizen Petition:

Public Citizen filed a Citizen Petition on April 10, 2006 (2006P-0154 CP1) to remove prescription Orlistat from the market for safety reasons. The petitioner purports that aberrant crypt foci are a biomarker for colon cancer. The CP particularly cites concern over a study in which rats injected with a chemical carcinogen and fed a high-fat diet plus orlistat developed a larger number of aberrant colonic crypts than rats fed a high-fat diet alone. The petitioner's contention is that this result indicates that orlistat increases the risk for colorectal carcinoma in humans who might take orlistat.

The petitioner also suggests that there is a "still unresolved potential" of orlistat to cause breast cancer. This issue has been rigorously evaluated by the Agency as there was an imbalance in the number of women diagnosed with breast cancer between those treated with orlistat compared to placebo during participation in original phase 3 clinical trials. Despite the lack of biologic plausibility, it was because of this finding orlistat was not approved (despite recommendations of approval from an advisory panel) until there were adequate data to more firmly support a conclusion that orlistat does not increase the risk of breast cancer (details in the Petition Response).

Although the response to the Citizen Petition has not yet issued at the time of this memo, I and the Division have been actively involved in examining this issue and advising on the contents of the Agency's response. I would refer the reader to the response to the Citizen Petition upon it's publication for a detailed discussion, but I do not believe that the available evidence supports a causal relationship between Orlistat and colorectal carcinoma, or breast cancer, or even a significant potential for such a relationship. It is my opinion that the available data neither warrant market withdrawal nor preclude OTC availability.

Pediatric:

The Agency, on 8/18/05 issued a waiver for pediatric studies in patients ages 0 to 11 years old and a deferral for studies in patients ages 12 to 17 years old. Treatment of obesity with the intent of weight loss in 12 to 17 year olds is complicated by the factor that this age group includes individuals that may still be in an active growth phase with continued bone and other organ, maturation and where nutritional requirements are different from those of adults. Therefore, the balance between active weight loss, while still continuing to have adequate nutritional requirements, would best be achieved in my judgment with active health care provider interaction. As such, I do not feel that this age group should be included in an over-the-counter label. I therefore feel that any PREA requirement for this age group for an over-the-counter 60

mg dosage regimen should be waived. I note also, that this age group has been studied with the 120mg dose regimen and is included in the prescription label, so we do have studies to inform the use of orlistat in this age range, albeit for the prescription dose in a medically supervised setting.

Planned Action

This application action should be **approved** based on resolution of all significant issues in our April 2006 approvable action.

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/s/

Curtis Rosebraugh
2/6/2007 03:36:01 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

DIVISION DIRECTOR MEMO

NDA #:	21-887
Sponsor:	GlaxoSmithKline
Drug Name:	Orlistat OTC
Indication:	Nonprescription use for weight loss in adults who are overweight and obese
Date of Memo:	January 29, 2007

This memo addresses GlaxoSmithKline's resubmission for its NDA proposing the approval of orlistat for nonprescription use in the treatment of overweight and obese adults. In my original memo dated 22 March 2006, I summarized the deficiencies of the program under two broad categories: method of use and collateral measures. Under *Method of Use* I felt that the program needed the following:

- improvements on instructions against use if the patient is taking cyclosporine or warfarin
- instructions on appropriateness of orlistat if the patient is taking an anti-diabetic medication
- improvements on use of orlistat with a multivitamin

I argued that these modifications were to be applied to a target population that was similar to the prescription orlistat label based on BMI criteria and that no limit on duration of use be included in labeling since overweight and obesity are considered chronic conditions where studies have shown that discontinuation of treatment results in regain of weight lost.

Collateral measures referred specifically to the educational materials proposed by the applicant to assist the patient in dietary and lifestyle modification. As already presented in previous reviews by Drs. Golden, Colman and me, these interventions are a crucial part of any weight-loss program and should be tested to determine their contribution to overall efficacy.

This applicant received an approvable letter on 6 April 2006 which outlined 9 deficiencies that the applicant needed to address. The resubmission targeted each of these deficiencies and also included a second label comprehension study testing a revised Drug Facts Label and the package insert and a second self-selection study in organ transplant recipients. These two studies were reviewed by staff in the Division of Nonprescription Clinical Evaluation. Overall, the applicant has satisfactorily addressed my concerns outlined under *Method of Use* and this memo will not delve any further into the results of these studies already summarized by other reviews in the action package. Specifically, the program has removed the 6 months limit on duration of use and labeling includes a BMI chart and instructions to select according to an individual's BMI.

A Citizen Petition submitted by Public Citizen Health Research Group requesting that the agency remove orlistat from the market and, by extension, not approve this application based on a single rat study that suggests an increase in colonic aberrant crypt foci (ACF) associated with orlistat has been addressed by Drs. Colman and Davis-Bruno from the Division of Metabolism and Endocrinology. In summary, the

petition was denied and arguments for this decision can be reviewed in the Agency's official response to the Citizen Petition.

I maintain that educational materials need to be tested if they are considered critical to a drug's efficacy. [redacted] orlistat OTC can be approved with the Drug Facts Label and accompanying "Read me First" sheet as FDA-approved materials. Other educational materials will not be required and are not considered a part of the NDA. As such, the educational materials are not FDA-approved. This approach avoids the requirement to test the education materials/program to be launched by the applicant and can not be used by them in barring approval of generics that do not propose co-packaging with similar educational materials/programs.

I do not view this application as precedent setting for the over-the-counter availability of other drugs targeting chronic conditions, including other drugs for overweight and obesity. Clearly a non-absorbable weight loss drug carries fewer safety concerns than a systemically absorbed drug. However, even a non-absorbable drug may not be a reasonable OTC candidate if the disease requires extensive intervention by a learned intermediary to ensure appropriateness of treatment and interpretation of drug response. This would certainly be the case for conditions such as diabetes and hypercholesterolemia for which there are approved prescription drugs that have minimal systemic availability.

It remains to be seen what impact nonprescription orlistat will have on the epidemic of overweight and obesity in the United States but as stated in my previous memo, there are few serious safety concerns associated with orlistat therapy to continue objecting to its availability in the over-the-counter setting. With the exception of Dr. Golden's recent discovery of a potential for interaction with levothyroxine (this finding is to be incorporated in the Drug Facts label as well as the prescription labels for orlistat and levothyroxine products), there have been no additional safety concerns since the approvable letter was issued to preclude its approval. Consequently, this application can be approved.

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/s/

Mary Parks
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MEDICAL OFFICER

MEMORANDUM

Medical Team Leader
Division of Metabolism and Endocrinology Products

January 15, 2007

NDA: 21-887

DRUG: Orlistat 60 mg capsules

INDICATION: Weight loss in the nonprescription setting

COMPANY: GlaxoSmithKline

SUBJECT: Complete response to an approvable letter

I. BACKGROUND

On June 6, 2005, GSK submitted NDA 21-887 for the 60 mg dose of orlistat. The company was seeking approval of orlistat as an aid to weight loss in the nonprescription setting. In a memorandum dated 16 March 2006, I considered the NDA approvable pending resolution of a number of issues outline below:

1 GSK has not confirmed that the proposed orlistat plus lifestyle modification program is effective compared with placebo plus the lifestyle modification program when used long term in the nonprescription setting.
2 GSK has not confirmed that patients in the high overweight range with comorbidities or patients in the obese range can appropriately self-select for orlistat in the nonprescription setting. Deficiencies 1 and 2 could be addressed through conduct of a randomized, double-blind, placebo-controlled 12-month "actual-use" trial. Efficacy would be defined by the criteria set forth in the Agency's weight-loss drug guidance document.
3 GSK needs to define an acceptable level of incorrect self-selection for orlistat in patients taking cyclosporine.
4 GSK then needs to demonstrate that labeling/educational material would effectively prevent patients on cyclosporine from self-selecting orlistat. Effectiveness would be defined by the response to point # 3.
5 GSK needs to demonstrate that an appropriate percentage of patients who self-select for orlistat adhere to the recommendation to take a daily multivitamin at least 2 hours before or 2 hours after ingestion of orlistat.

On April 6, 2006, the Agency issued an approvable letter for NDA 21-887. The letter listed the following major deficiencies that GSK needed to address before the NDA could be considered for approval:

1. Recommended duration of use. The company was given the option of removing the six-month limitation of use, with the possible need to revise the labeling and test consumer comprehension, or keep the six-month limitation of use and test whether consumers understand the implications of this limitation.
2. Improve the labeled warnings about the use of cyclosporine with orlistat and test consumer comprehension.
3. Improve the labeled instructions for multivitamin supplementation and test consumer comprehension.
4. Provide information to consumers that will allow them to calculate their BMI prior to purchasing the drug.
5. Include a warning about pancreatitis in the labeling.
6. Provide information on lifestyle modification in the product's educational material and test consumer comprehension.

On 7 August 2006, GSK submitted a complete response to the approvable letter. The response included the results of a second label comprehension study and a second self-selection study in organ transplant patients. These studies have been reviewed by members of the Office of Nonprescription Products. The sponsor's response to the approvable letter also included proposed changes to the product labeling.

II. SECOND LABEL COMPREHENSION STUDY

This was a study of 558 consumers (401 general population and 157 low literacy) conducted at 18 mall sites in the United States. Sixty-six percent of the subjects were female, roughly 62% were Caucasian, and approximately 45% of the participants were between the ages of 30 and 49 years.

All consumers were asked to read the Drug Facts label and the Key to Successful Weight Loss package insert and were then asked to answer a series of questions.

Based on her review of the results, Susanna Weiss, Ph.D., J.D., concluded that a) 99.8% of the general population and 98.7% of the low literacy groups understood that the product was to be used for weight loss; b) 81.5% of the general population and 69.5% of the low literacy groups understood the instructions to take one capsule with each meal containing fat and to not exceed 3 capsules daily; c) 88.3% of the general population and 79.0% of the low literacy groups gave correct responses to the entire three-part sequence of questions concerning multivitamin use; and d) comprehension of the information contained in the "Keys to Successful Weight Loss" was reasonably good; although the results in Dr. Weiss's opinion should be viewed with caution given the simplistic nature of the scenarios and questions that were used to test consumer knowledge.

III. SELF-SELECTION STUDY IN ORGAN TRANSPLANT RECIPIENTS

This was a study of 60 post-transplant patients conducted at two sites in the United States. The average age of the participants was 48 years, 55% were male, and 52% were Caucasian.

All subjects were asked to review the Drug Facts label and were then asked whether they considered the drug appropriate for them. The warning against using orlistat if you have had an organ transplant was highlighted in yellow. One of the 60 subjects made an incorrect selection decision based on the new labeling language. This individual stated that according to his physician he could take almost anything except ibuprofen. He also stated that he would ask his doctor if orlistat was appropriate for him before he would use the product. The lower bound of the 95% confidence interval for the correct selection rate was 92%.

After reviewing the data, Laura Shay, RN, MS, C-ANP, concluded that individuals who have had an organ transplant are able to correctly determine that orlistat is not appropriate for them to use when a yellow highlight is added to the organ transplant warning.

IV. SAFETY UPDATE

Julie Golden, MD, the Division of Metabolism and Endocrinology Products' primary medical officer for this NDA conducted a review of the safety data submitted in GSK's August 7, 2006, complete response to the Agency's approvable letter.

No new significant safety issues were identified. Dr. Golden did note publication of a case report of a patient with thyroid cancer receiving thyroxine for TSH suppression who became hypothyroid within two weeks of initiating therapy with orlistat. Orlistat was discontinued, the dose of thyroxine was increased, and symptoms of hypothyroidism reportedly resolved.

A search of AERS for drug-drug interactions between orlistat and thyroxine revealed potential cases. As is often the case, the reports provided insufficient information to adequately assess drug-relatedness. Nevertheless, given that malabsorption syndromes may reduce the bioavailability of thyroxine, I agree with Dr. Golden that both the prescription and nonprescription labeling for orlistat should include a warning about co-use of orlistat with thyroxine.

V. LABELING

Of note, GSK has removed the 6-month duration of use statement from the labeling. I agree with the change. I defer specific comments regarding the appropriateness of the final labeling to personnel from the Office of Nonprescription Products.

VI. CITIZEN'S PETITION

On April 10, 2006, FDA received a citizen's petition from Public Citizen requesting that prescription strength orlistat (120 mg tid) be removed from the market due to an unacceptable risk for colon cancer. Much of the petitioner's rationale is based on the results of a 30-day study in which rats injected with a chemical carcinogen and fed a high-fat diet plus orlistat developed a larger number of aberrant colonic crypts than rats fed a high-fat diet alone. The petitioners believe that these results indicate that orlistat increases the risk for colorectal carcinoma.

As detailed in a consult to the Office of Regulatory Policy, I do not believe that there is any scientific merit to the petitioner's position and do not support removal of the 120 mg dose of orlistat from the market. This issue should therefore not influence the regulatory action taken on the nonprescription orlistat NDA.

VII. CONCLUSION/RECOMMENDATION

While it appears that the sponsor has improved the proposed product's labeling – in particular they have demonstrated improved patient comprehension about the need to avoid orlistat if one has had an organ transplant – for the reasons stated in my original memorandum, I continue to believe that the efficacy and safety of the nonprescription orlistat product (including the behavior modification program) should, to the extent possible, be tested in an environment that simulates the OTC setting.

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/s/

Eric Colman
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MEDICAL OFFICER

Mary Parks
1/29/2007 02:53:27 PM
MEDICAL OFFICER

MEMORANDUM

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

Date: **January 12, 2007**

From: **Andrea Leonard-Segal, M.D.**
Director

Subject: **NDA 21-887**
Alli™ (Orlistat 60 mg)

Sponsor: **GlaxoSmithKline Consumer Healthcare**

Background:
On April 6, 2006, the FDA issued GlaxoSmithKline (GSK) an approvable action letter for NDA 21-887 for Alli™ (orlistat 60 mg capsules), a product intended as a nonprescription weight loss aid in adults ages 18 years and older. The approvable letter listed nine deficiencies that the sponsor needed to address before the NDA could be approved and provided additional labeling requests.
The nine deficiencies were:

1. Inadequate data to support the proposed 6-month duration of orlistat use. GSK could remove the limitation on duration of use and support the revised labeling with additional consumer comprehension testing.
2. The need to emphasize in the Drug Facts that an appropriate diet with exercise should be tried first, before medication is taken, to lose weight
3. Labeling was inadequate to help consumers understand that orlistat must not be used by someone with an organ transplant or who is receiving cyclosporine. New labeling language addressing these populations would need to demonstrate adequate consumer comprehension and self-selection.
4. Inadequate labeling regarding multivitamin use. New labeling language about the need to take a multivitamin would need to be tested for consumer comprehension.
5. Need to reduce the recommended amount of orlistat to 60 mg per dose from up to 120 mg per dose.
6. Inadequate labeling information on calculating body mass index (BMI).
7. Inadequate information on gastrointestinal adverse effects in the Drug Facts.
8. Lack of a pancreatitis warning in the Drug Facts.
9. Educational materials about the importance of behavioral modification to achieve weight loss need to be tested for consumer comprehension.

On August 4, 2006, GSK submitted a complete response to the April 6, 2006 approvable letter. In that response the sponsor provided labeling changes that include the following:

- a change in the daily dose of orlistat to one 60 mg capsule with each meal containing fat, not to exceed 3 capsules per day. GSK removed the 6-month limitation on duration of use.
- information about the importance of diet and exercise as a foundation of a weight loss program
- a yellow-highlighted organ transplant alert
- yellow-highlighted multivitamin use information
- a BMI chart and information on how to use it
- more information about gastrointestinal adverse effects
- a pancreatitis warning

The sponsor also added a new consumer educational insert called "Keys to Successful Weight Loss" in addition to other informational booklets that they previously provided. The "Keys to Successful Weight Loss" introduces consumers to the weight loss program by providing information about the need for behavioral modification with regard to eating, keeping records, exercise, and persistence with the weight loss program.

In the complete response, GSK provided data from a label comprehension study testing comprehension of the:

- new dosing instructions for orlistat
- multivitamin warning
- "Keys to Successful Weight Loss"

They provided data from a new self-selection study on a subpopulation of organ transplant recipients. They also submitted a safety update.

Safety Update:
On 12/20/06, Dr. Julie Golden reviewed the safety update submitted in the complete response to the approvable letter. The safety update included safety data for orlistat 120 mg from the medical literature and also from postmarketing safety databases covering the period from August 16, 2005 through May 31, 2006. It also summarized safety data from Australia and New Zealand, two countries in which orlistat 120 mg is sold as a pharmacy-only nonprescription medication. Additionally, Dr. Golden reviewed safety data from a clinical study included in an annual report for IND 62,758 (orlistat 60 mg capsules) that was submitted to the Agency on September 14, 2006.

Dr. Golden did not find new safety signals for orlistat, with the possible exception of one case report that suggests a drug-drug interaction with thyroxine. She recommended that a warning to ask a doctor or pharmacist if taking thyroid medication be added to the label. The Agency requested that GSK add a "thyroid disease" warning to the label in a FAX regarding labeling that the Agency sent to the sponsor on December 22, 2006.

During a meeting with GSK on June 14, 2006, FDA asked GSK to submit information they may have on concomitant use of orlistat and other immunosuppressant drugs. During that meeting a question arose as to whether orlistat might interfere with the

absorption of lipid soluble immunosuppressive drugs other than cyclosporine (e.g., tacrolimus). The sponsor did not provide data. However, Dr. Golden reviewed a small study in liver transplant patients published in December, 2006 looking at the safety of six months of orlistat use in patients taking tacrolimus to prevent liver transplant rejection. There appeared to be safe co-administration of the two drugs, but two patients needed their tacrolimus dosages increased. No specific drug-drug interaction study has been performed with tacrolimus and thus whether a drug-drug interaction, in fact, exists remains to be determined. To err on the side of safety, Dr. Golden recommends that the nonprescription label should have a general organ transplant alert. I agree with her. Indeed, the label has this alert and the impact of the alert was tested in the self-selection study described below.

Label Comprehension Study:
Refer to the review dated 12/22/06 by Dr. Susanna Weiss and the Clinical Team Leader review dated 12/26/06 by Dr. Bindi Nikhar. In the label comprehension study there were three key objectives: to assess comprehension of dosing instructions, multivitamin instructions, and "Keys to Successful Weight Loss." With regard to the dosing instructions, based upon their interpretation of the data, the sponsor determined that 95% of the General Population (GP) and 93% of the Low Literacy population (LL) fully comprehended that one capsule of orlistat should be taken with each fat containing meal, not to exceed 3 capsules daily. Dr. Weiss disagreed with the sponsor's categorization of "acceptable" versus "incorrect" comprehension responses in this study. (See page 9 of her review.) She thought that respondents who did not specifically cover all three cognitive steps of the dosing instructions (underlined in the sentence above) in their response should be considered to be "incorrect" because their responses were not complete. Based upon her analysis 81.5% of the GP and 69.5% of the LL were considered to have fully comprehended the dosing instructions.

Technically, in her approach to the LC study data analysis, Dr. Weiss is correct. However, it is important to remember that this product does not present unusually complicated cognitive processing compared to other nonprescription products. Actually, there are nonprescription products that require even more than three cognitive steps for perfect compliance with dosing. For example, Prilosec® OTC has four cognitive steps (with regard to number of tablets per dose and per day, taking with regard to meals, and maximum duration of use) and post-marketing data has not raised particular concerns related to inadvertent misuse for this product. Also, a lack of compliance with a perfect dosing schedule for orlistat would not present undue safety concerns.

The data on dosing comprehension is acceptable, in my view. The data does not lead to the concern that consumers would overuse orlistat since according to Dr. Weiss' review responses do not indicate that consumers will take more than three capsules per day or more than one capsule per dose. There is no limitation on dosing duration to consider. The downside of taking orlistat in the absence of a fatty meal is that it will not work, but, in that instance, there are no adverse events of concern.

Dr. Weiss expressed her worry that orlistat would be routinely taken at bedtime by some respondents who stated "three times a day" is the correct way to dose (without linking the response to meals). If so, she posits orlistat could interfere with multivitamin use. Her concern is largely hypothetical because respondents did not state that orlistat should be taken at bedtime. Further, even if orlistat were to be taken at bedtime, because of the mechanism of action, orlistat should not interfere with multivitamin absorption unless a fatty meal were to be ingested at the same time. Taking orlistat in the absence of a fatty meal should not impact vitamin absorption one way or the other.

The new highlighted labeling information improved upon the comprehension of the need to take a multivitamin and when to take it (88.3% of the GP and 79% of the LL) compared to the comprehension of this information in the Label Comprehension study submitted with the June 6, 2005 NDA. In that study, 69% of the GP and 50% of the LL knew that a multivitamin should be taken once a day and 48% of the GP and 34% of the LL group understood that the multivitamin should be taken 2 hours before or 2 hours after orlistat. Now the labeling simply recommends taking a multivitamin once a day at bedtime. Respondents did not demonstrate perfect comprehension, but considering that the risk of clinically significant vitamin deficiency is low with orlistat 120 mg and that the 60 mg dose of orlistat is less likely to interfere with fat soluble vitamin absorption than 120 mg doses, this comprehension rate is acceptable. It is not a premonition of a substantial safety concern.

The results of the comprehension assessment of the "Keys to Successful Weight Loss" were excellent. Dr. Weiss points out that the instrument used to assess comprehension of this educational material had some simplistic questions and that this factor must be considered in assessing the value of the data. However, taking this into consideration, it appears from the testing, that the message that behavioral modification in the form of eating right, exercise and sticking to the program gets through to consumers. The message is also delivered in the Drug Facts label. Some dieters will have the will power to change their eating and exercise behaviors and others will not. Those who can modify their behavior will succeed in losing weight; those who cannot, will not. Those who do not lose weight will ultimately stop taking orlistat.

Self-Selection Study

Refer to the review by Captain Laura Shay dated November 28, 2006. GSK modified the Drug Facts labeling for orlistat to include a new "organ transplant alert" that they highlighted in yellow. GSK also put the "cyclosporine" warning in bold lettering. To test the effectiveness of the new warnings, they submitted results of a self-selection study conducted on a subpopulation of organ transplant recipients. Captain Shay found the study to be designed in a way that would generally not bias the results.

Sixty organ transplant recipients from two transplant centers in the United States who expressed an interest in losing weight were eligible to participate in the study. The study participants did not know they had been selected because of their organ transplant or use of immunosuppressive drugs. Study participants reviewed the Drug Facts label and then stated whether they considered orlistat to be appropriate for them to use and the reasons

for their answer. Of the 60 participants, 59 made a correct self-selection decision. The one participant who incorrectly stated that orlistat would be appropriate for him stated that he would ask his doctor first and that he could take almost any medication he wants except for ibuprofen according to his doctor. Although he made a self-selection error, he tempered it with plans for a cautionary action that would have kept him safe.

Captain Shay states that since cyclosporine is the only absolute contraindication for orlistat, it appears reasonable to approve this label without further testing. Based upon the results of consumer studies, I agree with her conclusion.

Citizen Petition:
Public Citizen filed a Citizen Petition on April 10, 2006 (2006P-0154 CP1) to remove prescription orlistat (Xenical®) from the market because of data suggesting that orlistat increases aberrant crypt foci, a purported biomarker for colon cancer, in rat colons. Roche and GSK collaborated to respond to the Citizen Petition. In her safety update review, Dr. Golden states that no new data suggesting that orlistat increases cancer risk in humans have emerged during the reporting period. Dr. Eric Colman reviewed the available data on the implications of the aberrant crypt foci for human safety and did not find that there was a safety reason to remove prescription orlistat from the market. He wrote that "the petitioners have not provided data or rationale to alter our favorable assessment of the risk-benefit profile of the prescription orlistat dose or our interim assessment of the proposed non-prescription dose of orlistat, as summarized in the April 2006 approvable letter to the over-the-counter orlistat NDA." He recommended that "the Agency deny the request to remove prescription orlistat from the market and disregard the petitioners' call to not approve the pending non-prescription orlistat NDA." As of the date of this division director memorandum, the Agency has not responded to the Citizen Petition.

Labeling:
The information on the Alli™ package and the "Keys to Successful Weight Loss" clearly constitute "labeling" and have been reviewed in intricate detail, as is always done with drug labeling. On December 22, 2006 the Agency sent a FAX requesting that the sponsor make many modifications to the Alli™ package label and the "Keys to Successful Weight Loss." At the time of this review, the sponsor has not provided final labeling that complies with all Agency requested changes.

The sponsor has provided informational booklets about dieting, exercise, menus, and calorie counting to help consumers benefit the most from their weight loss program. GSK intends to place these booklets inside the Alli™ package. The information contained within these booklets cannot be reviewed in detail for their accuracy (e.g., how many calories and grams of fat are in a specific quantity of a specific food; the nutritional content of a specific recipe).

Pediatric:
The agency informed GSK that a partial waiver would be granted for pediatric studies in children less than 12 years of age but studies for orlistat 60 mg would need to be performed in children aged 12 – 17 years.

Conclusion:
The safety update, revised label, and the testing of the requested elements of that label in the comprehension and the self-selection studies satisfy the safety and communication concerns raised in the approvable letter. At the time of this memorandum, the Agency has yet to review the sponsor's final labeling to be sure that it incorporates all of the changes that we have requested in the December 22, 2006 FAX.

Approval of this NDA depends upon the Agency's final decision regarding the Citizen Petition. If, ultimately, the Agency's position is that orlistat increases the risk of colon cancer, then orlistat cannot be approved for nonprescription use.

[ ]

Recommendations:
NDA 21-887 should be approved, provided that the sponsor makes all of the requested labeling modifications and that the Agency denies the CP.

With the approval of this NDA, the sponsor should commit to conduct postmarketing studies of the efficacy and safety of orlistat 60 mg in children aged 12 – 17 years for weight loss.

[ ]

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/s/

Andrea Segal
1/16/2007 09:12:34 AM
MEDICAL OFFICER

Team Leader memo for Orlistat
Division of Nonprescription Clinical Evaluation (DNCE)

NDA#: 21,887 **Date: 12/22/06**
Drug: Alli (proposed trade name)
Active ingredient: Orlistat
Pharmaceutical category: Weight loss aid

Background:
This team leader memo for NDA 21,887 (orlistat) pertains to label comprehension studies conducted by the sponsor and is supplementary to the Social Science review by Dr. Susanna Weiss. Please refer to her review in DFS (12/21/06). Orlistat is a weight loss aid that works primarily by preventing the absorption of fat and is indicated for overweight adults 18 years of age and older. It is meant to be used in conjunction with a healthy lifestyle that includes a reduced calorie, low fat diet and regular exercise.

Brief Review:
The sponsor had submitted the original NDA on 6/6/2005; this was reviewed and found to be approvable on 4/6/2006. As part of the approvable letter, the sponsor was asked to repeat the label comprehension study, incorporating elements that were felt to not have been appropriately explored in the original study.

The label comprehension study explored three primary objectives: assess consumers' understanding of the dosing instructions; assess consumers' understanding of the multivitamin instructions; assess consumers' understanding of key lifestyle modifications in the package insert "Keys to Successful Weight Loss".

Study results included the following:

- 99.8% of the General Population and 98.7% of the Low Literacy group were able to comprehend that orlistat is indicated for weight loss.
- Regarding the recommended dose and dosing instructions (1 capsule with each meal containing fat and to not exceed 3 capsules daily), according to the sponsor, 95% of the General Population and 93% of the Low Literacy population had fully comprehended dosing instructions. In this section, the responses '3 times a day' and 'with meals' were considered too broad and left room for ambiguity; when moved from 'Acceptable' to 'Incorrect', 81.5% (as opposed to 95%) of the General population and 69.5% (as opposed to 93%) of the Low Literacy population were considered to have fully comprehended dosing instructions.
- Regarding the need to take a multivitamin tablet once a day at bedtime, 88.3% of the General Population and 79% of the Low Literacy group fully comprehended the instruction. The label used in the study included yellow highlighting in two places, similar to the final approved label for orlistat; a) the multivitamin instruction *and* b) the organ transplant alert.
- Regarding the 'Keys to Successful Weight Loss', comprehension of six communication objectives was as follows: above the 80th percentile on one; 90th percentile on 10 of the 12 questions; and 100% on one. Questions and answers for

this testing could have been more probing, but were considered acceptable overall.

Summary/Conclusions:

The repeat label comprehension study conducted by the sponsor for orlistat appears to have focused on key points mentioned in the Agency 'Approvable Letter'. While the study design, in terms of certain questions and responses was not optimal, overall study results are considered acceptable and show that consumers (overweight adults) should be able to comprehend appropriate use of orlistat for weight loss.

Although highlighting helped improve consumers' understanding of the multivitamins use instruction, it is possible that this may have affected/detracted comprehension of other portions of the label. Comprehensive study results showed a satisfactory comprehension of key elements of the label. Assessment of post-marketing safety for orlistat in the OTC setting may help determine whether further label comprehension studies are needed.

The 'Keys to Successful Weight Loss' pamphlet contains healthy living guidelines that the sponsor incorporated in response to Agency request to provide educational materials for appropriate use of the drug in the OTC setting. It is complimentary to the use of orlistat in overweight adults and incorporates general elements of a healthy lifestyle, including eating habits, exercise and measures to reduce weight appropriately.

Recommendations:

There are no recommendations for sponsor.

Bindi Nikhar, M.D.

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/s/

Bindi Nikhar
12/26/2006 03:31:03 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-887
Submission Code	000
Letter Date	August 4, 2006
Stamp Date	August 7, 2006
PDUFA Goal Date	February 7, 2006
Reviewer Name	Julie Golden, M.D.
Review Completion Date	December 13, 2006
Established Name	Orlistat
(Proposed) Trade Name	ALLĪ
Therapeutic Class	Obesity (lipase inhibitor)
Applicant	GlaxoSmithKline
Priority Designation	S
Formulation	Capsule
Dosing Regimen	60 mg TID with meals
Indication	Weight loss
Intended Population	Overweight

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

A regulatory action recommendation is being deferred until all reviews are completed; however, this reviewer's conclusions regarding this application are generally unchanged from the original NDA review.

From this reviewer's perspective, the labeling should indicate that a patient taking thyroxine should consult with his or her physician prior to taking orlistat concomitantly. This recommendation is based on a case report of a potential drug-drug interaction between thyroxine and orlistat, and biological plausibility for such an interaction. Patients taking thyroid hormone for hypothyroidism and other conditions are monitored clinically, and the involvement of the physician will facilitate such monitoring.

1.2 Recommendation on Post-marketing Actions

No other post-marketing actions are being recommended at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview

This document reviews the safety update (excluding the sponsor's response to the pending citizen's petition) submitted with the complete response to an Approvable (AE) letter issued to the sponsor April 6, 2006.

1.3.3 Safety

There were no new safety issues that were identified during this safety update review, with the exception of a possible drug-drug interaction noted in one case report of orlistat and thyroxine. This case highlights the importance of drug-drug interactions in the overall safety profile of orlistat. The most commonly reported adverse events continue to be gastrointestinal (bowel pattern-related), as is expected from orlistat's pharmacodynamic activity.

1.3.5 Drug-Drug Interactions

Orlistat has a well-described interaction (decreases intestinal absorption) with fat-soluble drugs and vitamins. One case report describing a potential interaction between orlistat and thyroxine in a patient with thyroid cancer on thyroxine for thyroid stimulating hormone (TSH) suppression was reviewed. Although suggestive, it is difficult to make a definitive determination based on a

single case report. No other unexpected drug-drug or drug-nutrient interactions surfaced as a result of this safety update review.

2 INTRODUCTION AND BACKGROUND

This document reviews the safety update submitted with the complete response to an Approvable (AE) letter issued to the sponsor April 6, 2006. The original clinical NDA review was completed by this reviewer March 8, 2006, and therefore, information included in that document will not be repeated here. In addition to the safety update, the sponsor's complete response includes draft labeling with modifications designed to address specific issues raised in the AE letter and final study reports for the self-selection study in organ transplant recipients and the label comprehension study. These items will be reviewed by personnel in the Division of Nonprescription Clinical Evaluation.

Numbering for this review will follow the clinical review template. Missing numerical headers are purposeful and represent sections that are not relevant to this safety update review.

2.5 Presubmission Regulatory Activity

An End-of-Review meeting was held between the Agency (Division of Metabolic and Endocrine Products, DMEP and Division of Nonprescription Clinical Evaluation, DNCE) and the sponsor (GlaxoSmith Kline, GSK) on June 14, 2006 to reach agreement on the sponsor's proposed labeling revisions. A second follow-up meeting was held between the sponsor and DNCE to discuss issues related to the labeling study protocols.

2.6 Other Relevant Background Information

Public Citizen filed a citizen's petition April 10, 2006 with FDA to remove prescription orlistat (Xenical, Roche Pharmaceuticals) from the market because of data suggesting that orlistat increases aberrant crypt foci (ACF), a purported biomarker for colon cancer, in rat colons.[1] Roche and GSK collaborated to respond to this citizen's petition by providing an assessment of the issues raised and the concordance of an external Advisory Board assembled by the two companies. This response will be reviewed in detail by Dr. Eric Colman, Deputy Director of DMEP, in a separate review of the citizen's petition, and therefore will not be specifically addressed in this review.

1 CP 2006P-0154

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The safety update includes safety data for orlistat 120 mg from the literature and post-marketing safety databases covering the period of August 16, 2005 through May 31, 2006. It also summarizes the available safety data from Australia and New Zealand, two markets in which orlistat 120 mg is available as a pharmacy-only nonprescription medicine.

An Annual Report for IND 62,758 (orlistat 60 mg capsules) was submitted to the Agency on September 14, 2006. This covered the reporting period of July 14, 2005 through July 13, 2006. A brief summary of one clinical study was included in the Annual Report; this was a four-day Proof of Principle study intended to evaluate the ability of calcium stearate and methylcellulose to reduce the gastrointestinal-related adverse events associated with orlistat use (all subjects received orlistat and the three treatment arms were calcium stearate, methylcellulose, and placebo). Because this was only a summary rather than a complete study report, a complete review of the safety data cannot be done in this document. This study was not discussed in the NDA complete response. *Reviewer comment: Gastrointestinal adverse events in the four-day study period appear to have occurred at a similar incidence to what has been seen previously with orlistat use. According to the sponsor, neither calcium stearate nor methylcellulose appeared to produce any beneficial change in the GI side effect profile of orlistat. There were no deaths or serious adverse events (AEs) reported in the study. One subject discontinued the study due to a diffuse papular rash associated with pruritus; the AE resolved with antihistamine administration.*

4.3 Review Strategy

This reviewer reviewed the safety update (excluding the response to the citizen petition). Personnel in DNCE reviewed the draft label annotations and full study reports for the self-selection and label comprehension studies. Dr. Colman reviewed the response to the citizen's petition. This document comprises only the safety update review.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Because only literature and post-marketing reports were included in this safety update, the portion of the clinical template that addresses primary data sources (typically obtained from clinical trial data) are not included. This review refers to only these secondary data sources. As the 60 mg dose of orlistat is not marketed in any country, the safety update only describes those events occurring with the 120 mg dose.

7.1.1 Deaths

The sponsor did not specifically identify post-marketing or literature reports that demonstrated death as an outcome of orlistat treatment. This reviewer identified two post-marketing reports from FDA AERS Datamart that resulted in death in this time period, and no literature reports. In one AERS report regarding the death a female of unknown age, the cause of death was reported as "blood evacuation"; the reporter was the patient's friend. No other relevant information was provided. The second report occurred in a 57-year old male patient who suffered a fatal myocardial infarction. This patient had multiple risk factors for cardiovascular disease including a previous heart attack. The physician considered the association with orlistat as not related.

7.1.2 Other Serious Adverse Events

The database in which serious adverse events were specifically classified was from the Roche Worldwide Safety Database. During the period of August 16, 2005 through May 31, 2006, a total of 222 adverse events (105 classified as serious unlisted events) were reported in medically confirmed, serious cases; see Appendix 10.3. The most common reported adverse events were in the gastrointestinal system organ class (SOC), with 23 events of constipation (one being classified as serious unlisted) and 16 events of nausea (two being classified as serious unlisted).

7.1.5 Common Adverse Events

The most common adverse events noted in this safety update were gastrointestinal in nature, which is consistent with the known safety profile of orlistat.

7.1.6 Less Common Adverse Events

Incidence rates and causality of less common adverse events are difficult to determine without access to safety data from randomized controlled trials. Adverse event rates from such trials were discussed in the original NDA review; since then no other clinical trials for complete review have been submitted. Less common adverse events that have surfaced in post-marketing reports have included pancreatitis (discussed in the original NDA review and below) and hepatotoxicity (discussed in the original NDA review). Other adverse events related to fat soluble vitamin- and drug-drug interactions were discussed in the original NDA review and in other sections of this review.

7.1.11 Human Carcinogenicity

Although no new data suggesting that orlistat increases cancer risk in humans have emerged during the reporting period of this safety update, one published study in rats demonstrated increases of aberrant crypt foci in rat colons,[2] a finding that has provoked concern as a possible

2 Garcia SB, et al. The antiobesity agent Orlistat is associated to increase in colonic preneoplastic markers in rats treated with a chemical carcinogen. Cancer Lett. 2005 Dec 22.

marker of increased colonic carcinogenicity. The relevance of these and other data to humans will be addressed by Dr. Colman.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No new relevant data were provided in this safety update.

7.1.14 Human Reproduction and Pregnancy Data

The AERS Database included nine separate reports of pregnancy during the reporting period. Preferred terms included: premature labour, premature rupture of membranes, premature separation of placenta, pre-eclampsia, oligohydramnios, normal newborn, pregnancy, and pregnancy on oral contraceptive (*reviewer comment: prescription labeling states that in drug-drug interaction studies, orlistat has been shown to have no effect on the phamacokinetics and/or pharmacodynamics of oral contraceptives*).

The WHO Database had one report of pre-eclampsia, one report of pregnancy unintended (*reviewer comment: weight loss is believed to improve fertility in some women*[3]), one report of death foetal, two reports of drug exposure in pregnancy, and one report of oligohydramnios.

The following reports were tabulated in the Roche Worldwide Safety Database under the SOC Pregnancy, Puerperium, and Perinatal Conditions:

Preferred Term	All AEs Period	All AEs Cum to 31 May 2006
Abortion Spontaneous	1	55
Ectopic Pregnancy	1	4
Normal Newborn	3	150
Oligohydramnios	1	1
Pre-Eclampsia	1	1
Pregnancy	26	312
Premature Labour	1	7
Premature Rupture of Membranes	1	1
Premature Separation of Placenta	1	1
Total	36	532

In general, the raw number of reports of pregnancy-related adverse events does not appear to be greater than that seen in previous reporting periods. There were no literature reports of orlistat and pregnancy noted by this reviewer within the reporting period.

7.1.16 Overdose Experience

No new relevant data were provided in this safety update.

3 Pasquali R. Obesity, fat distribution and infertility. Maturitas. 2006 Jul 20;54(4):363-71.

7.1.17 Post-marketing Experience

The AERS Database search revealed 121 reports containing 389 adverse events (see Appendix 10.1). The most frequent adverse events reported were in the gastrointestinal SOC, with diarrhea (12 events), abdominal pain (10 events), haematochezia (9 events), and constipation (8 events) being reported. Furthermore, drug interaction (12 events) and dizziness (10 events) were other events of note reported at a similar frequency.

The WHO Database search revealed 142 reports containing 274 adverse events (see Appendix 10.2). The most common adverse events reported were abdominal pain (11 events), diarrhea (8 events), and pruritus (8 events).

The total number of adverse events in the Roche Worldwide Safety Database received was 2705, with the most commonly reported events being constipation, steatorrhoea, and diarrhea (187, 136, and 122 events respectively).

The sponsor also presented, separately, safety data from the Australia and New Zealand markets, two markets in which Xenical® (orlistat) 120 mg capsules are available as a pharmacy-only nonprescription medicine. As noted by this reviewer in the original NDA review, the relevance of these data to the current proposal is not clear, as a specific pharmacy protocol has been developed by Roche in association with professional pharmacy/pharmaceutical societies. This protocol is intended to be used by the consulted pharmacist in the dispensing of orlistat as a pharmacy-only medicine. 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. None of these assessments will be done with nonprescription purchase by U.S. consumers.

During the period of August 16, 2005 through May 31, 2006, a total of 13 adverse events (9 classified as serious unlisted events) were reported in medically confirmed cases from the Roche Worldwide Safety Database. Three of these serious unlisted events (nausea, anal hemorrhage, and acute pancreatitis; see below for a discussion of pancreatitis) were in the gastrointestinal disorder SOC and two (both acute cholelithiasis) were in the hepatobiliary disorder SOC. Therefore, according to the sponsor, the adverse event profile in Australia and New Zealand was comparable to the overall pattern of worldwide adverse events in the current reporting period.

Pancreatitis is a post-marketing adverse event of interest and was discussed at the Joint Nonprescription Drug and Endocrine and Metabolic Drug Advisory Committee in January 2006. As discussed at that meeting, FDA reviewers have noted that an excess number of post-marketing reports of pancreatitis were seen for orlistat when compared with sibutramine, the other approved drug for long-term weight loss in the United States. The following is a table of the pancreatitis-related raw number of adverse events for this reporting period, and, in the case of the Roche Worldwide Safety Database, cumulative through May 2006. There may be pancreatitis-related adverse events that were seen in other reporting periods that are not listed

below, but in general, the number of pancreatitis-related adverse events from the current reporting period appears relatively comparable to previous time periods (when compared to all adverse event tallies).

Database	Preferred Term	Number of AEs per period	Total AEs (cumulative)
AERS	Oedematous pancreatitis	1	NR
	Pancreatitis	1	NR
	All AEs	NR	NR
WHO	Lipase increased	1	NR
	Pancreatitis	4	NR
	All AEs	274	NR
Roche	Oedematous pancreatitis	1	1
	Pancreatitis	1	50
	Acute pancreatitis	2	13
	Amylase increased	1	9
	All AEs	222	2632

NR = Not reported by GSK; AE = adverse event; overlap between databases is possible

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.2 Post-marketing experience

The current safety update contains:

- A search of the AERS Database over the period of April 1, 2005 through Dec 31, 2005, the date of public release of the latest data.
- A search of the WHO Database over the period of August 16, 2005 through May 31, 2006.
- A search of the Roche Worldwide Safety Database over the period of August 16, 2005 through May 31, 2006.

The sponsor did not provide any information other than tabulated lists of events; therefore, the safety update did not include a comprehensive review of the post-marketing safety database. Adverse events are not mutually exclusive to the different databases.

7.2.2.3 Literature

The sponsor used the following criteria to identify publications addressing orlistat and safety issues in the timeframe of this latest safety update:

- Orlistat, Xenical, orlipastat, tetrahydrolipstatin, lipstatin, RN=96829-58-2, Ro-18-0647
- Adverse events, AE, contraindications, CT, poisoning, PO, toxicity, TO, drug interaction, DI
- Preclinical, animal*, model, rat*, mouse, mice, dog, rhesus
  *denotes truncation

A total of 161 articles were identified. The search criteria are deemed adequate.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

As this entire document addresses orlistat safety for the safety update reporting period, conclusions can be found in Section 9.1. Limitations to the data presented in the safety update are intrinsic to post-marketing and literature reports over a particular time point; data may be missing, redundant, and uncontrolled. Post-marketing events were provided in tabulated format. No clinical data were provided to assess new safety concerns.

8 ADDITIONAL CLINICAL ISSUES

8.2 Drug-Drug Interactions

Meeting minutes from June 14, 2006 document that the following request was made by the agency to the company:

Submit information you may have on concomitant use of orlistat and other immunosuppressant drugs. Does orlistat reduce the absorption of other lipid-soluble immunosuppressant drugs such as tacrolimus?

It should be noted that this reviewer has not been made aware of any additional information provided by the company on this issue in the safety update. A small study, published in late 2006, studied the safety of six months of orlistat tid in 15 patients who were status post liver transplant on tacrolimus-based immunosuppressant regimens.[4] Although this study is suggestive of safe co-administration in the setting of judicious monitoring and orlistat/tacrolimus dose separation, it was limited by lack of a placebo control, small sample size, no documentation of orlistat and dietary compliance (although it is notable that there were no gastrointestinal complaints during the study), and few details about the two patients who required tacrolimus dosage upwards. Therefore, until a specific drug-drug interaction is performed, it is prudent to continue to state on the nonprescription label that subjects who have had an organ transplant must not take orlistat (i.e., not just those on cyclosporine).

The potential interaction between orlistat and thyroxine is discussed in detail in Section 8.6 (literature review), below. No other unexpected drug-drug or drug-nutrient interactions have surfaced as a result of this safety update review.

8.3 Special Populations

Safety in special populations was not specifically addressed in this safety update.

4 Cassiman D, et al. Transpl Int. 2006 Dec;19(12):1000-5.

8.4 Pediatrics

Safety in pediatric populations was not specifically addressed in this safety update.

8.6 Literature Review

Three case reports related to the use of orlistat were published during this time period, one of which[5] was previously discussed with the original NDA review in the context of liver events. The other two case reports are described here. The first described a case of lichenoid drug eruption (LDE) believed to be secondary to orlistat.[6] The authors of the article did not appear to confirm causality, as the patient was not re-challenged with orlistat and their conclusions were based on the timing, pathology, and resolution of the eruptions.

The second published case report described a case of symptomatic hypothyroidism in a patient with a complete thyroidectomy resulting from papillary carcinoma of the thyroid who was taking both orlistat with thyroxine at a dose to suppress thyroid-stimulating hormone (TSH).[7] Symptoms of hypothyroidism began in this apparently compliant patient within two weeks of commencing orlistat therapy, and the diagnosis was confirmed biochemically with serum T_4 and TSH concentrations. Orlistat therapy was discontinued, the thyroxine dose was increased, and symptoms resolved within two weeks.

Given that drug-drug interactions, with respect to orlistat's effect on drug absorption, are among the most important safety concerns and potentially the most problematic from a nonprescription labeling standpoint, this individual event (orlistat and thyroxine interaction) was investigated further.

To the knowledge of this reviewer, specific drug-drug interaction studies with orlistat and thyroxine have not been done. The case described above is the only known published report of an interaction between orlistat and thyroxine.

Levothyroxine product labeling lists a number of drugs (orlistat not being one of them) that affect thyroid hormone pharmacokinetics and metabolism (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response). Drugs that are reported to decrease T_4 absorption include aluminum and magnesium antacids, simethicone, bile acid sequestrants, calcium carbonate, kayexelate, ferrous sulfate, and sucralfate. It is further noted that T_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. It therefore seems plausible that orlistat could affect the absorption of thyroxine.

5 Thurairajah PH, et al. Eur J Gastroenterol Hepatol. 2005 Dec;17(12):1437-8.
6 Sergeant A, et al. Lichenoid eruption associated with orlistat. Br J Dermatol. 2006 May;154(5):1020-1.
7 Madhava K and Hartley A. Hypothyroidism in thyroid carcinoma follow-up: orlistat may inhibit the absorption of thyroxine. Clin Oncol (R Coll Radiol). 2005 Sep;17(6):492.

The FDA AERS Database was searched by this reviewer for possible drug-drug interactions between orlistat and thyroxine. The database search revealed six cases that resulted in such adverse events as elevated thyroid stimulating hormone (TSH), hypothyroidism, and goiter. However, most of these reports provided little if any information in which to confirm a drug-drug interaction. In one case, however, discontinuation of orlistat in addition to raising the levothyroxine dose in a patient with previously well-controlled thyroid values appeared to resolve the thyroid abnormalities.

It therefore remains unclear at this time what the precise risk is to those on concomitant orlistat and thyroxine. At a minimum, labeling should reflect the possibility of an interaction, and ideally, a drug interaction study would be performed. This case also highlights the concern about fat-soluble drug interactions in general with orlistat, and begs the question: how many other unknown drug interactions with orlistat are there?

In addition to these two case reports, the sponsor provided a bibliography for 159 other articles and published abstracts identified by the described search criteria that were published in this timeframe. Of note is an article by Garcia et al., published in December 2005, which describes an association between orlistat ingestion and colonic preneoplastic markers in rats.[2] As this article will be reviewed in full in response to the citizen's petition by Dr. Colman, this reviewer will not be commenting on this article further.

9 OVERALL ASSESSMENT

9.1 Conclusions

There were no new safety issues that were identified during this safety update review, with the exception of a possible drug-drug interaction noted in one case report of orlistat and thyroxine. This case highlights the importance of drug-drug interactions in the overall safety profile of orlistat. The most commonly reported adverse events continue to be gastrointestinal (bowel pattern-related), as is expected from orlistat's pharmacodynamic activity.

9.2 Recommendation on Regulatory Action

A regulatory action recommendation is being deferred until all reviews are completed; however, this reviewer's conclusions regarding this application are generally unchanged from the original NDA review.

From this reviewer's perspective, the labeling should indicate that a person on thyroxine should consult with his or her physician prior to taking orlistat. This recommendation is based on a case report of a potential drug-drug interaction between thyroxine and orlistat, and biological plausibility for such an interaction. Patients taking thyroid hormone for hypothyroidism and other conditions are monitored clinically, and the involvement of the physician will facilitate such monitoring.

9.3 Recommendation on Post-marketing Actions

No other post-marketing actions are being recommended at this time.

9.5 Comments to Applicant

Please add the following to the Warnings section of the Drug Facts label (new section **bolded**):

Ask a doctor or pharmacist before use if you are
• taking warfarin (blood thinning medicine). You should have your blood tested regularly during weight loss.
• taking medicine for diabetes. Your medication dose may need to be adjusted during weight loss.
• taking medicine for a thyroid condition. Your medication dose may need to be adjusted.*
• taking other weight loss products.

* Specific labeling language will be deferred to DNCE in order to maintain consistency with other nonprescription product labels.

10 APPENDICES

10.1 Results from AERS Database

SOC	HLGT	HLT	PT	Number of Adverse Events
Blood	Anaemias nonhaemolytic and marrow depression	Anaemias NEC	Anaemia	1
Blood	Anaemias nonhaemolytic and marrow depression	Marrow depression and hypoplastic anaemias	Pancytopenia	1
Blood	Coagulopathies and bleeding diatheses (excl thrombocytopenic)	Coagulopathies	Coagulopathy	1
Blood	Platelet disorders	Thrombocytopenias	Thrombocytopenia	1
Blood	Platelet disorders	Thrombocytopenias	Thrombocytopenic purpura	1
Blood	White blood cell disorders	Leukocytoses NEC	Leukocytosis	1
Card	Cardiac arrhythmias	Cardiac conduction disorders	Long QT syndrome	1
Card	Cardiac arrhythmias	Rate and rhythm disorders NEC	Arrhythmia	1
Card	Coronary artery disorders	Coronary artery disorders NEC	Coronary artery occlusion	1
Card	Coronary artery disorders	Ischaemic coronary artery disorders	Angina pectoris	2
Card	Heart failures	Heart failures NEC	Cardiogenic shock	1
Card	Pericardial disorders	Pericardial disorders NEC	Cardiac tamponade	1
Ear	Inner ear and VIIIth cranial nerve disorders	Inner ear signs and symptoms	Tinnitus	1
Endo	Thyroid gland disorders	Thyroid hypofunction disorders	Hypothyroidism	1
Eye	Vision disorders	Blindness (excl colour blindness)	Blindness	1
Eye	Vision disorders	Blindness (excl colour blindness)	Blindness transient	1
Eye	Vision disorders	Visual disorders NEC	Vision blurred	7
Gastr	Anal and rectal conditions NEC	Anal and rectal disorders NEC	Anal fissure	1
Gastr	Anal and rectal conditions NEC	Anal and rectal signs and symptoms	Rectal discharge	1
Gastr	Anal and rectal conditions NEC	Anal and rectal signs and symptoms	Rectal spasm	1
Gastr	Benign neoplasms gastrointestinal	Benign neoplasms gastrointestinal (excl oral cavity)	Colonic polyp	1
Gastr	Diverticular disorders	Diverticulum inflammations	Diverticulitis intestinal haemorrhagic	1
Gastr	Exocrine pancreas conditions	Acute and chronic pancreatitis	Oedematous pancreatitis	1
Gastr	Exocrine pancreas conditions	Acute and chronic pancreatitis	Pancreatitis	2
Gastr	Gastrointestinal conditions NEC	Gastrointestinal disorders NEC	Gastrointestinal disorder	1
Gastr	Gastrointestinal conditions NEC	Gastrointestinal fistulae	Intestinal fistula	1
Gastr	Gastrointestinal haemorrhages NEC	Intestinal haemorrhages	Rectal haemorrhage	5
Gastr	Gastrointestinal haemorrhages NEC	Non-site specific gastrointestinal haemorrhages	Gastrointestinal haemorrhage	2
Gastr	Gastrointestinal haemorrhages NEC	Non-site specific gastrointestinal haemorrhages	Haematemesis	1
Gastr	Gastrointestinal haemorrhages NEC	Non-site specific gastrointestinal haemorrhages	Haematochezia	9
Gastr	Gastrointestinal haemorrhages NEC	Non-site specific gastrointestinal haemorrhages	Melaena	1
Gastr	Gastrointestinal inflammatory conditions	Colitis (excl infective)	Colitis	2
Gastr	Gastrointestinal inflammatory conditions	Colitis (excl infective)	Colitis ulcerative	1
Gastr	Gastrointestinal motility and defaecation conditions	Diarrhoea (excl infective)	Diarrhoea	12
Gastr	Gastrointestinal motility and defaecation conditions	Gastrointestinal atonic and hypomotility disorders NEC	Constipation	8
Gastr	Gastrointestinal motility and defaecation conditions	Gastrointestinal atonic and hypomotility disorders NEC	Gastrooesophageal reflux disease	1
Gastr	Gastrointestinal signs and symptoms	Abdominal findings abnormal	Abdominal rigidity	1
Gastr	Gastrointestinal signs and symptoms	Dyspeptic signs and symptoms	Dyspepsia	2
Gastr	Gastrointestinal signs and symptoms	Dyspeptic signs and symptoms	Eructation	1

SOC	HLGT	HLT	PT	Number of Adverse Events
Gastr	Gastrointestinal signs and symptoms	Faecal abnormalities NEC	Abnormal faeces	2
Gastr	Gastrointestinal signs and symptoms	Flatulence, bloating and distension	Abdominal distension	2
Gastr	Gastrointestinal signs and symptoms	Flatulence, bloating and distension	Flatulence	1
Gastr	Gastrointestinal signs and symptoms	Gastrointestinal and abdominal pains (excl oral and throat)	Abdominal pain	10
Gastr	Gastrointestinal signs and symptoms	Gastrointestinal and abdominal pains (excl oral and throat)	Abdominal pain lower	1
Gastr	Gastrointestinal signs and symptoms	Gastrointestinal and abdominal pains (excl oral and throat)	Abdominal pain upper	6
Gastr	Gastrointestinal signs and symptoms	Gastrointestinal signs and symptoms NEC	Breath odour	1
Gastr	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms	Nausea	5
Gastr	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms	Vomiting	6
Gastr	Gastrointestinal stenosis and obstruction	Gastrointestinal stenosis and obstruction NEC	Intestinal obstruction	1
Gastr	Gastrointestinal ulceration and perforation	Duodenal ulcers and perforation	Duodenal ulcer	2
Gastr	Gastrointestinal ulceration and perforation	Gastric ulcers and perforation	Gastric ulcer haemorrhage	2
Gastr	Gastrointestinal vascular conditions	Gastrointestinal vascular occlusion and infarction	Intestinal ischaemia	1
Gastr	Malabsorption conditions	Malabsorption syndromes	Steatorrhoea	4
Gastr	Peritoneal and retroperitoneal conditions	Peritoneal and retroperitoneal disorders	Peritonitis	1
Gastr	Salivary gland conditions	Oral dryness and saliva altered	Dry mouth	1
Genrl	Administration site reactions	Application and instillation site reactions	Application site reaction	1
Genrl	Body temperature conditions	Body temperature altered	Hypothermia	1
Genrl	Fatal outcomes	Death and sudden death	Death	1
Genrl	General system disorders NEC	Asthenic conditions	Asthenia	8
Genrl	General system disorders NEC	Asthenic conditions	Fatigue	1
Genrl	General system disorders NEC	Asthenic conditions	Malaise	3
Genrl	General system disorders NEC	General signs and symptoms NEC	Hunger	1
Genrl	General system disorders NEC	General signs and symptoms NEC	Ill-defined disorder	1
Genrl	General system disorders NEC	General signs and symptoms NEC	Multi-organ failure	1
Genrl	General system disorders NEC	General signs and symptoms NEC	Thirst	1
Genrl	General system disorders NEC	General signs and symptoms NEC	Unevaluable event	1
Genrl	General system disorders NEC	Pain and discomfort NEC	Chest pain	4
Genrl	General system disorders NEC	Pain and discomfort NEC	Non-cardiac chest pain	1
Genrl	General system disorders NEC	Pain and discomfort NEC	Pain	2
Genrl	Therapeutic and nontherapeutic effects (excl toxicity)	Interactions	Drug interaction	12
Genrl	Therapeutic and nontherapeutic effects (excl toxicity)	Therapeutic and nontherapeutic responses	Drug ineffective	1
Genrl	Therapeutic and nontherapeutic effects (excl toxicity)	Therapeutic and nontherapeutic responses	Pharmaceutical product complaint	1
Hepat	Gallbladder disorders	Cholecystitis and cholelithiasis	Cholelithiasis	4
Hepat	Gallbladder disorders	Gallbladder disorders NEC	Gallbladder disorder	2
Hepat	Hepatic and hepatobiliary disorders	Cholestasis and jaundice	Hepatitis cholestatic	1
Hepat	Hepatic and hepatobiliary disorders	Cholestasis and jaundice	Jaundice	2
Hepat	Hepatic and hepatobiliary disorders	Hepatic and hepatobiliary disorders NEC	Liver disorder	1
Hepat	Hepatic and hepatobiliary disorders	Hepatic failure and associated disorders	Hepatic failure	1
Hepat	Hepatic and hepatobiliary disorders	Hepatobiliary signs and symptoms	Hepatomegaly	2
Hepat	Hepatic and hepatobiliary disorders	Hepatocellular damage and hepatitis NEC	Cytolytic hepatitis	1
Hepat	Hepatic and hepatobiliary disorders	Hepatocellular damage and hepatitis NEC	Hepatic steatosis	1
Hepat	Hepatic and hepatobiliary disorders	Hepatocellular damage and hepatitis NEC	Hepatitis	1

SOC	HLGT	HLT	PT	Number of Adverse Events
Hepat	Hepatic and hepatobiliary disorders	Hepatocellular damage and hepatitis NEC	Hepatocellular damage	1
Immun	Autoimmune disorders	Autoimmune disorders NEC	Autoimmune disorder	1
Infec	Bacterial infectious disorders	Bacterial infections NEC	Bacterial infection	1
Infec	Bacterial infectious disorders	Escherichia infections	Escherichia bacteraemia	1
Infec	Bacterial infectious disorders	Escherichia infections	Escherichia sepsis	1
Infec	Bacterial infectious disorders	Escherichia infections	Escherichia urinary tract infection	1
Infec	Bacterial infectious disorders	Staphylococcal infections	Staphylococcal infection	1
Infec	Helminthic disorders	Nematode infections	Ascariasis	1
Infec	Infections - pathogen class unspecified	Abdominal and gastrointestinal infections	Abscess intestinal	1
Infec	Infections - pathogen class unspecified	Abdominal and gastrointestinal infections	Appendicitis	1
Infec	Infections - pathogen class unspecified	Abdominal and gastrointestinal infections	Diverticulitis	6
Infec	Infections - pathogen class unspecified	Abdominal and gastrointestinal infections	Perianal abscess	1
Infec	Infections - pathogen class unspecified	Hepatobiliary and spleen infections	Cholecystitis infective	1
Infec	Infections - pathogen class unspecified	Skin structures and soft tissue infections	Carbuncle	1
Infec	Infections - pathogen class unspecified	Skin structures and soft tissue infections	Furuncle	1
Infec	Infections - pathogen class unspecified	Skin structures and soft tissue infections	Subcutaneous abscess	1
Infec	Infections - pathogen class unspecified	Urinary tract infections	Kidney infection	1
Inj&P	Chemical injury and poisoning	Poisoning and toxicity	Drug toxicity	1
Inj&P	Injuries NEC	Skin injuries NEC	Contusion	2
Inj&P	Medication errors	Medication errors due to accidental exposures	Drug exposure during pregnancy	6
Inj&P	Procedural and device related injuries and complications NEC	Non-site specific procedural complications	Incisional hernia	1
Inv	Enzyme investigations NEC	Tissue enzyme analyses NEC	Blood alkaline phosphatase increased	2
Inv	Gastrointestinal investigations	Digestive enzymes	Blood amylase increased	1
Inv	Gastrointestinal investigations	Digestive enzymes	Lipase increased	1
Inv	Haematology investigations (incl blood groups)	Coagulation and bleeding analyses	International normalised ratio increased	1
Inv	Haematology investigations (incl blood groups)	Platelet analyses	Platelet count decreased	1
Inv	Haematology investigations (incl blood groups)	Red blood cell analyses	Haemoglobin decreased	2
Inv	Hepatobiliary investigations	Liver function analyses	Alanine aminotransferase increased	4
Inv	Hepatobiliary investigations	Liver function analyses	Aspartate aminotransferase increased	3
Inv	Hepatobiliary investigations	Liver function analyses	Bilirubin conjugated increased	1
Inv	Hepatobiliary investigations	Liver function analyses	Blood bilirubin increased	1
Inv	Hepatobiliary investigations	Liver function analyses	Blood bilirubin unconjugated increased	1
Inv	Hepatobiliary investigations	Liver function analyses	Gamma-glutamyltransferase increased	2
Inv	Hepatobiliary investigations	Liver function analyses	Liver function test abnormal	1

SOC	HLGT	HLT	PT	Number of Adverse Events
Inv	Lipid analyses	Cholesterol analyses	Blood cholesterol increased	1
Inv	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	Blood glucose decreased	2
Inv	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	Blood glucose increased	1
Inv	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	Glycosylated haemoglobin increased	1
Inv	Physical examination topics	Physical examination procedures	Weight decreased	1
Inv	Physical examination topics	Physical examination procedures	Weight increased	4
Inv	Renal and urinary tract investigations and urinalyses	Renal function analyses	Blood creatinine increased	1
Inv	Renal and urinary tract investigations and urinalyses	Urinalysis NEC	Blood urine present	1
Inv	Renal and urinary tract investigations and urinalyses	Urinalysis NEC	Urine calcium increased	1
Inv	Renal and urinary tract investigations and urinalyses	Urinalysis NEC	Urine sodium increased	1
Inv	Toxicology and therapeutic drug monitoring	Therapeutic drug monitoring analyses	Drug level increased	1
Inv	Water, electrolyte and mineral investigations	Mineral and electrolyte analyses	Blood potassium decreased	1
Metab	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	Lactic acidosis	5
Metab	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	Metabolic acidosis	3
Metab	Acid-base disorders	Mixed acid-base disorders	Acidosis	1
Metab	Appetite and general nutritional disorders	Appetite disorders	Decreased appetite	1
Metab	Appetite and general nutritional disorders	Appetite disorders	Oral intake reduced	1
Metab	Appetite and general nutritional disorders	General nutritional disorders NEC	Obesity	1
Metab	Appetite and general nutritional disorders	General nutritional disorders NEC	Weight loss poor	1
Metab	Electrolyte and fluid balance conditions	Fluid intake increased	Polydipsia	1
Metab	Electrolyte and fluid balance conditions	Potassium imbalance	Hypokalaemia	1
Metab	Electrolyte and fluid balance conditions	Total fluid volume decreased	Dehydration	1
Metab	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	Diabetes mellitus	1
Metab	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	Hyperglycaemia	1
Metab	Vitamin related disorders	Fat soluble vitamin deficiencies and disorders	Vitamin K deficiency	1
Musc	Joint disorders	Joint related signs and symptoms	Arthralgia	1
Musc	Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)	Intervertebral disc disorders NEC	Intervertebral disc degeneration	1
Musc	Musculoskeletal and connective tissue disorders NEC	Musculoskeletal and connective tissue signs and symptoms NEC	Pain in extremity	1
Musc	Musculoskeletal and connective tissue disorders NEC	Soft tissue disorders NEC	Fistula	1

SOC	HLGT	HLT	PT	Number of Adverse Events
Neopl	Breast neoplasms malignant and unspecified (incl nipple)	Breast and nipple neoplasms malignant	Breast cancer	1
Neopl	Endocrine neoplasms malignant and unspecified	Carcinoid tumours	Carcinoid tumour of the gastrointestinal tract	1
Neopl	Gastrointestinal neoplasms malignant and unspecified	Gastrointestinal neoplasms malignant NEC	Peritoneal carcinoma	1
Neopl	Hepatobiliary neoplasms malignant and unspecified	Bile duct neoplasms malignant	Bile duct cancer	1
Neopl	Lymphomas non-Hodgkin's unspecified histology	Non-Hodgkin's lymphomas NEC	Non-Hodgkin's lymphoma	1
Nerv	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Cerebral infarction	1
Nerv	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Cerebrovascular accident	1
Nerv	Central nervous system vascular disorders	Central nervous system vascular disorders NEC	Cerebrovascular disorder	1
Nerv	Encephalopathies	Encephalopathies toxic and metabolic	Hepatic encephalopathy	1
Nerv	Headaches	Headaches NEC	Headache	3
Nerv	Increased intracranial pressure and hydrocephalus	Increased intracranial pressure disorders	Intracranial pressure increased	1
Nerv	Neurological disorders NEC	Disturbances in consciousness NEC	Depressed level of consciousness	5
Nerv	Neurological disorders NEC	Disturbances in consciousness NEC	Lethargy	1
Nerv	Neurological disorders NEC	Disturbances in consciousness NEC	Loss of consciousness	1
Nerv	Neurological disorders NEC	Disturbances in consciousness NEC	Syncope vasovagal	1
Nerv	Neurological disorders NEC	Nervous system disorders NEC	Nervous system disorder	1
Nerv	Neurological disorders NEC	Neurological signs and symptoms NEC	Dizziness	10
Nerv	Neurological disorders NEC	Paraesthesias and dysaesthesias	Burning sensation	1
Nerv	Neurological disorders NEC	Paraesthesias and dysaesthesias	Paraesthesia	1
Nerv	Neurological disorders NEC	Sensory abnormalities NEC	Sensory disturbance	1
Nerv	Neurological disorders NEC	Speech and language abnormalities	Dysarthria	5
Nerv	Seizures (incl subtypes)	Seizures and seizure disorders NEC	Epilepsy	1
Preg	Abortions and stillbirth	Abortions spontaneous	Abortion spontaneous	1
Preg	Maternal complications of labour and delivery	Labour onset and length abnormalities	Premature labour	1
Preg	Maternal complications of labour and delivery	Labour onset and length abnormalities	Premature rupture of membranes	1
Preg	Maternal complications of pregnancy	Haemorrhagic complications of pregnancy	Premature separation of placenta	1
Preg	Maternal complications of pregnancy	Hypertension associated disorders of pregnancy	Pre-eclampsia	1
Preg	Placental, amniotic and cavity disorders (excl haemorrhages)	Amniotic fluid and cavity disorders of pregnancy NEC	Oligohydramnios	1
Preg	Pregnancy, labour, delivery and postpartum conditions	Normal newborn status	Normal newborn	1
Preg	Pregnancy, labour, delivery and postpartum conditions	Normal pregnancy, labour and delivery	Pregnancy	1
Preg	Pregnancy, labour, delivery and postpartum conditions	Unintended pregnancies	Pregnancy on oral contraceptive	1
Psych	Anxiety disorders and symptoms	Anxiety symptoms	Agitation	3
Psych	Changes in physical activity	Increased physical activity levels	Restlessness	1
Psych	Deliria (incl confusion)	Confusion and disorientation	Confusional state	1
Psych	Deliria (incl confusion)	Confusion and disorientation	Disorientation	1

SOC	HLGT	HLT	PT	Number of Adverse Events
Psych	Disturbances in thinking and perception	Perception disturbances	Hallucination	1
Psych	Mood disorders and disturbances NEC	Fluctuating mood symptoms	Mood swings	1
Psych	Psychiatric disorders NEC	Mental disorders NEC	Mental status changes	1
Psych	Schizophrenia and other psychotic disorders	Psychotic disorder NEC	Psychotic disorder	3
Psych	Schizophrenia and other psychotic disorders	Schizoaffective and schizophreniform disorders	Schizoaffective disorder	1
Psych	Sleep disorders and disturbances	Disturbances in initiating and maintaining sleep	Insomnia	1
Psych	Sleep disorders and disturbances	Disturbances in initiating and maintaining sleep	Middle insomnia	1
Renal	Nephropathies	Glomerulonephritis and nephrotic syndrome	Nephrotic syndrome	1
Renal	Renal disorders (excl nephropathies)	Renal failure and impairment	Acute prerenal failure	2
Renal	Renal disorders (excl nephropathies)	Renal failure and impairment	Anuria	1
Renal	Renal disorders (excl nephropathies)	Renal failure and impairment	Renal failure	1
Renal	Renal disorders (excl nephropathies)	Renal failure and impairment	Renal failure acute	5
Renal	Urinary tract signs and symptoms	Bladder and urethral symptoms	Dysuria	1
Renal	Urinary tract signs and symptoms	Bladder and urethral symptoms	Incontinence	1
Renal	Urinary tract signs and symptoms	Bladder and urethral symptoms	Pollakiuria	1
Renal	Urinary tract signs and symptoms	Urinary abnormalities	Haematuria	2
Renal	Urinary tract signs and symptoms	Urinary abnormalities	Lipiduria	1
Renal	Urinary tract signs and symptoms	Urinary tract signs and symptoms NEC	Polyuria	1
Repro	Uterine, pelvic and broad ligament disorders	Uterine disorders NEC	Uterine haemorrhage	1
Repro	Vulvovaginal disorders (excl infections and inflammations)	Vulvovaginal signs and symptoms	Vaginal discharge	1
Resp	Respiratory disorders NEC	Breathing abnormalities	Dyspnoea	3
Resp	Respiratory disorders NEC	Coughing and associated symptoms	Haemoptysis	1
Resp	Respiratory disorders NEC	Respiratory signs and symptoms NEC	Suffocation feeling	1
Resp	Upper respiratory tract disorders (excl infections)	Nasal disorders NEC	Epistaxis	1
Skin	Cornification and dystrophic skin disorders	Hyperkeratoses	Lichenoid keratosis	1
Skin	Epidermal and dermal conditions	Dermal and epidermal conditions NEC	Skin reaction	1
Skin	Epidermal and dermal conditions	Dermal and epidermal conditions NEC	Swelling face	1
Skin	Epidermal and dermal conditions	Dermal and epidermal conditions NEC	Yellow skin	1
Skin	Epidermal and dermal conditions	Dermatitis and eczema	Eczema	1
Skin	Epidermal and dermal conditions	Dermatitis and eczema	Stasis dermatitis	1
Skin	Epidermal and dermal conditions	Erythemas	Rash erythematous	1
Skin	Skin appendage conditions	Alopecias	Alopecia	1
SocCi	Lifestyle issues	Alcohol product use	Alcohol use	1
Surg	Obstetric and gynaecological therapeutic procedures	Induced abortions	Abortion induced	1
Surg	Obstetric and gynaecological therapeutic procedures	Obstetric therapeutic procedures	Caesarean section	1
Vasc	Decreased and nonspecific blood pressure disorders and shock	Circulatory collapse and shock	Circulatory collapse	4
Vasc	Decreased and nonspecific blood pressure disorders and shock	Circulatory collapse and shock	Shock	2
Vasc	Decreased and nonspecific blood pressure disorders and shock	Vascular hypotensive disorders	Hypotension	4

SOC	HLGT	HLT	PT	Number of Adverse Events
Vasc	Vascular disorders NEC	Peripheral vascular disorders NEC	Flushing	1
Vasc	Vascular disorders NEC	Site specific vascular disorders NEC	Pallor	1
Vasc	Vascular hypertensive disorders	Vascular hypertensive disorders NEC	Hypertension	1

10.2 Results from WHO Database

Selection criteria:

Years:	2005-08-16 to 2006-05-31
Countries:	All
Drugname(s):	ORLISTAT
Reactions:	All

Number of reports in search: 142

Adverse reaction	Number of adverse events
ABDOMEN ENLARGED	2
ABDOMINAL PAIN	11
ACNE	2
ADENOCARCINOMA NOS	1
AGITATION	2
ALLERGIC REACTION	2
ALOPECIA	6
ANAPHYLACTIC REACTION	1
ANGIOEDEMA	2
ANXIETY	1
APPENDICITIS	1
ARTHRALGIA	3
ASCITES	1
ASTHENIA	4
ASTHMA EXTRINSIC	1
BREAST NEOPLASM MALIGNANT FEMALE	1
CACHEXIA	1
CARDIAC FAILURE	1
CARDIAC TAMPONADE	1
CEREBRAL INFARCTION	1
CEREBROVASCULAR DISORDER	1
CERVICAL CARCINOMA	1
CHANGE IN BOWEL HABITS	1
CHEST PAIN	6
CHOLELITHIASIS	1
CLEFT PALATE	1
COLITIS HAEMORRHAGIC	1
CONFUSION	1
CONSTIPATION	1
CONVULSIONS	3
CONVULSIONS GRAND MAL	1
COUGHING	1
CRYING ABNORMAL	1
DEATH FOETAL	1
DEPERSONALIZATION	1
DEPRESSION	2
DIARRHOEA	8
DIVERTICULITIS	2
DIZZINESS	6

DRUG ABUSE	1
DRUG EXPOSURE IN PREGNANCY	2
DRUG LEVEL DECREASED	1
DYSAESTHESIA	1
DYSPNOEA	6
EMBOLISM - BLOOD CLOT	1
EMOTIONAL LABILITY	1
FACE OEDEMA	1
FATIGUE	1
FEVER	2
FLATULENCE	2
FLUSHING	1
GAIT ABNORMAL	1
GI HAEMORRHAGE	1
GINGIVAL BLEEDING	1
GINGIVITIS	1
GLUCOSE TOLERANCE ABNORMAL	1
GOUT	1
GUM HYPERPLASIA	1
HAEMATURIA	1
HAEMOPTYSIS	1
HAEMORRHAGE RECTUM	3
HAEMORRHOIDS	1
HAIR DISORDER NOS	1
HALLUCINATION	1
HEADACHE	4
HEART DISORDER	1
HEPATIC FAILURE	1
HEPATIC FUNCTION ABNORMAL	2
HEPATITIS	4
HICCUP	1
HYPERGLYCAEMIA	1
HYPERKINESIA	1
HYPOAESTHESIA	2
HYPOGLYCAEMIA	2
HYPOKALAEMIA	1
HYPONATRAEMIA	1
HYPOPHOSPHATAEMIA	1
HYPOPROTEINAEMIA	1
HYPOTHYROIDISM	1
HYPOVOLAEMIA	1
INCREASED STOOL FREQUENCY	1
INFLUENZA-LIKE SYMPTOMS	2
INSOMNIA	2
INTESTINAL ISCHAEMIA	1
JAUNDICE	1
KERATITIS	1
LARYNX OEDEMA	1
LEG PAIN	1
LEUKORRHOEA	1
LIPASE INCREASED	1
MEDICINE INEFFECTIVE	2
MENSTRUAL DISORDER	3

MICTURITION FREQUENCY	1
MOUTH DRY	2
MULTIPLE ORGAN FAILURE	1
MYALGIA	4
MYDRIASIS	1
MYELOPROLIFERATIVE DISORDER	1
MYOCARDIAL INFARCTION	1
MYOSITIS	1
NAIL DISORDER	1
NAUSEA	2
OEDEMA MOUTH	3
OLIGOHYDRAMNIOS	1
PAIN	1
PALPITATION	3
PANCREATITIS	4
PANCYTOPENIA	1
PARAESTHESIA	3
PHARYNGITIS	1
PHOTOSENSITIVITY REACTION	2
POLYURIA	1
PRE-ECLAMPSIA	1
PREGNANCY UNINTENDED	1
PROCTALGIA	1
PRURITUS	8
PSYCHOSIS	3
PULMONARY INFILTRATION	1
PURPURA	1
PURPURA THROMBOCYTOPENIC	1
RASH	7
RASH ERYTHEMATOUS	4
RENAL CALCULUS	1
RENAL FAILURE ACUTE	1
RENAL PAIN	2
SGOT INCREASED	2
SGPT INCREASED	1
SINUSITIS	1
SKIN DISCOLOURATION	1
SKIN DRY	1
STEATORRHOEA	2
STOMATITIS	1
STRIDOR	1
SWEATING INCREASED	1
SYNCOPE	1
TACHYCARDIA	1
TASTE PERVERSION	1
TERM NOT ACCEPTED IN WHO-ART	5
TERM UNDER ASSESSMENT FOR WHO-ART	5
THROMBOPHLEBITIS DEEP	1
THROMBOSIS CORONARY	1
TONGUE OEDEMA	1
URINE ABNORMAL	2
URINE FLOW DECREASED	1
URTICARIA	5

WEIGHT INCREASE	5
VISION ABNORMAL	1
VITAMIN K DEFICIENCY	1
VOMITING	3
	274

10.3 Results from Roche Worldwide Database (SAEs only)

SOC Name	Preferred Term	Serious Unlisted AEs of Period	All AEs Period	Serious Unlisted AEs Cumulative To 31MAY2006	All AEs Cumulative To 31MAY2006
Infections And Infestations	Abscess Intestinal	1	1	2	2
	Diverticulitis	3	4	51	73
		4	5	53	75
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Adenocarcinoma	1	1	3	3
	Bile Duct Cancer	1	1	1	1
	Colon Cancer	1	1	1	2
		3	3	11	11
Blood And Lymphatic System Disorders	Anaemia	2	3	6	15
	Autoimmune Thrombocytopenia	1	1	1	1
	Haemolytic Anaemia	1	1	2	2
	Thrombocytopenia	1	1	17	17
	Thrombocytopenic Purpura	1	1	1	1
		6	7	22	36
Metabolism And Nutrition Disorders	Diabetes Mellitus	1	1	10	11
	Hyperglycaemia	1	1	3	12
	Hypoglycaemia	1	3	17	29
	Hypokalaemia	1	2	10	17
		4	7	35	69
Psychiatric Disorders	Confusional State	1	1	6	11
	Hallucination, Visual	1	1	1	1
	Psychiatric Symptom	2	2	2	2
		4	4	9	14
Nervous System Disorders	Amnesia	1	1	3	8

SOC Name	Preferred Term	Serious Unlisted AEs of Period	All AEs Period	Serious Unlisted AEs Cumulative To 31MAY2006	All AEs Cumulative To 31MAY2006
	Burning Sensation	1	2	4	18
	Cerebral Infarction	1	1	3	3
	Cerebrovascular Accident	1	1	14	14
	Convulsion	1	1	24	25
	Dizziness	1	14	13	198
	Paraesthesia	1	2	3	50
	Syncope	2	4	11	23
		9	27	77	339
Eye Disorders	Blindness	1	1	2	2
	Conjunctivitis	1	2	1	4
		2	3	3	6
Cardiac Disorders	Atrial Fibrillation	2	2	23	23
	Long Qt Syndrome	1	1	1	1
	Palpitations	1	3	9	58
	Supraventricular Tachycardia	1	1	4	4
	Tachyarrhythmia	1	1	1	1
		6	8	38	87
Vascular Disorders	Hypotension	1	3	8	19
	Pallor	1	1	3	5
		2	4	10	24
Respiratory, Thoracic And Mediastinal Disorders	Choking	1	1	1	2
	Cough	1	2	3	26
	Dyspnoea	2	8	28	120
		4	11	32	148

SOC Name	Preferred Term	Serious Unlisted AEs of Period	All AEs Period	Serious Unlisted AEs Cumulative To 31MAY2006	All AEs Cumulative To 31MAY2006
Gastrointestinal Disorders	Anal Haemorrhage	1	2	3	9
	Ascites	1	1	1	2
	Breath Odour	1	2	1	6
	Constipation	1	23	17	346
	Eructation	1	1	1	6
	Faeces Discoloured	1	5	1	82
	Gastric Ulcer Haemorrhage	3	3	6	6
	Gastritis Haemorrhagic	1	1	2	2
	Haematochezia	3	5	17	52
	Intestinal Fistula	1	1	1	1
	Nausea	2	16	20	242
	Oedematous Pancreatitis	1	1	1	1
	Pancreatic Insufficiency	2	2	2	2
	Pancreatitis	1	1	50	50
	Pancreatitis Acute	2	2	13	13
	Rectal Haemorrhage	1	5	18	98
	Swollen Tongue	2	2	1	8
	Vomiting	2	9	33	152
		27	**82**	**192**	**1078**
Hepatobiliary Disorders	Cholecystitis	1	2	23	32
	Cholelithiasis	3	3	90	114
	Hepatic Failure	1	1	8	9
	Liver Disorder	1	1	3	6
		6	**9**	**127**	**161**

SOC Name	Preferred Term	Serious Unlisted AEs of Period	All AEs Period	Serious Unlisted AEs Cumulative To 31MAY2006	All AEs Cumulative To 31MAY2006
Skin And Subcutaneous Tissue Disorders	Swelling Face	1	4	2	30
		1	**4**	**2**	**30**
Musculoskeletal And Connective Tissue Disorders	Myalgia	1	5	10	51
		1	**5**	**10**	**51**
Renal And Urinary Disorders	Renal Failure Acute	1	1	1	7
		1	**1**	**1**	**7**
Pregnancy, Puerperium And Perinatal Conditions	Pre-Eclampsia	1	1	1	1
		1	**1**	**1**	**1**
General Disorders And Administration Site Conditions	Asthenia	1	3	6	68
	Chest Pain	2	5	28	66
	Disease Progression	1	2	1	3
	Drug Interaction	5	12	58	172
	Malaise	4	6	11	73
	Unevaluable Event	1	1	1	1
		14	**29**	**105**	**383**
Investigations	Blood Amylase Increased	1	1	3	9
	Blood Creatinine Increased	1	1	1	6
	Blood Parathyroid Hormone	1	1	1	1
	Blood Pressure Increased	1	2	5	41
	High Density Lipoprotein Decreased	1	1	1	10
	Lipase Increased	1	2	4	13
		6	**8**	**19**	**80**
Injury, Poisoning And Procedural Complications	Contusion	1	1	3	22

SOC Name	Preferred Term	Serious Unlisted AEs of Period	All AEs Period	Serious Unlisted AEs Cumulative To 31MAY2006	All AEs Cumulative To 31MAY2006
	Drug Toxicity	1	1	1	1
	Fall	1	1	6	7
	Foot Fracture	1	1	1	2
		4	**4**	**11**	**32**
		105	**222**	**764**	**2632**

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/s/

Julie Golden
12/20/2006 12:25:32 PM
MEDICAL OFFICER

Eric Colman
12/20/2006 12:53:14 PM
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DNCE 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: Self-Selection Study Cyclosporin Protocol
Product/Ingredient Name: Alli (Orlistat)
Proposed Indication: Weight loss aid
Dosage Form/Route of Administration: 60 mg tablet/oral
Sponsor: GlaxoSmithKline Consumer Healthcare (GSK)
Date Submitted: May 3, 2006

Background

This meeting is intended as a follow-up to the April 6, 2006 Approvable letter for GlaxoSmithKline's (GSK) new drug application NDA 21-887 for the use of Orlistat 60 mg Capsules (Alli™) as an over-the-counter weight loss aid. The purpose of the meeting is to discuss the content of the approvable action letter for Orlistat and GSK's proposals to address the outstanding items so that NDA 21-887 can be approved.

Orlistat 120 mg (Xenical®--Roche) was approved for the prescription treatment of obesity and weight management in April, 1999 with an unlimited duration of use. On June 6, 2005, GlaxoSmithKline (GSK) Consumer Healthcare, L.P., submitted NDA 21-887 for Orlistat 60 mg capsules to be marketed over-the-counter (OTC) to promote weight loss in overweight adults, age 18 years and older, when used along with a reduced calorie, low-fat diet.

Roche previously performed an Actual Use Study (AUS), and GSK subsequently designed a new label and performed a Label Comprehension (LC) and three self-selection studies (on cyclosporine users, warfarin users, and teenagers 14 – 17 years of age). These studies were submitted to NDA 21-887 for the Orlistat switch. On April 6, 2006, GSK received an approvable action for this OTC switch application. The original proposed dosing regimen was 1 – 2 capsules (60 – 120 mg) with each fat-containing meal, up to three times per day (TID), but the Sponsor is eliminating the 120 mg dose. The current self-selection study will use a new label which directs consumers to use a single 60 mg capsule with each meal, not to exceed 3 capsules daily.

Orlistat is a pancreatic lipase inhibitor that acts by inhibiting the absorption of approximately 25% of dietary fat with a 60 mg dose. 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 draft label and the labels used in the actual use and label comprehension studies all contained a warning that stateed:
Do not use if you are taking cyclosporine (a drug given after transplant surgery).

The previous actual use study enrolled two subjects using cyclosporine, of whom 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. Based on this data, GSK conducted an **online self-selection study on 46 cyclosporine users, which showed an 89% correct self-selection rate**. A higher correct selection rate is needed since the interaction between Orlistat and cyclosporine can result in organ rejection; thus the FDA is requiring an additional self-selection study in organ transplant patients as part of a response to the AE action letter for NDA 21-887.

Summary of Key FDA Issues Identified in Action Letter

On April 6, 2006, GlaxoSmithKline (GSK) received an action letter for its new drug application for Alli™ (Orlistat) 60 mg capsules (NDA 21-887), classifying the NDA as "approvable" pending resolution of certain labeling issues. Specifically, the Approvable letter listed nine items that GSK needed to address prior to NDA approval:

1. Removal of the 6-month restriction of use and the inclusion of the concepts of goals for treatment and methods of maintaining weight;
2. Emphasis of the concepts of diet and exercise prior to the consideration of medication for weight loss;
3. Improved self-selection based on the cyclosporine warning, including understanding of any self-selection failures;
4. Improved comprehension of the multivitamin label statement;
5. Revision of the proposed dose to 60 mg tid;
6. Addition of information to help consumers identify if they are overweight, determine if Orlistat is right for them, and define an appropriate weight loss goal;
7. Increased prominence of side effects: oily spotting, fecal incontinence, and flatus with discharge
8. Addition of warning statement related to pancreatitis (if consumer has severe or continuous abdominal pain, should discontinue use and consult an MD) ; and
9. Demonstration that consumers understand the basic principles of behavioral modification and lifestyle change required for successful weight loss as communicated in the educational materials that accompany the product.

In addition to the issues noted above, the Agency provided specific comments and recommendations related to the principal display panel (PDP), drug facts labeling, and tamper-evident statement. Lastly, GSK was also requested to include a safety update as part of the response to the action letter.

GSK believes they understand the spirit and intent of the Agency's comments as reflected in the 06 April 2006 letter and agree in principle. GSK has developed labeling solutions to respond to each of the issues raised. A copy of the revised label is attached in the Appendix.

An outline the Sponsor's proposed **Self-Selection Study in cyclosporine users** follows:

TITLE: Orlistat Self-Selection Study in Cyclosporine Users
PROTOCOL NUMBER: W2900424
SPONSOR: GlaxoSmithKline Consumer Healthcare
CRO: [redacted]

Objective(s)
The primary objective of this study is to evaluate whether current cyclosporine users who are taking cyclosporine for organ transplant and who are interested in losing weight can correctly decide that OTC Orlistat is not appropriate for them to use based on their understanding of the package label and their own medical history.

Study Design
This is a self-selection study designed to understand how cyclosporine users determine whether or not OTC Orlistat is appropriate to use based on the label instructions. Subjects who underwent organ transplant and are currently receiving cyclosporine will be identified from physicians' databases of transplant patients. A flyer describing the nature of the survey and inviting the subjects to participate will be handed out to the identified subjects when the subjects visit the physicians' offices. When subjects call the phone number provided in the flyer, trained staff from [redacted] will receive the calls and screen the subjects for an interest in weight loss. To avoid introducing a bias, subjects who are interested in weight loss will be invited to participate in a survey without knowing the basis for the invitation. To minimize screening failure at the site, questions related to inclusion and exclusion criteria will be asked during the call in order to screen out subjects who do not meet the entry criteria. Subjects who are interested in losing weight and who meet the screening criteria will be asked to come to designated market research facilities to participate in a survey.

Subjects will be provided with a copy of the Drug Facts label to review and determine if the product is appropriate for them to use. Subjects will then be asked to describe the reasons behind their decisions. Subjects who indicate that the product is appropriate for them to use will be asked additional questions to clarify their understanding of the label instructions and reasoning. After that, the recruitment criteria (post transplant, cyclosporine users) will be revealed and subjects will be asked whether they are taking cyclosporine and whether they are a transplant recipient. For subjects who made an

incorrect selection, additional questions will be asked to understand reasons for their selection. Additionally, demographic information including age, gender, and race will be obtained.

Rationale for Study Design

The study population will be **50 subjects** who are 1) current cyclosporine users, 2) using cyclosporine for organ transplant and 3) also interested in losing weight, as these subjects will be a subset of intended users who will be at risk if they decide to use Orlistat. Since the study is designed to gather data on how cyclosporine users self-select based on the information provided in the OTC label, minimal entry criteria will be applied in order to mimic the non-prescription setting. Since subjects will be identified from physicians' databases based on their medical and medication histories (post transplant, current cyclosporine users), **any subject who responds that the product is appropriate for him/her to use will be regarded as an incorrect selector.** Only the product label will be used to assess self-selection; no medication will be dispensed. **Previous Xenical (Rx Orlistat) users will be included**, as their familiarity with the product may predispose them to use OTC Orlistat without carefully reading the OTC label. However, **current Xenical users will be excluded**, as their decisions will be heavily influenced by their physicians' decisions to prescribe Orlistat, and the warning conditions for Rx Orlistat are different from those for OTC Orlistat.

Inclusion Criteria

- Subject must be interested in losing weight.
- Subject must be $\geq$ 18 years of age.
- Subject must review and sign a confidentiality disclosure and study participation agreement.
- Subject must be able to speak, read, and understand English sufficiently to understand the nature of the study, and be willing, able and likely to comply with all study procedures.

Exclusion Criteria

- Subject is an employee of the sponsor or the CRO conducting the study, employee of other pharmaceutical companies, or a healthcare professional.
- Subject is currently taking Xenical (Rx Orlistat).
- Subject has participated in a web-based or marketing research survey in the past 6 months for a weight loss product.
- If the subject normally wears corrective lenses, contacts or glasses to read and does not have them with him/her. This subject can be re-scheduled if he/she is willing to come back to the site with his/her lenses, contacts or glasses.

Data Analysis

The **outcome variable** is the number of subjects who indicate that Orlistat is appropriate for them. This variable will be used to estimate the rate of correct selection.

The rate of correct selection will be computed as the number of eligible subjects who make a correct selection decision divided by the number of eligible subjects. A **one-tailed** 95% confidence interval will be computed for the true correct selection rate.

Data will be collected on paper questionnaires.

Comments

- The following statement in the flyer used for recruitment can bias results of the self-selection study and should be deleted: "It is important that the information on the label is correctly understood by the consumer so they can decide for themselves whether the product is appropriate to use." This statement cues subjects to more closely examine the label for the proper self-selection criteria.
- Prompting participants to read the entire label, and telling participants that they can refer to the label as often as they would like, and *please not to guess at the answers but instead refer back to the label*, does not simulate an actual-use situation.
- The confidentiality disclosure and study participation agreement form should be free of bias.
- Those <18 year of age should be allowed to participate.
- Statistically, a larger N is needed to provide a tighter confidence interval for the estimated proportional rate of the number self-selecting appropriately.

Label

- The warning section should include an Organ transplant alert—the alert should be broader and not confined only to cyclosporine; it should inform consumers that if they are taking cyclosporine or other immunosupressants, Orlistat can lower blood levels of the medication which could lead to transplant rejection.
- An additional statement stating that an exercise regimen should be discussed with a doctor is needed (both in the label and Read Me First—Keys to successful weight loss insert). For example, "Before starting any exercise program, check with your doctor
- "Bowel movements may be hard to control" should also be listed as a possible side effect of the product
- The Sponsor should provide data to support the label statements:
    - "**You should start to lose weight within the first 2 weeks**"
    - "These bowel changes are related to how the product works **and usually subside in a few weeks.**"
- Drug Facts information should generally be in black; it is not clear if the sponsor intends for most of the text to be grey or black. The blue part of the text is in a larger font and is more prominent by virtue of the blue color—this detracts from the rest of the label.

Note

- The label comprehension study protocol submitted by GSK is reviewed by Susanna Weiss, PhD, JD

- Responses to the sponsor's submitted questions can be found in the meeting minutes from June 14, 2006

1 Page(s) Withheld

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/s/

Linda Hu
7/10/2006 11:39:09 AM
MEDICAL OFFICER

Karen Feibus
7/13/2006 11:19:26 AM
MEDICAL OFFICER
I concur with Dr. Hu's review and comments