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*APPLICATION NUMBER:*

**21-887**

# APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-887

GlaxoSmithKline Consumer Healthcare, L.P.
Attention: Erin Oliver
Assistant Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Oliver:

Please refer to your new drug application (NDA) dated June 6, 2005, received June 7, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alli (orlistat) Capsules, 60 mg.

We acknowledge receipt of your submissions dated June 10, August 2 and 16, October 6 and 18, November 11 and 21, and December 19, 2005, and January 13, 16, 17 (3), and 31, February 6, 8, 23, and 27, and March 21 and 23, 2006.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following issues:

1. You have not adequately supported the six-month limit on the duration of use of orlistat. The current clinical approach toward drug use for weight loss does not limit the duration of therapy. Placing a duration of therapy limit on drug therapy is not consistent with current treatment standards. You supported your planned six-month limitation on use based on results from the submitted studies demonstrating that mean weight loss change plateaus at six months. However, this does not take into account that some individuals may continue to lose weight after six months and also does not take into account the possible necessity of drug therapy for weight maintenance. Consumers should understand the use of this product and these concepts without needing to talk to their physician. Limiting the duration of use to six months may mislead consumers into believing that treatment of weight loss does not require a long-term commitment to dietary intervention, lifestyle modifications, and possibly drug therapy and is, therefore, not an appropriate message.

   We do not believe it is necessary to have a duration of use limitation on orlistat. This raises some other issues in labeling regarding adequately conveying the concept of treatment toward a goal and methods of maintaining weight. This drug should not be viewed as a panacea but should provide a logical choice for consumers who have had

limited success using diet and exercise alone. If you agree to remove the six-month limitation of use, revisions to the labeling may require some additional testing for consumer comprehension.

Alternatively, if you elect to have a six-month duration of use, you will need to provide consumer comprehension and actual use data that demonstrate that consumers accurately understand this limitation and data that show what consumers may do in response to such a limitation (e.g., do they understand that they should stop at that time and, if they stop, what other measures they would need to do to forestall weight gain).

2. The proposed Drug Facts label does not adequately convey that the foundation of any weight loss program is to first emphasize an appropriate diet and exercise before medication is considered. You will need to emphasize this concept in the Drug Facts label.

3. In both the self-selection study of cyclosporine users and in the actual use study, a proportion of cyclosporine users failed to correctly determine that they should not use this product. The failure rate was slightly greater than ten percent in the self-selection study and this is not acceptable considering the possible grave consequences (organ rejection). You will need to improve the labeling to help consumers understand that orlistat must not be used if a patient has an organ transplant or is receiving cyclosporine. This may require a separate warning such as is used for the "Allergy alert". Once you have decided upon a label statement, you will need to conduct study/ies in a population of cyclosporine and organ transplant patients and achieve adequate comprehension and self-selection. For anyone who does not understand the instructions, you should be able to explain why the error occurred and make appropriate labeling adjustments to influence consumer behavior. It will be incumbent upon you to collect sufficient information from self-selection failures upon which to make rational remediation.

4. In the label comprehension study, approximately 30 % of subjects did not understand the appropriate use of multivitamins in conjunction with orlistat. Some subjects did not understand the need for multivitamins while others may have understood the need but did not understand the timing of vitamin dosing relative to orlistat dosing. It is important that you improve the labeling statement regarding vitamin use and test it in a label comprehension study.

5. We believe that limiting the dose to 60 mg three times a day is appropriate for introduction of orlistat into the over-the-counter market. Because of the safety questions related to the incorrect concomitant use with other drugs, the need for concomitant use of multivitamins, and the possible use of orlistat OTC in populations with relative contraindications, limiting the dose to 60 mg three times a day will provide a greater margin of safety. We have come to this conclusion because it has been established that the 60-mg dose causes less excretion of fat compared to the 120-mg dose. While this means some degree of decreased efficacy, it also lessens the concerns above and the likelihood of other adverse events reflective of decreased tolerability.

6. You need to provide information to consumers that will allow them to calculate their body mass index (BMI) and understand what that value means. It is not a prerequisite that they self-select correctly based on BMI but consumers should be informed when considering use of the product. The proposed label does not convey information that will help a consumer at the point of purchase determine whether they are overweight or provide information as to when to consider initiating drug therapy. It is also important that additional labeling information be provided, possibly inside the package with the educational materials, that allows consumers to determine their ideal body weight and a weight-loss goal, based on BMI.

7. The primary side effects associated with orlistat are gastrointestinal and include oily spotting, fecal incontinence, and flatus with discharge. These are the most common adverse events leading to the discontinuation of use of orlistat. It is important that consumers be aware of these symptoms. These side effects should be made more prominent in the Drug Facts labeling.

8. Pancreatitis has been reported with orlistat use. Although the relationship between orlistat and pancreatitis remains unclear, severe or continuous abdominal pain should prompt a user to discontinue use and seek medical advice. You will need to add this warning to the Drug Facts labeling. You will need to add that consumers with a history of pancreatitis should talk to a physician before use of the product.

9. It is important to provide educational materials with the OTC product in lieu of the consultation that otherwise may be provided by a health care provider in the prescription setting. Effective weight loss requires behavioral modification as well as drug therapy. The educational materials included with this application, which are the behavior modification component, should provide information on lifestyle modification that a consumer understands. However, these materials have not been tested for consumer understanding. Therefore, you will need to conduct testing that demonstrates consumer understanding of these materials.

In addition to the changes in labeling described above, the draft labeling submitted in response to this letter should address the following comments and recommendations:

**Starter Pack Labeling**

Primary Display Panel (PDP)

- In the gold box with the words "Starter Pack", we recommend including the phrase "up to 20 day supply" for the 60 count, "up to 30 day supply" for the 90 count and "up to 40 day supply" for the 120 count cartons. Also, use a larger font.
- The phrase [redacted] should be revised to read "FDA approved non-prescription weight loss drug".

Drug Facts Labeling

- Under *Purpose*, replace the "L" in "Loss" and the "A" in "Aid" with small letters (i.e., "l" and "a") in accordance with 21 CFR 201.66(d)-(1).

- Under *Use*, change "promotes weight loss" to "for weight loss".
- Under *Warnings*, add an allergy alert, which reads as follows: "Allergy alert: Do not use if you are allergic to any of the ingredients in orlistat capsules", in accordance with 21 CFR 201.66(c)-(5)-(ii)-(B). This replaces the third bullet under "Do not use" which refers to allergies to ingredients in orlistat capsules.
- Under *Warnings,* under "Do not use": Delete the third bullet about allergies to orlistat capsules. This will be replaced by the Allergy alert.
- Under *Warnings,* under "Ask a doctor or pharmacist before use if you are":
  - Make the second bulleted statement about warfarin the first bulleted statement.
  - Bold the warfarin warning statement. This and the above bullet are to address FDA's and the Advisory Committees' concerns about strengthening the warfarin labeling.
  - Revise the third bullet to read "taking other weight loss products".
- Under *Directions*, revise the first bulleted statement to read as follows: read the enclosed for important information".
- Under *Questions or comments,*

Back Panel/Right

- Revise the last sentence in the tamper-evident statement to read "DO NOT USE THIS PRODUCT IF ANY OF THESE TAMPER-EVIDENT FEATURES ARE MISSING, TORN, OR BROKEN."

**Refill Pack Labeling**

The changes recommended for the starter pack are applicable to the refill pack.

We reserve further comment on the labeling until the above deficiencies are satisfactorily addressed.

In addition, when you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Metabolism and Endocrinology Products and the Division of Nonprescription Clinical Evaluation to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

Curtis Rosebraugh, M.D., M.P.H.
Deputy Director
Office of Drug Evaluation II
Center for Drug Evaluation Research

Sincerely,

*{See appended electronic signature page}*

Charles Ganley, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation Research

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

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/s/
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Charles Ganley
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Curtis Rosebraugh
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