DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
CDER/OND/ONP

Office Director Memorandum

NDA: 21-887
Drug Name: Alli (orlistat) 60 mg Capsules
Indication(s): Weight Loss Aid
Applicant: GlaxoSmithKline
Date(s): Submitted June 6, 2005

Memo Date: April 6, 2006

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

Subject: Prescription to OTC Switch of Orlistat

Introduction

This application highlights conflicts between public recommendations on the use of drugs (pharmacotherapy) to treat obesity from the National Institute of Health (NIH)[1], FDA approval of these drugs and FDA policy on the use of drugs by an overweight population in the over-the-counter (OTC) setting. As a result, there are conflicting opinions amongst the review staff regarding the availability of OTC drug products for weight loss which are apparent in the respective reviews. This memo addresses issues raised in the reviews and provides recommendations based on my interpretation of the scientific data, the current labeling of the prescription product and past agency policy regarding availability of OTC weight control drugs. My recommendations for some of these issues are driven in part by the mechanism of action and the intrinsic safety of orlistat. Because of the difference in intrinsic efficacy and safety between ingredients, each application leads to different interpretation of the benefit/risk assessment. But, for applications seeking this OTC claim, FDA should be consistent on general policy issues related to the marketing of OTC weight loss drugs.

Orlistat (Xenical) is a lipase inhibitor that acts by inhibiting the absorption of fats. It is indicated:

- For obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet;
- To reduce the risk for weight regain after prior weight loss;
- For obese patients with an initial body mass index (BMI) $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).[2]

The recommended dose is 120 mg three times per day with each main meal containing fat. Patients should be on a nutritionally balanced diet that contains approximately 30% calories from fat.

The sponsor has proposed an initial OTC dose of 60 mg three times per day which can be titrated to 120 mg three times a day based on effectiveness for an individual consumer. The labeling suggests use for up to six months after which the user should talk to their doctor.

It is important to note that the orlistat OTC program changed sponsors in the midst of development. Roche originally was directing the OTC product at an overweight, but not obese population, proposing a 60 mg dose three times a day. They were asked by FDA to justify why the 120 mg dose three times per day could not be OTC and were encouraged to consider the 120 dose unless safety issues preempted consideration of it. Additional efficacy studies were conducted at the request of FDA in subjects with a BMI of 25 – 27 kg/m^2 because Roche was primarily targeting this population. They also initiated an actual use study to determine whether subjects could self select to use the product based on labeled limitations. Glaxo Smith Kline entered

1 Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adult, NIH publication 90-4083s, September 1998

2 The World Health Organization has defined obesity as a BMI > 30 kg/m^2.

the picture after these studies were completed and redefined the population to include any person who is overweight. The indication would now include anybody overweight with a BMI > 25 kg/m^2.

A joint advisory committee of the Endocrine Metabolism and Nonprescription committees was convened on January 23, 2006 to consider the switch of orlistat. The committee supported the switch and provided comments that warrant additional consideration prior to final approval.

This memo is not a comprehensive summary of the data. It will address issues raised in the reviews and assess whether sufficient efficacy and safety data has been provided. I refer you to the division memos for more comprehensive explanations of the data. This memo will (1) provide a recommendation for regulatory action; (2) describe deficiencies in the application; and, (3) provide a discussion of important issues.

Recommendation for Regulatory Action

The application is approvable. The deficiencies listed below require resolution before the application can be approved.

Deficiencies

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 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

A. <u>Is weight loss an acceptable OTC claim?</u>

There are two relevant FDA rulemakings that address this issue: (1) the advanced notice of proposed rulemaking (ANPR) of OTC weight control products published in 1982 (47 FR 8466); and (2) the final rule for dietary supplement structure function claims published in 2000 (65 FR 1000).

In the ANPR for OTC weight control products, the Advisory Review Panel on OTC Miscellaneous Drug Products recommended conditions under which OTC weight control drugs are generally recognized as safe and effective. Most of the discussion in this notice revolved around appetite suppressants. The following positions are stated:

- the use is directed at an obese population (47 FR 8466 @ 8472);
- significant weight loss can be achieved only if accompanied by a reduction in daily caloric intake (47 FR 8466 @ 8472);
- only intended for temporary use, no more than 3 month duration (47 FR 8466 @ 8473);
- the indications focused on the effect, such as "For appetite control to aid weight reduction", and not on the populations to be treated (47 FR 8466 @ 8476);

- labeling that includes the statement "This product's effectiveness is directly related to the degree to which you reduce your usual daily food intake." (47 FR 8466 @ 8476).

There are some positions in the notice that are outdated. The most glaring is the limitation of use to three months. During the 1990's, there was an evolution in thinking about the use of drug therapy for weight control. Rather than being a short term therapy to evoke permanent changes in behavior, it may be considered for long periods of time (e.g., years). The one prominent position that is still relevant today is the emphasis on diet as a mainstay of effective weight control and the importance of including this information in the labeling. Consumers should not be lead to believe that the drug therapy alone is sufficient to have successful weight loss.

The second document that has some relevance is the final rule for dietary supplement claims. The rule has a discussion on the agency position of weight loss and obesity claims. Weight loss is a structure function claim and obesity is a disease claim (65 FR1000 @ 1026 - 1028). A structure function claim for weight loss is an acceptable claim for dietary supplements but disease claims are not. Drug products can also have structure function claims. The rule recognizes the close relationship between the claims for dietary supplements and drug products as evidenced in this statement, "Structure/function claims under section 403(r)(6) of the act are closely related to structure/ function claims under 201(g)(1)(C) of the act and therefore should encompass weight loss claims". A claim such as "use as part of your weight loss plan" is an acceptable structure function claim. There is one statement that adds some confusion to this issue. "Being overweight, i.e., being more than one' ideal weight but less than obese, however, is not a disease. FDA believes that it is commonly understood that "weight loss plans" relate to a broad range of overweight statuses." This seems to suggest on one hand that being overweight is less than obese and on the other "weight loss plans" cover a **broad** range (emphasis added) of overweight statuses but are not so narrowly associated with a disease.

Based on the discussion in both of these documents, the agency will consider weight loss or obesity as acceptable claims in an over-the-counter setting. Weight loss is a structure function claim (permitted for dietary supplements and drugs) whereas obesity is a disease claim (drugs).

B. Is weight loss in an overweight population who is not obese (BMI > 25 but < 30) "cosmetic" weight loss?

The terminology "cosmetic" weight loss was used in the NIH guideline on the treatment of overweight and obesity[3] and repeated in some of the reviewer's memos. In the guideline, it is used mainly in the context of describing the weight loss in subjects who fall under or outside the recommended body mass index range when pharmacotherapy should be considered ($\geq$ 30 kg/m^2 with no concomitant risk factors or diseases or $\geq$ 27 kg/m^2 obesity related concomitant risk factors as specified in the guidance). The use of this terminology is short sighted for the following reasons:

1. The guideline discusses the importance of losing weight because the risk for developing various illnesses is increased at BMIs of 25 kg/m^2 and above. To suggest that it is "cosmetic" if a drug is used but it is not if a behavior modification program is used is illogical. If weight lose in the 25 - 29.9 kg/m^2 range (and no underling comorbidities) is cosmetic, then it should be considered so regardless of the method by which it is achieved.
2. It does not account for people in this weight range who have conditions other than cardiovascular disease, lipid disorders or diabetes mellitus who are impacted by being overweight (e.g., degenerative arthritis). These folks are likely to benefit even from weight loss of ten pounds.
3. It suggests that for someone with no comorbidities who starts at a BMI of 31 kg/m^2, any additional weight loss after they get down to less than 30 kg/m^2 is cosmetic weight loss.
4. It underestimates the psychological impact that excessive weight has on some people.
5. People in the BMI range of 25 to 30 kg/m^2 are at risk to become obese.

It is important that FDA not adopt this terminology in describing the overweight population. FDA should be open-minded about the treatment and prevention of the overweight population with drug therapy. The relative risks for Type 2 diabetes, hypertension, and coronary heart disease increase in this weight range [4].

---

[3] Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adult, NIH publication 90-4083s, September 1998

[4] NEJM 1999;341(6):427 - 434.

C. Should the NIH guideline recommendations for pharmacotherapy serve as basis for FDA in determining which populations should be considered for drug therapy in the over-the-counter setting?

The current NIH guidelines are deficient and should not be considered the benchmark for FDA in determining the populations to be treated with drug therapy in the over-the-counter setting.

1. The major deficiency is that they do not take the intrinsic efficacy and safety of a drug into account when considering the population who should take it. If a drug has an innocuous safety profile, it should be something to consider in an overweight, non-obese population who is failing behavior modification. The intrinsic efficacy and safety of a drug has to be considered when identifying an appropriate population for use and this is lacking in the NIH guidelines.
2. They weight ranges for use of pharmacotherapy are arbitrary. There is no rationale provided that explains how the limits for pharmacotherapy were derived.[5]
3. It limits therapy to only those who are already obese or developed a weight related disease. When a person reaches either of these milestones, then we have waited too long. If a drug is safe enough, and someone continues to gain weight despite attempts at behavior modification, drug therapy should be an option. We shouldn't wait until they reach the criteria for obesity.
4. It does not recommend drug therapy for someone who has an underlying illness (e.g., hypertension) and a BMI of 26 kg/m^2. How is this person much different from someone with hypertension and a BMI of 27 kg/m^2 (which fulfills the guideline weight criteria for pharmacotherapy)?
5. There is minimal discussion of pharmacotherapy for weight loss in the over-the-counter setting. According to the guideline, the use of pharmacotherapy depends on delivery by a "practitioner". In an ideal world, it might be preferable to have strict oversight by a healthcare provider. The delivery of health care is not ideal and many physicians do not have the time to spend with patients for weight counseling. In this case, perfection is the enemy of the good. The percentage of the population who is identified as being obese continues to rise. If weight loss is to be managed only under the guidance of a physician, then the battle against obesity is already lost.

D. Has the sponsor provided adequate data to support the efficacy of the ingredient in the population likely to use it?

If the drug receives a general claim for weight loss, the population of users is likely to include subjects with a BMI of 25 – 29.9 kg/m^2 (overweight) and > 30 kg/m^2 (obese) with or without comorbidities. Study BM14149 and NM14161 support the efficacy of orlistat 60 mg and 120 mg administered three times per day at 6 months in people with BMI $\geq$ 28 kg/m^2. Study BM14149 enrolled subjects with a BMI of 28 – 43 kg/m^2 and included an intensive behavior modification program. Study NM14161 enrolled subjects with BMI > 30 kg/m^2 and had minimal behavior modification compared to study BM 14149. Despite the difference in behavior modification, the drug was able to demonstrate a significant treatment effect. The average weight loss was slightly greater in the study that included more extensive behavior modification (BM14149) but the drug treatment effect was greater in the study with less extensive behavior modification (NM14161). This supports the notion that the less someone would adhere to a diet, the greater the treatment effect of the drug. This would be expected given the mechanism of action of orlistat.

Roche conducted a 4 month efficacy study, NM17247, which included subjects with a BMI of 25 - < 28 kg/m^2. Subjects were randomized to placebo or orlistat 60 mg three times per day. The percentage of subjects who achieved a 5% decrease in weight was 27% (53/195) for placebo and 36% (71/196) for orlistat (p = 0.065, Fisher's Exact test)[6]. Ten percent of the orlistat subjects achieved a 10% weight loss. This was approximately double the percent of placebo subjects.

The mean change in weight for orlistat differed by only -1.1 kg compared to placebo (p= .0002) in NM17247. The statistical reviewer raises the issue of whether this mean difference is clinically meaningful. This is a valid question. But, it should be noted that the placebo subtracted mean change in studies NM14161 and BM14149 was -2.0 and -1.5 kg respectively, not exactly awe-inspiring. For these types of studies, it is better to conduct categorical analyses such as the 5% weight loss, to better assess the impact of the drug on individuals. When the results from study NM17247 are compared to the data from the long term studies BM14149 and

[5] Mike Weintraub, a panel member and FDA employee while on the panel, confirmed that pharmacotherapy recommendations were arbitrary. [personal communication: 3-24-06]

[6] Statistical review page 15

NM14161, the comparison provides some comfort that the results are similar. At 4 months, the average percent weight change with 60 mg of orlistat was -4.2% in NM17247, -3.3% in NM14161 and -3.95% in BM14149. It should be acknowledged that study NM17247 did not have a placebo run-in period during which patients generally lose weight. They are then usually randomized after their weight loss plateaus. This design could inflate the total weight loss attributed to diet plus drug which would permit them to more easily meet the 5% weight loss analysis. This design could also inflate the effect attributable to diet or other behavior measures. I think this is evident in the placebo group of study NM17247 where 29% of the subjects achieved a 5% weight loss at 4 months. This compares to 14% and 20% in the placebo groups for NM14161 and BM14149 respectively.

There was some concern that the empirical data provided for the population with a BMI of 25 - 27 kg/m^2 was not sufficient to support efficacy. I believe the data in study NM17247, and the similarity of it to the data in studies BM14149 and NM14161 at a similar point in time (4 months), provides sufficient evidence to support efficacy in people with BMIs in the 25 – 27 kg/m^2 range. It is also important to note that orlistat is currently approved down to 27 kg/m^2 even though there was no evaluation in people with BMIs of 27 kg/m^2 in the prescription approval. I believe we have already crossed this bridge because of the current labeling of prescription orlistat. Patients are instructed to continue to use the product even as their weight decreases through the 25 – 27 kg/m^2 range. If we don't believe that orlistat is efficacious in this BMI range then the prescription labeling should be reassessed.

E. Is the 6 month limit on use adequately supported in the application?

The sponsor proposed a limit of 6 months of use after which the consumer should contact their doctor for advice. They decided on a finite duration of use based on the Panel's recommendation of 3 months in the 1982 ANPR. But, instead of 3 months, the sponsor chose 6 months because the mean change (decrease) in weight in studies Bm14149 and NM14161 appears to plateau at 6 months. They surmised that consumers would not lose additional weight on therapy.

Their proposal of 6 month duration of use is not supportable at this time. There has been a shift in thinking to more chronic therapy in the management of overweight and obese individuals since the 1982 report. Prescription therapies are currently approved as chronic therapies and as such are studied over several years. A limit on duration of use in the OTC setting is not desirable for the following reasons:

- The mean change in weight is not a good surrogate for the effect in individual subjects. There are likely to be consumers who will benefit from continued use of the drug past 6 months and it not clear why they should have to discuss continued use with their doctor.
- The limit on duration will lead some consumers to believe that short periods of intermittent drug use are the best way to manage weight. Evidence suggests that weight will increase once orlistat is discontinued. We should not be encouraging this type of behavior by placing an artificial limit on the duration of use. This is not consistent with current recommendations for weight control where emphasis has been on chronic treatment whether it is behavior modification or drug therapy. For the OTC setting, a drug should be safe for long term therapy.
- We should recognize that some people are likely to use it chronically despite the labeling. The decision on approvability should take this into consideration. If the sponsor is convinced it should only be used for 6 months then they should provide data that demonstrates consumers will follow these directions.
- Success should be determined by achieving a goal. The limit on duration of use deemphasizes a goal oriented approach. Additionally, in the label comprehension study, approximately 25% of subjects[7] did not understand the label instructions about what should be done if goal weight was not met after 6 months.

Because weight management requires a long term approach and drug therapy in the prescription setting is generally viewed as chronic, a similar approach should be applied to the OTC setting. So, the intrinsic safety of the drug should be such that it can be considered for long term use in the OTC setting. If safety considerations would necessitate a limited duration of use, then a sponsor should establish that consumers will follow the limitations.

If orlistat is labeled for chronic use, the 60 mg three times a day dose proposed in Dr. Rosebraugh's memo is acceptable.

[7] Page 33 of Dr. Weiss review

F. Should the sponsor be required to conduct a study that establishes efficacy in the OTC actual use setting?

The efficacy of orlistat has already been established by the studies submitted. There were various levels of educational material or intervention provided in the efficacy studies and in each study orlistat demonstrated a treatment effect. Based on the mechanism of action of the ingredient, this observation is not surprising. We cannot require that educational materials be effective or be used in an OTC product because the current prescription label does not require that an effective, specific behavior modification plan be initiated when orlistat is prescribed by a physician. Although some physicians may be diligent in providing information, it has not been documented to be the case nor has the effectiveness of a specific program been a prerequisite for approval of a weight loss drug.

G. Should the sponsor be required to include educational information to the consumer?

Although educational materials are not provided with the prescription product, it is important to provide them with the OTC product in lieu of advice that may be provided by a health provider in the prescription setting when orlistat is prescribed. There is likely a wide range of advice provided by prescribers, from none to active participation in behavior modification. There should be some assurance that the materials provided with orlistat are useful and understood. The education materials need to emphasize the importance of diet and exercise in maximizing weight loss and discourage reliance on drug therapy alone. Among those who used the educational material in the actual use study, approximately 80% found it useful. But, the percentage of users of the individual pieces ranged from 31% to 64%. These are not overwhelming numbers given that the labeling should emphasize the importance of behavior modification.

Twenty percent of the participants in the actual use study were not following any kind of diet at day 14 and the percentage increased to forty percent by day 90. No explanation for this decline is provided. This may be as good as what occurs in the prescription setting. But, it is important to attempt to understand why adherence to a diet declined and whether something can be done to improve compliance with diet. Maximal benefit is likely to occur if users follow a diet and exercise regardless of its method of distribution.

It is important to determine what educational material is needed and how use of the material can be maximized and understood. Based on the results from the actual use study, it would lead one to believe that people did not understand the importance of diet and lifestyle modification. The educational material provided with the starter kit has not been tested so we do not know if it will be understood. It will also be helpful to determine if there are ways to enhance the use of the materials. Additional consumer behavior testing of this material is warranted.

H. Has the sponsor provided sufficient information to warn consumers to not use the product with cyclosporine?

The current prescription labeling for orlistat permits concomitant use of cyclosporine and orlistat if the dosing is separated by two hours. There have been several cases of organ rejection reported with concomitant use. In the OTC setting, cyclosporine should not be co-administered with orlistat. The data from the actual use study for multivitamin use with orlistat, where there was a two hour window between dosing, has already established that consumers will have difficulty with these directions. Taking a multivitamin is much different than taking cyclosporine, so there should be labeling that reinforces that they should not be used together.

The sponsor conducted a self-selection study in patients on cyclosporine. Of forty-six cyclosporine patients enrolled, five subjects erroneously felt it was appropriate to use cyclosporine with orlistat. Three of the patients did not see the restriction. Information was not available for the other two. The information on cyclosporine was located in the Do Not Use section of labeling. This failure is unacceptable and the sponsor will need to make this restriction more prominent even to the point of making it a separate warning similar to an "Allergy alert". The sponsor will need to restudy revised labeling in a similar number of patients on cyclosporine and determine whether there is improved self-selection. They will need to be very successful and collect information on failures that help to identify the source of confusion.

It is not clear whether tacrolimus, another drug used by patients with organ transplants, interacts with orlistat. Absorption of tacrolimus decreases when administered with high fat diets. Because information on possible interaction with orlistat is unknown, it is probably best that any organ transplant recipient refrain from using orlistat. Drug Facts labeling should reflect it.

I. Are there populations who should not use OTC orlistat without the supervision of a doctor?

The following populations were identified in the reviews to have either absolute or relative contraindications for use of orlistat in the OTC setting:

- Cyclosporine users or have a history of organ transplant;
- Pregnant or breast feeding;
- Diabetics on diabetes medicine;
- History of gallbladder disease;
- Warfarin users;
- Anyone under 18 years of age;

I agree that these populations should be identified in the labeling as having a relative or absolute contraindication for use and should seek the advice of a doctor.

J. Is use of the product in the < 18 years of age population acceptable?

The prescription labeling already describes a study that establishes the safety and efficacy of orlistat. The sponsor does not plan to label for use in this population. The Division of Pediatric Drug Development recommended against labeling for use less than 18 years of age because this population should have a work-up by a health provider to determine if there are secondary causes of obesity for an individual patient. They also have concerns about vitamin deficiency in a population who is in the growth phase of development. Labeling should be limited to adults 18 or over but I do not have significant concerns about the issues related to vitamin deficiency. Sub-clinical vitamin deficiency is identified in 1% or less of subjects evaluated in clinical studies and it does not appear to pose a significant problem even if some adolescents less than 18 use the product.

In addition, I am amendable to granting a waiver for any additional pediatric studies in all pediatric populations. The 120 mg dose has already been established to be safe and effective in children 12 – 17 and adults. Studies in adults have established the safety and efficacy of 60 mg three times a day. I believe the 60 mg efficacy data from adults can be extrapolated to children 12 – 17.

K. Are consumers adequately warned about the most common side effects associated with the use of the product?

Gastrointestinal symptoms are the most common side effects associated with use of orlistat. The proposed labeling is nebulous in describing these symptoms. Given that gastrointestinal symptoms were the primary reasons users discontinued orlistat in clinical studies, it is important to convey some of these symptoms to consumers in the Drug Facts label. The Advisory Committee emphasized that consumers should be aware of the consequences of taking the medicine. The proposed Drug Facts labeling is not adequate in conveying this message.

L. Is there sufficient information provided so that a consumer can identify whether they are overweight and is this necessary for the marketing of an OTC weight loss drug?

In the actual use study, 92% of the subjects who enrolled were overweight or obese. This was accomplished without any information in the Drug Facts label to guide them. The proposed label gives no information that will help a consumer determine whether they are overweight and by how much. Despite the success with self-selection in the actual use study, it is important to have some information available at the point of purchase that will help people determine their weight status based on BMI. They can choose to use this information or not. It is not a prerequisite that they self-select correctly based on BMI but it may be helpful for some who are considering use of the product.

It is important that information be provided that allows consumers to determine their ideal body weight based on BMI. This will allow them to determine weight loss goals. Much of this information can be provided on the inside of the package.

M. Are there any other safety issues to be concerned about?

Pancreatitis has been reported with orlistat use. Relative to use, the cases are infrequent. Although it is not clear if there is an association between orlistat use and pancreatitis, severe or continuous abdominal pain should prompt a user to discontinue use and seek medical advice. Also, until this is further clarified, consumers with a history of pancreatitis should not use the product unless they talk to their doctor first. The Drug Facts label should be revised accordingly.

Concerns about the interaction of orlistat with warfarin are raised because of the possible decrease in the amount of vitamin K absorbed by an individual. This could lead to an increase in the International Normalized Ratio (INR) while on the same dose of warfarin. This is not cause for great concern because it will not happen immediately. The INR for people on warfarin is measured on a monthly basis so any changes related to decreased availability of vitamin K will be detected by blood testing and permit an adjustment in warfarin dose. So, standard warnings about warfarin interaction can be included on the labeling similar to other OTC products.

The clinical significance of an interaction between orlistat and amiodarone is less clear. There is one report (J Clin Pharmacol. 2003 Apr;43(4):428-35.) of decreased Cmax and AUC for amiodarone when it is administered with orlistat. This, however, was a short term pharmacokinetic study. The relevance of this result is unclear because amiodarone has a very long half life, has variable bioavailability between individuals, and has a food effect (high fat diet) for both Cmax (increase by 3.8 fold) and AUC (increase by 2.3 fold) after a single dose. Amiodarone is not a labeled interaction in the prescription labeling. Labeling for an amiodarone interaction may not be warranted at this time.

N. Is the name Alli acceptable?

The Division of Medication Errors and Technical Support (DMETS) recommended that the brand name Alli should not be permitted. The methodology used by DMETS to assess the suitability of the name is more applicable to prescription names. The information they provided is not sufficient to prevent use of the name Alli on the OTC product. The brand name Alli is acceptable because it does not appear to be misleading or imply any claim. Although there may be some similarity to the brand name "Aleve", they are different dosages and they are used for different conditions. It would be a concern if both were intended for the same indication. DMETS also expressed concern about the availability of an OTC and Rx product with the same ingredient. In this situation, even if someone would to use the OTC and prescription products simultaneously, the primary side effect may be increased gastrointestinal symptoms. It is clearly not life threatening.

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

/s/

Charles Ganley
4/6/2006 10:03:19 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, April 04, 2006
NDA:	21-887
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSK)
Proprietary Name:	Alli (orlistat)
Author:	Curtis J. Rosebraugh, MD, MPH, Deputy Director, ODE II

To orient the reader I have organized my review into three main sections in the following order:

A. Executive summary
1. Introduction
2. ODE II recommendations including:
    a) Labeling
    b) Dosing
    c) Required studies
    d) Summary
3. Planned Action

B. Detailed review of application
1. Efficacy
2. Safety
3. Actual Use Study (AUS) and Label Comprehension Study
4. Summary of Advisory Committee Vote

C. Discussion of Divisional Recommendations
1. Introduction
2. Response to the Division of Metabolism and Endocrinology Products (DMEP) comments
    a) Target Population*
    b) Duration of Use
    c) Safety
    d) Educational program
    e) DMEP recommendations

* Note these headings correspond to the sections of the divisional review to which I'm making comments.

3. Response to the Division of Nonprescription Clinical Evaluation (DNCE) comments
    a) Efficacy*
    b) Safety

c) Labeling

*Dr. Segal has not organized her review into sections but comments on these three issues.

A. EXECUTIVE SUMMARY

Introduction

The decisional authority for this application was delegated to me by Dr. Robert Meyer, the Director, Office of Drug Evaluation II.

This is the first review cycle for the potential Over-The-Counter (OTC) marketing of orlistat, NDA 21-887, a pancreatic lipase inhibitor used for weight loss. The intended population is in overweight adults (self-identified by consumer) ages 18 years and older, and the dosage proposed is one to two 60mg capsules three times a day, taken with fat containing meals. For this application, the sponsor has submitted efficacy and safety data (studies NM14149 & 14161- both studies containing 60mg and 120 mg arms) from the original application for orlistat as a prescription (Rx) drug, as well as new studies that include an efficacy study (NM17247) in an overweight population and a label comprehension and actual use study (NM17285). Safety was also supplemented with post-marketing data from the FDA adverse event reporting system and published literature. Presently the prescription indication states: *Xenical (orlistat) is indicated as prescription therapy for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss. XENICAL is indicated for obese patients with an initial body mass index (BMI) >/=30 kg/m^2 or >/= 27 kg/m^2 in the presence of other risk factor (eg, hypertension, diabetes, dyslipidemia). The recommended dose of XENICAL is one 120-mg capsule three times a day with each main meal containing fat. Because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counseled to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition.*

The labeling included with the NDA for OTC are requesting that the 'use section' state: *promote weight loss in overweight adults when used along with a reduced calorie and low fat diet.*

The Division of Metabolism and Endocrinology Products (DMEP) and The Division of Nonprescription Clinical Evaluation (DNCE) have both agreed that this application should receive an Approvable action, but have recommended different requirements for remediation. The greatest issue of disagreement is that DMEP feels a study demonstrating ***effectiveness*** (although DMEP is calling it an ***efficacy*** study) in an OTC environment is required whereas DNCE does not. I will address this issue in detail in the 'Discussion of Divisional Recommendations' section in my review of the application.

ODE II Recommendations

Labeling

As I discuss in detail below, I feel that the label at the point of purchase should indicate that subjects with a BMI of >/= 27 kg/m^2 will derive the best results with this product. I think this product should not have a duration of use limitation, but should be considered for chronic therapy. Otherwise, the sponsor must submit justification as to why short-term weight loss and a

limited duration of therapy fits into existing treatment paradigms. The label at the point of purchase should indicate not only that this product may be used chronically, but that stoppage may result in weight regain. The sponsor may want to indicate, in the internal labeling, that subjects can try to stop the drug to see if they have weight regain, but for purposes of informing consumer's purchasing, the consumer should be aware that this drug, most likely, will only work while being taken. The sponsor has not documented that the labeling contained within the package is understood by consumers. As such, they must still demonstrate that consumers understand the 'behavioral' component of the proposed program.

I continue to have concerns with the cyclosporine co-use issue and the sponsor needs to demonstrate that the use of orlistat with cyclosporine can be minimized in an OTC environment. The sponsor will need to demonstrate near perfect comprehension of this issue, and in reality this warning should broadly target transplant recipients, not just people using cyclosporine, as the absorption of tacrolimus, an immunosuppressant also used organ transplant, could be affected by orlistat since dietary fat affects its absorption. Instead of merely targeting an arbitrary label comprehension limit to achieve regarding cyclosporine use, I believe the sponsor should be informed that if orlistat were ultimately to achieve OTC marketing, reports of organ loss because of consumer co-administration could cause reevaluation of whether orlistat remains appropriate for the OTC market. This should provide the sponsor with motivation to continuously work to affect consumer behavior even after receiving marketing approval, not just as part of some threshold for marketing. We do have to recognize that drugs in the OTC market do carry risks (analgesics as an example) and that mistakes and severe adverse events do happen with OTC drugs. If we set as a hurdle that drug use in the OTC setting must be without potential for interactions or severe adverse events in order to be marketed OTC, there would be very few drugs available to consumers as virtually all OTC drugs have risks. We also have to recognize that co-administration of orlistat and cyclosporine is occurring now, even with the drug under physician prescribing. As such, we should not expect perfect use in the OTC setting, but rather well-informed use.

Dosing

I think the dosing levels for this drug in the OTC setting needs to be revisited. The sponsor originally wanted to limit dosing to 60mg tid. This amount was increased by the sponsor at the urging of the Agency, despite the Agency's own safety concerns (vitamin, cyclosporine, and other drug interactions). While reviewing the efficacy and safety data, efficacy for the 60mg dose was established, although it did not appear quite as good as the 120mg dose. The adverse events and tolerability issues that limit use of the product are fewer with the 60mg dose as compared to the 120mg dose. Further, the drug interactions/vitamin deficiencies we are concerned about occur as a consequence of diminished fat absorption, which is greater with the 120mg compared to the 60mg dose. As such, I would advocate that initial marketing should be limited to 60 mg until an adequate safety profile is developed that may allow marketing of 120mg. This is very consistent with how the Agency has introduced other new drug categories into the OTC market (analgesics, H2 blockers etc.).

A consequence of this recommendation, but by no means the reason to advocate for it, is that we would no longer have to address whether the current Rx marketing would violate Durham-

Humphrey if orlistat is moved to OTC status, since there would be a different dosage for OTC use as opposed to the Rx. This would also allow consumers dissatisfied with the OTC product to see the health care provider and obtain a stronger dosage form, perhaps with a different form of behavior intervention.

Required studies

DMEP is requesting a study to demonstrate drug effect in an OTC setting. Their concept of this study is to randomize consumers who have elected to take the product to either drug or matched-placebo without controlled conditions (but rather just with the proposed labeling) and then checking the consumer 6 months later to see if the drug had a greater effect than placebo. If this were to be conducted in the Rx setting, it would be analogous to randomizing patients whose physicians were going to prescribe orlistat in actual clinical practice to drug or placebo without a formal protocol and then following up the patients in 6 month. I have discussed this in greater detail under the 'Educational program' section of my response to DMEP, but in essence, DMEP is requesting a clinical **effectiveness** study (not a clinical efficacy study) as this design lacks the **'control'** component of an efficacy study and therefore tests more than ideal drug action. I do not agree with this recommendation because:

1) The efficacy of orlistat has been clearly documented.
2) It is not consistent from a regulatory standpoint to place different requirements for demonstrating a drug effect merely because of the mode of distribution (Rx vs OTC)
3) Orlistat presently is not labeled for Rx use with a behavioral modification program. The only instruction for physicians is to use as part of a diet. This concept can probably be transferred to the OTC environment.

I also do not think an AUS study is necessary, unless we have a specific issue that needs addressing for which an AUS is the necessary study type. Having said that, I am receptive to further discussion on the possibilty of an AUS, if an adequate explanation can be made to me as to what data are needed and why an AUS is necessary to provide those data.

Most of the concerns I outlined throughout my review can probably be addressed with label comprehension and self-selection studies.

Summary

I think weight loss is an OTCable indication, and I believe that orlistat can eventually be approved with changes discussed. I also think that consumers trying orlistat 60mg OTC that do not receive acceptable results can see their physician for a higher strength of orlistat or be placed on some other medication, along with what ever behavior modification plan that particular physician has at hand (if any).

I think from a pragmatic standpoint, although not the basis for a regulatory decision, we cannot be totally insensitive to the fact that there is a demand for readily accessible weight loss products in the population. The sponsor presented data that over 1 billion dollars a year is expended by the US population for dietary supplement weight reduction products, for which we do not have

knowledge regarding the safety or efficacy knowledge. It would be nice to provide consumers with a product for which the safety and efficacy has been defined and where the safety is quite favorable. I also suspect that in reality, there will be a modest OTC population that find orlistat effective and sufficiently tolerable. For the remaining consumers that try the product, there will be little perceived benefit and they will simply not continue to purchase the drug. I also suspect that the true value of orlistat is in its ability to act as a deterrent to eating a fat laden and therefore calorie dense diet, because of the socially unacceptable side-effects that result should the user show dietary indiscretion.

Planned Action

This application is **approvable** based on the issues discussed below.

1. The sponsor submitted a label that limits use of the product to 6 months. However, the approach toward drug therapy for overweight/obesity treatment has undergone an evolution such that drug therapy should be considered for chronic use for weight loss and maintenance of weight loss.[1] The sponsor has not provided neither adequate justification for limiting therapy to 6 months nor adequate directions to guide consumer's actions during and after the 6 month course of therapy.

2. If the sponsor can provide justification for a 6-month limitation, the actual use study was not of long enough duration to adequately predict consumer behaviors or use of the product after a 6-month interval.

3. The sponsor has not adequately communicated to consumers at the point of purchase that the effects of the drug are only demonstrated during use of the drug.

4. The sponsor has not adequately conveyed to consumers what 'overweight' means or that users with a Body Mass Index (BMI) ≥ 27 kg/m^2 should expect the greatest benefits or can self-identify.

5. The sponsor should reconsider whether to include a dosing recommendation that includes the 120 mg dose. I believe that for introduction to an OTC environment, the optimum risk/benefit ration would be accomplished by limiting the dosing to 60 mg TID.

6. The sponsor has not provided evidence of consumer comprehension of the supplemental behavioral labeling materials.

7. The sponsor has not demonstrated adequate use of multi-vitamins during the actual use study according to the labeled instructions. Alternatively, the sponsor has not adequately demonstrated that multi-vitamin use is not necessary during therapy with orlistat. The sponsor could consider co-packaging vitamins with this product.

[1] The practical guide identification, evaluation, and treatment of overweight and obesity in adults. NIH Publication Number 00-4084; October 2000.

8. The sponsor has not demonstrated that subjects taking medications for post-solid organ transplantation (cyclosporine) correctly decide not to use orlistat.

9. The sponsor should indicate at the point of purchase that soiling of undergarments may occur.

B. DETAILED REVIEW OF APPLICATION

Background

I refer the reader to reviews by Drs. Golden, Colman, Parks, Feibus, Leonard-Segal and Joy Mele, Arlene Solbeck and Suzanna Weiss for specific details of this application. Orlistat is a lipase inhibitor that acts by blocking triglyceride absorption in the stomach and small intestine with minimal systemic absorption of the drug itself. Orlistat 120 mg (NDA 20-766) was approved as a prescription product in April, 1999, and product development for OTC marketing originally began in 2001 (IND 62,758) by Hoffmann-La Roche, Inc. At that time, the sponsor was trying to carve out a population defined as a BMI 25-27 kg/m^2 and 27-30 kg/m^2 without co-morbidities (a population considered by the Agency a 'cosmetic' weight loss category) that would not be included in the Rx indication. This would have limited OTC to those individuals with a BMI</= 30 kg/m^2. If the sponsor would have considered the same indication and dose as that being used in the Rx market, the Durham-Humphrey Amendment would have mandated a "switch" of the product from Rx to OTC status. As such, I suspect that the sponsor was targeting the described population in order to also allow continued prescription marketing of their product as well as adding the product to the OTC market. It should be noted that at meetings occurring during this time, the Agency was inquiring why the 120 mg dose and indication was not being considered for OTC marketing and probably gave the impression that the Agency wondered why a full 'OTC switch' was not being considered.

For their program, the sponsor at that time performed a 'pilot' 12-week actual use study (AUS), which is the actual use study submitted for this application. Labeling for this AUS targeted an overweight but not obese population (normal defined as a BMI of 18.5 – 24.9 kg/m^2, overweight as a BMI of 25 – 29.9 kg/m^2, and obese as a BMI ≥ 30 kg/m^2). As can be seen by the review of Dr. Feibus, the sponsor was not very successful at limiting use of the product to the intended population, as the majority of users had a BMI >/=30 kg/m^2 (BMI 21-54, mean 32 kg/m^2).

In September 2004, GSK acquired ownership of IND 62,758 from Hoffmann-La Roche, Inc. and has continued forward with OTC development of orlistat. GSK expanded the population for OTC use to an "overweight" population, not in a regulatory sense, but more as a consumer self-perceived definition. As such, this could be a much broader patient population than that indicated for the Rx product, as it could encompass the prescription population as well as consumers that are overweight defined as BMI 25-27 kg/m^2 and 27-30 kg/m^2 without co-morbidities. This definition could also encompass normal or even less than normal weight individuals, as selection is based on consumer self-perception without any objective guidance. During a PreNDA meeting on December 8, 2004, the Agency gave a great deal of advice and expressed safety concerns, but also expressed that the 120 mg dose of orlistat may have the appropriate risk/benefit ratio in the OTC market. I will discuss later in my review whether the

120mg dose is really the appropriate dose to introduce into the OTC environment. When addressing the correct dose issue, it is important to realize that the efficacy and side-effects of orlistat are directly related to its pharmacodynamic effects on inhibiting fat absorption. The 60 and 120 mg dosages are associated with approximately 25% and 30% fat excretion respectively.

Subsequently, the NDA was filed and a joint meeting of the Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committee was held on January 23, 2006. I will review the salient points of the efficacy, safety, AC recommendation and Divisional reviews.

Efficacy summary

As part of the submission, GSK has submitted the efficacy studies mentioned above. At the time of Rx submission, BM 14149 and NM14161 while containing 60mg data were used only to seek approval for the 120mg dose. DMEP's present requirements to demonstrate efficacy are:

At least two weight-loss demonstrations are possible:

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

Review of the 60 mg data for this submission reveals that the 60 mg dose would probably also have fulfill efficacy criteria that would have allowed for Rx approval in subjects with BMIs >/= 28 kg/m^2. These two efficacy studies (BM14149 and NM14161) were conducted with similar populations, but had different amounts of behavioral and educational interventions. Subjects in study BM14149 had regular counseling by a dietician whereas subjects in study NM14161 did not receive counseling but had self-instructional videos, food records and follow-up every two months. At Month 6, BM14149 demonstrated that **28%** of placebo patients and **46%** of patients taking orlistat 60 mg had lost >/=5% of body weight, while in NM14161 **17%** of placebo patients and **35%** of patients taking orlistat 60 mg had lost >/= 5% of body weight. It is interesting to note that the placebo subtracted value from the treatment group in both studies is **18%**, demonstrating that orlistat's effect beyond placebo accounted for 18% of subjects achieving the >/=5% weight loss level in both studies, regardless of the amount of behavioral intervention. There was a difference between the studies, however, at the Month 12 evaluation of a placebo subtracted value from the treatment group of 19% for study BM1419 and 11% for NM14161.

While these studies had similar efficacy results (although BM14149 demonstrate greater numerical weight loss than NM14161) regarding the proportion of subjects losing >5% and >10% of baseline body weight, the placebo response in BM14149 was greater. DMEP interprets the amount of placebo response in these studies as demonstrating the effect that counseling has on total weight loss. Therefore, study BM14149 has a greater placebo response (and greater total weight loss) than BM14161, indicating the greater effect of intensive counseling used in study BM14149 compared the less intense counseling used in study NM14161. I feel if one were to carry that interpretation further, these results demonstrate that orlistat contributes a greater proportion of the total effect on weight loss in those subjects receiving less counseling. This

means that in subjects receiving less counseling, orlistat use takes on an even greater importance. This is demonstrated (see bolded) in the abbreviated tables below. I have obtained the values from Dr. Golden's review of the efficacy data at 6-month and 52-weeks and her tables follow the one directly below.

Percentage of Orlistat's contribution above placebo to total weight loss (Weight in kg)		
	6 month	52 week
BM14149 (↑ behavioral intervention)	-2.02/-4.89x100=**41%**	-2.04/-4.57x100=**45%**
NM14161 (↓ behavioral intervention)	-2.52/-3.37x100=**75%**	-3.15/-3.48x100=**91%**

This demonstrates that while the study with the greatest behavioral intervention (BM14149) had the greatest total weight loss, the percentage of effect attributed to drug took on greater importance in the study with less intervention (NM14161=75% and 91%) compared to the study with greater intervention (BM14149= 41% and 45%).

Table 6.1.4.4.1.3.A. Least Squares Mean Differences from Placebo at 6 Months (Weight in kg); LOCF ITT, All Study Sites

			Difference from Placebo		
Study	**Treatment Group**	**Adjusted Mean Change from BL +/- SE**	**Adjusted Mean +/- SE**	**95% Confidence Interval**	**P-Value**
BM14149	**Placebo**	**-2.88 ± 0.318**			
	Orlistat 60 mg	**-4.89 ± 0.311**	**-2.02 ± 0.433**	(-2.87, -1.17)	<0.001
	Orlistat 120 mg	-5.19 ± 0.314	-2.32 ± 0.430	(-3.16, -1.47)	<0.001
NM14161	**Placebo**	**-0.85 ± 0.310**			
	Orlistat 60 mg	**-3.37 ± 0.306**	**-2.52 ± 0.430**	(-3.36, -1.67)	<0.001
	Orlistat 120 mg	-4.21 ± 0.307	-3.36 ± 0.434	(-4.21, -2.50)	<0.001

*Applies to least square mean differences at the end of 4 months of therapy.
Studies BM14149, NM14161: means adjusted for site, lead-in weight loss category, baseline weight, baseline weight by site interaction, and interaction between treatment and site.
Pooled studies: means adjusted for study, site nested in study, lead-in weight loss category, baseline weight, baseline weight by site interaction, and interaction between treatment and site nested in study.
Study NM17247: means adjusted for site and baseline value.

Table 6.1.4.4.1.4.A. Least Square Mean (LSM) Change in Body Weight (kg) from the Start of Double-Blind Treatment to End of 52 Weeks of Treatment; Study BM14149

Analysis Population	Treatment Group	N	LSM Change from Randomization	Difference from Placebo		
				LSM +/- SE	95% CI	p-value
ITT	**Placebo**	234	**-2.53**			
	Orlistat 60	237	**-4.57**	**-2.04 +/- 0.55**	-3.11, -0.96	0.000
	Orlistat 120	240	-4.91	-2.38 +/- 0.55	-3.45, -1.31	0.000
Completers	**Placebo**	131	**-3.71**			
	Orlistat 60	155	**-5.15**	**-1.44 +/- 0.84**	-3.08, 0.20	0.085
	Orlistat 120	156	-6.24	-2.53 +/- 0.82	-4.15, -0.92	0.002

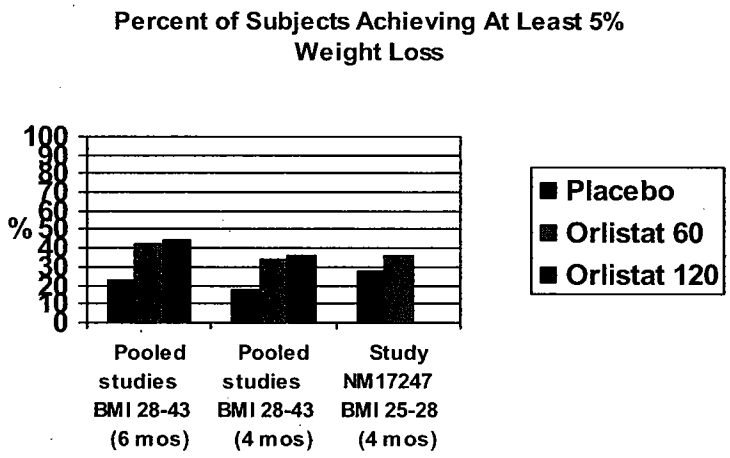
Table 6.1.4.4.1.4.B. Least Square Mean (LSM) Change in Body Weight (kg) from the Start of Double-Blind Treatment to End of 52 Weeks of Treatment; Study NM14161 (all sites)

Analysis Population	Treatment Group	N	LSM Change from Randomization	Difference from Placebo		
				LSM +/- SE	95% CI	p-value

ITT	**Placebo**	212	**-0.33**			
	Orlistat 60	237	**-3.48**	**-3.15 +/- 0.52**	-4.17, -2.12	0.000
	Orlistat 120	240	-4.12	-3.78 +/- 0.56	-4.81, -2.75	0.000
Completers	**Placebo**	120	**-1.20**			
	Orlistat 60	152	**-4.42**	**-3.22 +/- 0.79**	-4.77, -1.67	0.001
	Orlistat 120	149	-5.26	-4.05 +/- 0.79	-5.61, -2.50	0.000

Note that the 6 month and 12 month efficacy results for the 60mg and 120mg dose are similar.

Study NM17247 was a 4 month study in subject with a BMI of 25-28 Kg/m^2. It is unclear why this study was limited to 4 months. The sponsor indicated that subjects did not receive dietary instruction or intervention, did not have group meetings or counseling, and intervention consisted of self-instruction only. If this is the case, the design should closely mimic behavioral intervention in the OTC environment (note there is some confusion as to the amount of dietary intervention that was provided, as detailed in Dr. Golden's review). As can be seen from the graph below, while the overall percent of patients achieving at least a 5% weight loss is similar to the pooled data from the aforementioned studies (at the 4 mo time period), this study had a greater placebo response (DMEP marker for effect of behavior) than the pooled studies (graph from Dr. Golden's presentation at regulatory briefing on March 21, 2006). This would indicate, if we think placebo response predicts behavior, that subjects had a good behavioral effect from self-instruction alone. The placebo response in study NM17247 (-1.9 Kg at 4 mo.) was somewhere in-between the individual studies NM14161 (-0.85 Kg at 6 mo.) and BM14149 (-2.88 kg at 6 mo.) indicating at least as good of a behavior response as that seen with trials that had known physician intervention.



Study NM17285 is the AUS that the sponsor submitted to determine consumers' behaviors. While this study did contain some weight measurements, I think it is very hard to draw any efficacy conclusions from the AUS (NM17285). This study was not designed to assess for efficacy measures, but there were weight changes noted for those subjects that either had their weight checked at study conclusion (-7.2 lbs +/-9.6 lbs), or reported their weight at study

conclusion (mean -4.8 kg). These changes were similar to those seen in the pooled formal efficacy studies (-3.59 kg, SD=3.5, Dr. Golden's review Pg 48) at 3 months. It is interesting to note that >80% of subjects were either very satisfied or satisfied with their experience, citing weight loss as the reason.

Safety Summary

The safety of orlistat is well characterized in the other reviews and mainly reflects the drug's ability to increase the elimination of dietary fat in stool. Main considerations are gastrointestinal adverse events (oily spotting, fecal incontinence, flatus with discharge), the potential for decreased absorption of fat-soluble vitamins resulting in vitamin deficiency and potential drug interactions with coumadin (theoretic concern over increased levels of anticoagulation due to decreased vitamin K absorption, which has not been proven) and cyclosporine (decreased levels due to decreased absorption), all as a consequence of decreased fat absorption. It is important to note that there seems to be a dose-relatedness to AE's. In the pooled 'phase 3' studies, the premature withdrawal rate due to adverse events during the first year of treatment was 6.7% for the 60mg dose and 8.9% for the 120 mg dose. The main reason for discontinuation was gastrointestinal system disorders in 3.2% of those studied for the 60 mg dose and 5.4% of those studied for the 120 mg dose. It should also be noted that while across all studies the mean values for fat-soluble vitamin concentrations were within the normal range, the frequency of having two consecutive plasma levels of vitamins below the reference range seemed to occur in a dose-related fashion, as indicated in the table below from Dr. Golden's review (Page 89).

Table 7.1.7.3.1.1.A. Frequency of Two Consecutive Plasma Levels of Vitamins Below the Lower Limit of the Reference Range in 1 Year of Treatment (Integrated Database for 7 Phase III Trials, Prescription NDA)

Vitamin	Placebo		Orlistat 60 mg TID		Orlistat 120 mg TID	
Vitamin A	3/555	(0.5%)	2/203	(1.0%)	17/962	(1.8%)
Vitamin D	20/558	(3.6%)	8/209	(3.8%)*	73/954	(7.7%)
Vitamin E	3/565	(0.5%)	8/196	(4.1%)	37/944	(3.9%)
Beta-carotene	3/576	(0.5%)	4/207	(1.9%)*	53/977	(5.4%)

*p<0.05, 2-sided Fisher's exact test; significant difference in results for 60 mg vs. 120 mg orlistat. Statistical testing of orlistat versus placebo was not provided.

Actual Use and Label Comprehension

The review by Dr. Feibus contains a complete summary of the AUS. The AUS conducted by Roche was conducted to evaluate the ability of consumers to correctly select or de-select orlistat and provides information regarding consumer use without physician supervision. The self-selection results were poor if labeled "excluders" that limit the population (such as 'do not use if you have: hypertension, need to lose more than 30 pounds, have elevated serum lipids, are on a doctor recommended diet) are included, but improved somewhat if label restrictions (GSK's proposal) were not considered in the analysis. Most users dosed correctly, followed a diet plan and 92% were overweight or obese, with the remainder being of normal weight (Mean BMI=32 +/- 6, range 21-53 kg/m^2). The AUS included educational materials directing behavioral patterns that, while not identical to those proposed by GSK for use in the OTC marketing plan, were of similar concept. Thirty to 64% of subjects used the educational materials and 77-80% of

subjects who used the materials found the materials useful, depending on the component. Forty-six percent of subjects were still using orlistat at day 90.

Pertinent points from the AUS include that while 74% of orlistat users were reporting multivitamin use, only 54% were timing the dose (at least 2 hours before or after taking orlistat) as instructed by the label. The sponsor points out that even if vitamins were dosed with orlistat, they would expect that approximately 70% of the fat-soluble vitamin would still be absorbed, and between that and the vitamins included in food, should be more than adequate intake of these vitamins. There are some data in Dr. Feibus's review demonstrating the orlistat may not fully inhibit fat-soluble vitamin absorption, as she notes that concomitant orlistat administration reduces beta-carotene absorption by 30% and vitamin E absorption by 60%. We do not have data that I am aware of that documents the rate or timing of co-administration of vitamins and orlistat in the Rx setting. More concerning is that of two people taking cyclosporine that initially read the label, one person selected to take the medication.

Overall, the label comprehension study demonstrated that the Drug Facts Label did transfer information to the reader. Dr. Weiss points out that consumers did not perform well in determining what it meant to be overweight and recommended that some type of guidance needs to be included in external labeling to provide consumers information upon which to make purchase decisions. This study also demonstrated that consumers did not demonstrate comprehension on the issue of timing of dosing vitamins. In a separate self-selection study of cyclosporing users, 40 of 43 (93%) made a correct decision.

Advisory Committee Meeting Vote

There was a joint meeting of the Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committee on January 23, 2004. A summary of the votes on the questions was as follows (excerpted from the quick minutes):

1. **Has clinical effectiveness been demonstrated with orlistat 60 mg tid and 120 mg tid in the nonprescription setting? For each of these doses, please comment on the following:**
   - **a. A 6-month duration of use**
   - **b. Repeated use or chronic use**
   - **c. Use in the overweight individual**
   - **d. Use in the obese individual (with and without multiple co-morbid conditions)**
   - **e. Use with the proposed educational materials**

   a. Yes: 15
   No: 0
   Abstain: 0

   b. Question was dismissed due to lack clinical data in nonprescription setting presented on repeated use.

   c. This question was divided into two groups; overweight individuals with: (1.) BMI of 25-28 and (2.) individuals with a BMI of 28-29.9.

C1.	C2.
a. Yes: 9	a. Yes: 15
b. No: 5	b. No: 0

c. Abstain: 1

c. Abstain: 0

d. Yes: 15
No: 0
Abstain: 0

e. Question was withdrawn by the FDA.

2. **Are the safety and tolerability characteristics of orlistat 60 mg -120 mg tid acceptable for a nonprescription drug? Specifically comment on the following safety concerns and the ability of labeling to convey these concerns to the consumer.**
   a. **Fat-soluble vitamins**
   b. **Drug-drug interactions (specifically, cyclosporine and warfarin)**
   c. **Other concerns? (e.g., pancreatitis, liver toxicity, lithogenicity)**

   Yes: 12
   No: 3
   Abstain: 0

3. **This proposed nonprescription product is targeted for overweight adult's ≥ 18 yrs of age. Do you have specific concerns regarding possible use in the following populations?**
   a. **Pediatric patients**
   b. **Underweight or normal-weight individuals or in those with eating disorders**
   c. **Obese individuals (with and without multiple co-morbid conditions)**

   Discussion:
   FDA requested that the committee would discuss the adequacy of labeling presented, specifically, what mechanisms could be instituted that would discourage use of orlistat in the above population and the possible adversities if used. The Committee agreed that labels should clearly state product is not for use in individuals under the age of 18 and individuals with normal weight or eating disorders. The committee further recommended implementing a plan that would require the sponsor to provide usage data in these populations and revisit the issue recommending alternative strategies if necessary

4. **Based on data from the label comprehension study, did subjects demonstrate adequate comprehension to support safe and effective use of orlistat by consumers? Please describe the factors or data you considered in making your decision.**
   Yes: 13
   No: 1
   Abstain: 0
   Absent members: 1

5. **Do the results from the actual use study suggest:**
   a. **That consumers make correct self-selection/de-selection decisions?**
      Yes: 7
      No: 7
      Abstain:
      Absent members: 1

   b. **That consumers comply with dosing directions?**
      Yes: 13
      No: 1
      Abstain: 0
      Absent members: 1

6. **Do you believe that the potential benefits of nonprescription orlistat outweigh the risks?**

Yes: 11
No: 3
Abstain: 0
Absent member: 1

7. **Should orlistat be approved for nonprescription use?**
   a. **If no, please discuss the deficiencies of the clinical program.**
   b. **If yes, is the adult population for which orlistat is targeted in the prescription setting different from the adult population in the nonprescription setting? If so, how would each of the two populations be identified?**

   Yes: 11
   No: 3
   Abstain: 0
   Absent member: 1

Regarding the vote on question 5, panel members voting no mainly commented that the sponsor needed to improve the labeling. On the final vote regarding whether orlistat should be approved for nonprescription use, it is notable that all the members of the Endocrinologic Committee voted in the affirmative. The three negative votes came from the Nonprescription Committee. The persons voting against approval did so for reasons including:

1) the actual use study did not span twice the interval of recommended use and was relatively small,
2) cylosporine and warfarin interaction concerns,
3) that use should be chronic and not limited to 6 months,
4) minorities were under-represented in the studies.

C. DISCUSSION OF DIVISIONAL RECOMMENDATIONS

Introduction

While both the Divisions of Metabolism and Endocrinology Products (DMEP) and The Division of Nonprescription Clinical Evaluation (DNCE) have recommended approvable actions, which I agree with, they have recommended markedly different remediation actions by the sponsor necessary to obtain approval. I believe that, while something of an over-simplification of the recommendations, DNCE feels that orlistat can be approved with some labeling changes that should be successfully tested in labeling comprehension studies or self-selection studies. DMEP, however, believes that orlistat can only become an OTC drug after the sponsor repeats the efficacy studies (in reality not proving efficacy but establishing effectiveness as I'll discuss below) in an OTC environment. I will address some of the specific recommendations of each group later in this review. This disparity of views is due in large part to the philosophy and regulatory history under which each division has functioned.

DNCE has reached their conclusions and provided regulatory guidance based at least in part upon an Advance Notice of Proposed Rulemaking (ANPR), which details the requirements for OTC marketing of pre-1975 weight control drugs and recommends temporary use (defined as three months-the treatment period, which at the time was felt long enough to establish new eating habits) in an obese population, in conjunction with a diet. However, this ANPR was published over 20 years ago and is outdated and in need of rethought and updating. The notion that drug therapy for weight loss can be short-term has largely been discarded, and it is now widely

accepted that weight loss should be thought of as weight loss/maintenance of loss, which implies chronic drug therapy.

DMEP has been integrally involved in developing the recent concepts of drug therapy for overweight/obesity and has developed efficacy standards that are well recognized within the drug development industry and scientific community. DMEP has a strict way of viewing when drug therapy should be initiated (i.e., what patient population and only after a certain interval of diet therapy alone and under the supervision of a physician). This concern and tightly managed approach is due in large part to their desire to maximize safety/efficacy ratio of products and their recognition that any drug therapy likely will need to be chronic in nature. It could be argued that the safety/efficacy equation is largely driven by the safety component of the equation, as most of the drugs used for this indication have had significant safety concerns and some drugs used for weight loss have been removed from the Rx market due to safety issues. Further, no drug to date has been shown to have a positive effect on long-term outcomes, despite some data showing that weight loss may reduce CV risk factors. The DMEP approach is applied to weight loss drugs in general and ignores the unique safety attributes that may be found with an individual drug, such as orlistat. This approach does not allow an individual drug to be viewed based on its own safety profile. Their view also does not take into account the safety profile of other categories of OTC drugs and what the Agency's tolerances have been for OTC marketing safety considerations.

Response to DMEP Comments

Target Population

I will first comment on Dr. Parks review, using her review as the final divisional decision for recommendation of actions and remediation. I would like to state that I am deeply appreciative of the expertise within the Division regarding these issues and my interaction with DMEP experts has been instrumental in my present view of this application.

It should be noted that there is not consensus within the Division upon the appropriate action, or remediation, for this application. Dr. Parks has recommended an approvable action, with which I agree. She believes, however, on the issue of target population that the applicant should target the same adult population as that approved under the prescription NDA. I am in agreement to the extent that the label at the point of purchase should indicate that persons with a BMI >/= 27 kg/m^2 should expect the greatest benefit and the label should contain a method to help consumers determine their own BMI. This change in labeling should be tested and the sponsor should demonstrated adequate consumer comprehension. I am in disagreement that another actual use study is necessary to test this issue. This is partially an acknowledgement that I doubt the sponsor will every achieve perfect or even near perfect self-selection on this attribute. If the recommendation for an AUS by DMEP is to demonstrate that consumers with less than the recommended BMI do not select the drug, I am comfortable with consumers making their own decision on whether they want to use this product to lose weight even if their BMI is less than 27 Kg/m^2. The drug has a very good safety profile and as long as consumers are adequately informed as to what benefits they can expect should their BMI not be in this category, I believe the risk/benefit ratio in this population should not preclude OTC availability of this product.

Label comprehension studies should therefore be an adequate measure of consumer understanding.

Just as a note of interest, in this section of Dr. Parks review, she references the Division's interactions with the NAASO and pharmacist as well as other external experts in developing the target population criteria for weight loss products. The NAASO, American Diabetes Association, American pharmacists Association, American Obesity Association, National Medical Association and Dr. Foreyt (Author of the 1999 JAMA article on orlistat) all testified during the open public session of the advisory committee meeting that this application for use of orlistat in the OTC market should be approved even though it does not target a particular BMI population.

Duration of Use

Dr. Parks has made a very convincing argument that the duration of use of this drug in an OTC environment should reflect recommendations of use in the prescription environment. I agree because I feel that if overweight/obesity is considered a disease requiring chronic therapy, it would remain so regardless of how the drug is distributed (Rx vs OTC). I agree with her that consumers should be informed that weight loss and weight loss maintenance may require chronic drug therapy, and that a 6-month limitation should not be placed in the nonprescription label. In considering whether drugs can be used chronically in an OTC environment, we can examine available OTC products for precedence. Antihistamines do not have a limit to duration for allergy treatment and are labeled for hay fever and other allergies, which includes both seasonal and perennial allergens, which can occur year round depending on patients' allergies and locales. Elimination of the 6-month limitation on duration may not necessitate another AUS, whereas if the sponsor tries to make the case to maintain the 6-month duration, I would advocate for another AUS study. This position may seem somewhat paradoxical. However, I think this recommendation has to viewed in the context of what data are necessary to support a limited duration (or no limitation) and does an AUS study accomplish the need. If the sponsor persists in wanting to limit the duration to six months, I think we would need information regarding the behaviors of consumers who extend use or have repeat use beyond the 6 month limitation. These data can only be achieved through an AUS study. However, eliminating the duration eliminates that need to assess patients adherence to a limit. It is not clear to me what type of information we would expect to get from a longer AUS in a situation of chronic use. At present, I do not feel another AUS study is needed for this issue. However, the sponsor would have to provide labeling that tests the consumer's understanding that obesity is a chronic disease that usually requires chronic therapy. I am receptive to further discussions on this issue and the type of study or studies necessary.

Safety

Dr. Parks has raised concerns regarding cyclosporine. I agree with her that this is of great concern. I agree that the sponsor needs to make changes to try to eliminate as many medication errors as possible. We should impress upon the sponsor that, if this drug should ultimately achieve OTC marketing, we would expect continued educational programs and would be intolerant of reports of co-administration, particularly reports showing adverse consequences to

the patient and their allograft. It does not seem reasonable to expect perfect usage, however, as we have not achieved that in the prescription setting. I agree that the consequences of co-administration with anti-diabetic medications (as weight loss leads to reduced serum glucose levels), and the other things listed in the label seem of less consequence.

Educational Program

Whether or not another efficacy study needs to be performed is presently the biggest source of contention between the divisions and is addressed in this section of Dr. Park's review. Dr. Parks is advocating that lifestyle intervention is the cornerstone of any weight-loss program and that the 'orlistat program' has not been tested to see if it is effective in the OTC setting. DMEP questions if the educational materials proposed by the sponsor will affect behavioral changes that lead to efficacy for orlistat. Dr. Parks recommends that a placebo-controlled efficacy study in the actual use setting should be conducted. The design for this study as proposed by DMEP would be to randomize consumers who chose to use the drug to product (with appropriate packaging) containing either drug or placebo without controlled conditions and then assessing them 6 months later to see if the drug exposed group had a greater weight loss than the placebo exposed group. This would be similar on the Rx side to having physicians in general practice randomize patients who they feel are candidates for orlistat to drug or placebo in an actual clinical practice setting, without a protocol other than the Rx label and following their patients in their customary fashion with a 6 month 'effect' endpoint collection. I feel that in reality, this type of design is an **effectiveness** trial, not an **efficacy** trial, as I will discuss below.

This gets at the essence of what it is we require from a regulatory standpoint for drug approval. If we felt that this drug only worked with a well-defined behavior program and had Rx labeling expressing this concept, that might add weight to the argument. However, the studies that were the basis of prescription approval included varying degrees and approaches to behavioral modification, which resulted in the prescription labeling that neither recommends nor provides any details regarding a behavioral modification plan. The indications section only states to use with a weight loss diet. The clinical trial section does not discuss the behavioral modification component of the studies. From a regulatory standpoint, if behavior modification is necessary for the drug to have efficacy, it should be included as part of the Rx labeling. The lack of such labeling in the Rx setting makes it extremely difficult to argue that this should be a requirement in an OTC setting. In fact, the Rx label for orlistat only states to use with a reduced calorie diet, which I feel can easily be conveyed in an OTC environment.

The Request for an 'OTC' efficacy study, as DMEP conceives it, appears to confuse the distinction between proving **efficacy** and proving **effectiveness**, which from a regulatory standpoint are quite different. Proving **efficacy** means that there are substantive data showing that an intervention has its proported effects when properly taken under **controlled conditions**. Proving **effectiveness** means that there are data showing that an intervention is successful in **actual clinical practice**. To my knowledge, we have never required Rx or OTC medication to prove **effectiveness** (as defined here) in actual clinical practice, including nicotine OTC (discussed further below). Since proving effectiveness was not a requirement for Rx marketing, I cannot agree with placing a higher standard simply because of the mode of distribution. My position on whether method of distribution (Rx vs OTC) should effect regulatory expectations is

consistent whether it is in regard to duration of therapy (addressed early under the Duration heading), or requirements for efficacy.

To expand upon nicotine replacement products, the former Rx labeling for nicorette stated in the indications and usage section in detail that these products are recommended for use as part of a comprehensive behavioral smoking cessation program (which is lacking in any of the Rx weight-control product's labeling). The OTC switch for nicotine recognized this Rx labeling and also included many firsts for the OTC environment including selecting a dosing interval based on total amount of cigarettes smoked, a drug tapering schedule and chewing and 'parking' the gum, and stopping use of a possibly addicting substance, all of which required testing. However, the 'efficacy' protocol of the study did not include a placebo arm to demonstrate superiority of drug vs placebo in an otc environment as outlined by DMEP above, but instead only included collection of quit rates in the OTC environment compared to survey result (from mall intercepts) quit rates of persons treated by their private physician for 'similarity' of effect, with which approval was allowed.

For Rx approval, orlistat demonstrated fairly consistent drug effect with varying amounts of behavioral intervention (although maximal weight loss was achieved with the more intense behavioral intervention). Our regulatory action on the prescription use of orlistat indicates that the Agency felt that this drug indeed works as an addition to a reduced-calorie diet alone, as that is how it is labeled for Rx use. We did not label it to include behavioral modification programs, as had been done with nicotine replacement products. To now require proof of the adequacy of a behavioral intervention program (in essence proving effectiveness instead of efficacy) in the OTC setting would be invoking a requirement that wasn't placed upon Rx setting (where only efficacy was proven). This would therefore place a regulatory requirement upon the sponsor that is not consistent with how the Rx approval was determined and is a position I cannot support. I also think that it is not correct to assume that the average physician practicing has knowledge of, or time to perform, the behavioral interventions that were used in the efficacy studies that supported Rx approval of orlistat.

I think the efficacy previously demonstrated for Rx approval is transferable to the OTC environment. The unanimous vote of the advisory committee members that clinical effectiveness had been demonstrated with orlistat 60 mg tid in the nonprescription setting for a BMI of >/= 28 kg/m^2 helps build my confidence in this conclusion. Having said that, I do not dispute that studies have demonstrated that intense behavioral intervention combined with drug therapy **maximizes** weight loss. However, achieving **maximal effects** is not a regulatory requirement. If that were the case, a logical regulatory extension would be to limit distribution in the Rx setting to those individuals with that expertise. One should also bear in mind that the sponsor has a vested interest in making sure that this product is as effective as possible in the OTC environment as if it doesn't work, people will simple stop purchasing it. Additionally, GSK has a wealth of experience in developing OTC behavioral programs as they hold marketing approval for OTC nicotine products.

Similarly, it is interesting to note that the sibutramine's label also does not mention behavioral modification as a prerequisite of efficacy and only states to use with a reduced calorie diet. Opinions and data have been expressed in reviews and various meetings regarding the

importance of behavior in drug efficacy as document by published studies of sibutramine (Wadden TA, NEJM 2005; 353:2111-20). This study supports an overall focus on maximizing effects (using a total program), as opposed to whether the drug moiety itself has intrinsic activity (when used with a low calorie diet-which is in the Rx label). It should also be noted that in the sibutramine study, that the arm with the greatest weight loss included behavioral interventions which consisted of 30 visits for 90 minutes/visit over 1 year. It is probably unrealistic to expect that this type of intervention will occur in an average physician's office and thus a 'maximal effect' will never be attained in the Rx setting.

A case could be made that the planned labeling for orlistat OTC may actually provide more information to consumers regarding behaviors and dieting than what physicians not specializing in weight loss have access to either in their office or by orlistat's current Rx labeling.

DMEP Recommendations

I agree with Dr. Parks that the sponsor should improve label comprehension on issues of drug interactions and the timing of multivitamin dosing. I do not agree that an AUS study is needed for this.

I agree that the labeling should target consumers with a BMI>/= 27 kg/m^2. I do not agree that an AUS study is necessary to test whether adolescents will use the product in an OTC setting, as we have never tested age restriction before in this type of setting.

I do not agree that a clinical study is need to test the 'collateral measures' (labeling information included in the package) but do feel that these need tested in some fashion to demonstrate adequate consumer understanding.

Response to DNCE Comments

Efficacy

I agree with Dr. Segal's observation that reasonable people can interpret data differently and also have different thresholds of comfort in extrapolations from these data. As stated above, I agree that the totality of data demonstrate that orlistat 60mg and 120 mg has efficacy that appears to be independent of the amount of behavioral intervention, though overall weight loss is further enhanced with behavior interventions. Dr. Segal seems to indicate that orlistat OTC should not be limited to targeting a BMI >/= to 27 Kg/m^2. She makes a case that the BMI level of 27 was targeted for cardiovascular benefits and there are diseases (osteoarthritis) for which weight loss in lower BMI's are probably beneficial. She contends that weight loss in individuals with BMIs </= 27 Kg/m^2 may not be viewed as 'cosmetic' by rheumatologists, if patients have osteoarthritis. I think her statements have some merit, however, her arguments have not translated into Rx labeling for this product, or into the DMEP guidance. The risk/benefit ratio for orlistat use in the osteoarthritis population with a BMI </= 27 Kg/m^2 has not been studied. As such I can only support labeling for orlistat as an OTC product if it informs consumers that they should not expect to receive as much benefit from the product if their BMI is < 27 Kg/m^2.

That is not to say, especially in regard to the DMEP guidance, that this issue should not be revisited with input from Dr. Segal and rheumatologist colleagues.

Safety

I agree with Dr. Segal that we have not defined a precise threshold with regard to proper self-selection in the context of a cyclosporine co-administration. I also agree that the labeling needs strengthened and agree with her assessment that since cyclosporine co-administration has been reported with the Rx use of the drug, physicians are themselves are co-prescribing the medications. Therefore, some low level co-use in the OTC setting could not be regarded as less acceptable than some low level co-administration in the Rx setting. The sponsor reported that while there have been reports of acute organ rejection, there has not been a report of organ loss. This may be due to the fact that these patients are also followed very closely and perhaps the rejection was detected in a very early phase. The remainder of drug interactions are probably not as significant. A case could be made that those persons taking diabetic medicines should be self-monitoring their glucoses irrespective of orlistat use and therefore would detect slow declines in glucose levels (orlistat's effect is gradual in this regard as weight changes occur slowly). The warfarin interaction is still somewhat ill-defined, but those patients are likewise monitored irrespective of orlistat use.

Limiting the dose to 60 mg TID may be the most appropriate dose for introducing the drug into an OTC market, because a dose lower than 120mg would decrease the amount of adverse effects and may lessen some of the concerns with inadequate absorption of fat-soluble vitamins. Safety concerns regarding orlistat and its association with pancreatitis in small numbers is pending further evaluation and conclusions. However, as noted by Dr. Segal, there are drugs on the OTC market at present that had Rx labeling for pancreatitis, including omeprazole, which was had an Rx labeled listing *Pancreatitis (some fatal)* as an associated adverse event. For serious safety issues like this, the rate and strength of the association between the drug and the adverse event becomes very important in determining the appropriateness of a drug for OTC market. As Dr. Segal points out, if there is a causal association, the rate appears to be exceedingly low.

Labeling

Dr. Segal has indicated that the sponsor may not need a 6-month limitation of label duration of drug use. I would state it differently in that the sponsor has not indicated why the 6-month limitation makes sense for a weight loss product, nor have they provided data to show that a limit on the duration of use is justified. I agree that chronic drug use should not be mandated, but consumers should demonstrate comprehension that they could probably expect to regain weight if they quit taking the medication. Another reason that I do not agree that a limitation is appropriate for OTC use is that I do not see why the method of distribution should affect how we view the clinical treatment of an overweight state. Even if the sponsor is able to provide a justification for a 6-month limitation, important information to guide consumers purchase/use decisions is not available such as:

i) What do I do if I haven't hit my target at 6 months?
ii) What do I do if I start to regain weight?

iii) How often can I repeat Alli? (Noted that the companion guide states that "If you haven't taken the Brandname [Alli] capsules for at least three months, try them again" However, the sponsor has not provided justification for the 3 month time interval before re-treatment or provided further guidance as to the length of therapy with a second course of drug or repeat therapy beyond a second course)

iv) What do I do if I hit my targeted weight prior to the 6 month limitation?

My view is that treatment of overweight/obesity should be viewed as chronic whether Rx or OTC until data are presented to dissuade me of this concept.

CMC:
Reviews by Drs. Blair Fraser and Martin Haber indicated that the application can be approved from a CMC perspective.

Pharm-Tox:
There were no new data submitted for this application.

Clinical Pharmacology:
There were no new data submitted for this application.

Clinical/Statistical:
Please see discussion above.

Data Integrity/Financial Disclosure:
Dr. Golden reviewed all financial disclosure information and has found this information does not change the interpretation of the clinical data for this application.

Labeling/Nomenclature:
DMETS objects to the proposed trade name. Considering the nature of the action for this application, further internal discussion can occur regarding DMETS recommendations.

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

/s/

Curtis Rosebraugh
4/4/2006 07:52:07 AM
MEDICAL OFFICER
The authority to sign for this action has been delegated to me by Dr. Robert Meyer, Director of ODE 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

ACTING DIVISION DIRECTOR MEMO

NDA#	21-887
Sponsor:	GlaxoSmithKline
Drug name:	Orlistat
Indication:	Nonprescription use for weight loss in adults who are overweight and obese
Date of Memo:	March 21, 2006

EXECUTIVE SUMMARY

On January 23, 2006, members of the Non-prescription Drugs Advisory Committee (NDAC) and the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) convened in a joint session to consider an application for the non-prescription use of orlistat for the treatment of overweight adults. After a day of presentations, questions and answers, and lengthy discussions regarding the data, the committee members voted 11 to 3 (one member absent) in favor of making orlistat available over-the-counter. While clearly a majority vote, it would be an oversight on the agency's part to make its final recommendation on this application based solely on the tally of a categorical vote without considering the reservations voiced by those who voted *no*. Similarly, it would be imprudent of the agency to not consider the deficiencies of the program noted by even those who voted *yes*.

After reading the FDA reviews from the Division of Metabolism and Endocrinology Products (DMEP), Division of Nonprescription Clinical Evaluation (DNCE), and the Office of Biometrics, and after consideration of the discussions raised at the advisory committee, I am recommending that this application receive an *approvable* action. This memo will summarize the deficiencies of the nonprescription orlistat program and the measures to be considered for correction of these deficiencies.

BACKGROUND

Xenical® (orlistat) was approved as a prescription drug in 1999 for obesity management including weight loss, weight maintenance, and prevention of weight regain when used in conjunction with a reduced-calorie diet. The population for which it is indicated includes obese individuals with BMI $\geq$ 30 kg/m^2 and overweight individuals with BMI $\geq$ 27 kg/m^2 and other co-morbid risk factors (e.g., HTN, DM, or dyslipidemia). The recommended dosing regimen is 120 mg tid with meals. The prescription NDA is owned by Roche.

In June 2001, Roche opened an IND to develop orlistat for nonprescription use. The proposal was to market orlistat 60 mg for nonprescription use in overweight but not obese adults. GlaxoSmithKline (GSK) subsequently acquired ownership of this IND with right of reference to the prescription NDA. The recommended dosing regimen for nonprescription use is 60 to 120 mg tid with meals and the target population encompasses both overweight and obese adults. The recommended duration of use is 6 months.

The NDA for nonprescription orlistat included a re-evaluation of clinical efficacy from two pivotal studies conducted under the prescription NDA, the results from a 4-month clinical efficacy study conducted under the nonprescription IND, a 3-month, uncontrolled, pilot actual use study, and a label comprehension study. All studies, save the label comprehension study, were designed and conducted by Roche.

The reader is referred to the primary reviews from DMEP and DNCE for detailed discussions of the regulatory history of prescription and nonprescription weight-loss drugs and the individual studies submitted in support of NDA 21-887.

SUMMARY OF DEFICIENCIES

Target Population

The target population for nonprescription orlistat includes *overweight* adults who are 18 years and older. In the Drug Facts label employed in its actual use study and the Drug Facts label submitted to the NDA (Tables 10.4 and 10.5, respectively, in Dr. Feibus's review from ONP), the consumer is not required to identify whether he or she is overweight based on any objective measure (e.g., weight, body mass index, waist circumference, etc.). Overweight is identified by the consumer based on his or her own perception of meeting this criterion.

There has been much debate within the agency regarding the appropriateness of the proposed target population. Reviewers within the Office of Non-Prescription Products (ONP) are accepting of this general indication, without any requirement for self-selection based on objective measures of overweight or obesity. They place emphasis on advice provided by the Advisory Review Panel for OTC drugs and the Federal Register publication in January 1982 of the Advanced Notice of Proposed Rulemaking (ANPR) for Weight Control Products for OTC Human Use. Ms. Arlene Solbeck, senior regulatory review scientist for ONP, provided the Panel's definition of obesity in her presentation before the advisory committee as "*an increase in body weight beyond the limitation of skeletal and physical requirements as the result of an excessive accumulation of fat in the body; that physical state in which body weight in relation to height and body build is more than 10% above the ideal weight determined from the Metropolitan Life Insurance Company table of desirable weights.*"

In contrast, reviewers from DMEP object to targeting a broad population for nonprescription orlistat use that does not attempt to define overweight based on some objective measure. In her Executive Summary, Dr. Julie Golden, medical officer in DMEP, summarizes more recent recommendations for assessing overweight and obesity made in October 2000 by the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. This Panel was comprised of physicians, researchers, nutritionists, dietitians, and pharmacists from government agencies (NIH, NHLBI, FDA), academia, and medical organizations (NAASO). The consensus definition for overweight was a body mass index (BMI) of 25 to 29.9 kg/m^2. Obesity was divided into Class 1 (BMI 30 to 34.9 kg/m^2) and Class 2 (BMI 35 to 39.9 kg/m^2). Individuals with BMI $\geq$ 40 kg/m^2 were classified as having extreme obesity or Class 3 obesity. As stated in their report, "*BMI is recommended as a practical approach for assessing body fat in the clinical setting. It provides a more accurate measure of total body fat compared with the assessment of body weight alone.*" Furthermore, this Panel recommended pharmacotherapy only in those individuals with BMIs $\geq$ 27 kg/m^2 after dietary and lifestyle intervention failed to achieve desirable weight loss. This same recommendation is also applied by the FDA in the approval process of prescription weight-loss drugs.

Dr. Golden has summarized the efficacy of orlistat from the prescription NDA studies, BM14149 and NM14161. These two studies enrolled patients with baseline BMIs > 28 kg/m^2 and their results support the conclusion that when used in conjunction with a reduced-calorie diet and lifestyle modification,

orlistat 60 to 120 mg tid meets the agency's requirement for weight-loss efficacy at the 6-month time point. In order to establish efficacy as a weight-loss drug, one of two criteria[1] must be established:

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

Orlistat 60 to 120 mg tid in patients with baseline BMIs $\geq$ 28 kg/m^2 met the second criterion for efficacy. In contrast, there were insufficient clinical data from the prescription NDA to conclude that orlistat 60 to 120 mg tid would be effective in overweight patients with lower BMIs. From Table 6.1.4.2.A of Dr. Golden's review, one will note that only 18 patients with BMIs within the range of 25 to 28 kg/m^2 were enrolled in the two pivotal prescription NDA studies.

Both Roche and GSK were informed in separate meetings with the agency that efficacy would need to be established in the target population and that the standards for evaluating efficacy from the prescription setting would be applied to the nonprescription setting. Both Drs. Golden and Feibus have summarized minutes from these two meetings held in July 2002 (EOP2 meeting) and December 2004 (preNDA meeting) in which these recommendations were conveyed to the two companies.

Consequently, Study NM17247 was conducted and submitted to the nonprescription NDA. This was a 4-month, placebo-controlled study evaluating the efficacy and safety of orlistat 60 mg tid in overweight patients with baseline BMIs between 25 and 28 kg/m^2. The trial design and results have been discussed at length under Section 6 of Dr. Golden's review. Overall, this 4-month studied failed to meet either of the agency's criterion for weight-loss efficacy. The percentage of patients losing 5% of their initial body weight was 36.1% in orlistat-treated patients and 28.3% in placebo-treated patients (p=0.104). The mean drug-associated weight loss did not exceed the mean placebo weight loss by at least 5%; however, the difference of 1.6% was statistically significant. This 1.6% difference translates into a mean absolute difference of only 1.2 kg or 2.5 lbs.

The applicant applied a <u>less stringent</u> efficacy criterion of $\geq$ 3% loss of initial body weight. Using that analysis, a statistically significant difference was observed between the two treatment groups (56.7% orlistat vs. 41.8% placebo; p=0.004). However, if we accept this new analysis, we are modifying our efficacy criteria for prescription weight-loss drugs in order to make this product available in a broader patient population in the nonprescription setting. In my opinion, such a compromise has no scientific or public health merit.

Although the objectives of the 3-month actual use study did not include weight-loss efficacy, Dr. Feibus discusses such efficacy in her review of this study based on assessments of objective weight measures via a calibrated scale and self-reported weights. Under her conclusions on efficacy she states, "*During the actual use study, subjects appeared to lose some weight using orlistat 60-120 mg tid and the supportive educational materials provided. However, due to the lack of objective subject weight assessments, it is not possible to make evidence-based conclusions regarding weight loss achieved during the actual use study. Objective weight measurements were obtained in only 15-33% of subjects at any one assessment interval during the study, and no objective weight measurement was taken at the end of the study.*"

In my opinion, the weight-loss efficacy data from the 3-month pilot actual use study add little to nothing to our knowledge of orlistat's efficacy in the nonprescription setting, much less the low overweight population. The uncontrolled design and very low data ascertainment for objective weight measures preclude any meaningful interpretation of the study results. Furthermore, relying on consumer self-

[1] FDA's 1996 Draft Guidance for the Clinical Evaluations of Weight-Control Drugs

reports of weight loss in only those individuals who considered the drug to work for them introduces bias (self-report, recall, and selection) that is in contradistinction to the agency's standard of establishing efficacy.

Consequently, the deficiency that I note for the proposed target population is that it represents FDA's approval of orlistat's use in a new patient population for which efficacy has not been established. This new population would be comprised of overweight patients with BMIs in the lower range (25-27 kg/m^2) and who have no co-morbid risk factors.

One of the questions posed to the advisory committee was whether clinical effectiveness had been demonstrated with orlistat 60 to 120 mg tid in the nonprescription setting for patients with BMIs 25 to 28 kg/m^2. This question generated 9 *yes* votes and 5 *no* votes. At the advisory committee meeting, NDAC's patient representative member, Ms. Melanie G. Coffin, stated that patients cannot make such fine distinctions between low overweight and high overweight. While this sentiment may have influenced some members to lump all overweight patients into one category, it should be pointed out that the company has not formally tested consumer comprehension of BMIs for one to conclude that this objective measure for self-selection is inappropriate for a non-prescription drug.

As clinically meaningful weight loss has not been established in the low overweight patient population, I am recommending the applicant change the nonprescription drug label to target the same adult population approved under the prescription NDA. To assist consumers in selecting based on their BMIs, the applicant should design consumer-friendly tools and test comprehension of these new labels before employing the labels in an actual use study.

Duration of Use

The two Drug Facts labels submitted for review recommend continuous daily use of orlistat 60 to 120 mg tid for 6 months. Use beyond 6 months is not encouraged but the consumer is referred to an enclosed user's guide (label studied in actual use study) or is instructed to talk to his/her doctor (label submitted to NDA). In contrast, the prescription label for orlistat has no limit on duration of use, as the approval of weight-loss drugs in DMEP is with an understanding that overweight and obesity are chronic conditions.

The advisory committee members were asked whether clinical effectiveness has been established with orlistat 60 to 120 mg tid in the nonprescription setting for a 6-month duration of use, repeated use or chronic use. There was a unanimous vote of *yes* for the 6-month duration of use; however, the question was dismissed for repeated or chronic use due to lack of clinical data in the nonprescription setting for repeated use. I would add that there are no data for chronic use in the nonprescription setting as the actual use study only exposed consumers to drug for a 90-day period.

Again, there is disagreement within the agency regarding the appropriateness of the recommended duration of therapy. The Advisory Review Panel on OTC drugs recommended in January 1982 a duration of use that is limited to 3 months with labeling that states "*this product's effectiveness is directly related to the degree to which you reduce your usual daily food intake. Attempts at weight reduction which involve the use of this product should be limited to periods not exceeding three months, because that should be enough time to establish new eating habits.*"

In contrast, trials supporting the approval of two marketed prescription weight-loss drugs (orlistat and sibutramine) and a recent study of the cannabinoid receptor antagonist, rimonabant,[2] have been of two years' duration to evaluate durability of weight loss or weight regain after drug treatment is discontinued.

---

[2] Pi-Sunyer, F. Xavier et al. Effect of rimonabant, a cannabinoid-1-receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients. RIO-North America: A randomized controlled trial. *JAMA*. 2006; 295:761-775.

These studies establish efficacy within the first year and evaluate the durability of this effect in the second year where some patients are re-randomized to receive placebo while maintained on a eucaloric diet. In all studies, data support the conclusion that discontinuation of pharmacotherapy results in regain of weight lost. The study with rimonabant also showed that along with weight regain there was a lost of any beneficial effect on other cardiovascular risk factors.

Given this degree of evidence, it remains unclear to me the basis for marketing orlistat in the nonprescription setting with a recommended duration of use that differs from the prescription setting. Applying the duration of use recommended by the 1982 Advisory Review Panel for OTC drugs would be an anachronistic decision with complete disregard for more recent scientific understanding of overweight and obesity. Some have referred to this treatment approach as *cosmetic weight loss*; however, the advisory committee presentations made by the applicant's consultant, Dr. Caroline Apovian, would suggest that the company's intent is to market this product as a weight-loss product to reduce long-term co-morbidities associated with overweight and obesity.

I believe that a weight-loss drug should be prescribed (or initiated) with the understanding that this may be a chronic treatment in conjunction with dietary and lifestyle modifications. A consumer, at any point in time, may consider discontinuing drug therapy; however, given the clinical trial evidence, the product label must inform the consumer that discontinuation of drug may result in regain of weight lost and that successful long-term weight-loss maintenance requires continued dietary and lifestyle modification that may include chronic drug therapy. For this reason, I do not agree that the Drug Facts label should recommend continuous daily therapy with orlistat for only 6 months.

Reviewers in both DMEP and DNCE raised concerns that long-term use would increase the risk of adverse drug reactions in the nonprescription setting. I would counter that if this is a concern of nonprescription drugs, then NO applications should be accepted for the Rx-to-OTC switch of a drug intended to treat a chronic condition. Apparently this has not been the position taken by the agency, as several joint advisory committee meetings have already been held to discuss NDAs for the OTC use of lipid-altering drugs and companies continue to raise the possibility of other chronic conditions treated in the nonprescription setting (e.g., osteoporosis). As no policy on nonprescription treatment of chronic conditions has been established, I believe the consideration of such therapies requires a thorough assessment of the inherent safety profile of the drug and the consumer behavioral use pattern as evaluated in an appropriately designed actual use study.

The inherent safety profile of orlistat will be discussed in the *Safety* section below. However, given the very low systemic absorption of orlistat, it would appear that this product has few serious safety concerns that are not already identified. The behavioral use pattern of nonprescription orlistat has thus far only been studied in a 3-month actual use study (NM17285). As stated in Dr. Feibus's review, this was a *pilot* study conducted by Roche to gather information for a more definitive actual use study of orlistat 60 mg. After acquiring the rights to develop and market orlistat 60 mg capsules for nonprescription use, GSK felt that no additional actual use studies were necessary and relied upon study NM17285 as evidence of consumer behavior pattern.

Dr. Feibus has criticized the duration of this actual use study. On page 45 of her review she lists elements of the study design that may not support the product's proposed duration of use or may make interpretation of data difficult. Item 2 in this section of her review states the following:

"*This actual use study evaluated consumer use of orlistat over a 90-day use period. The proposed duration of use for orlistat OTC is six months. Data collected using this study design can not provide information on consumer use and discontinuation behaviors, and consumer compliance with recommended lifestyle modifications (diet and exercise) after 90 days of use. It is often preferable for actual use studies to last longer than a product's proposed duration of use.....*"

Dr. Feibus does not take issue with the recommended 6-month duration of therapy; however, it is evident that even she questions the interpretability of results from this 3-month actual use study, even if applied to 6 months of drug use.

With modification of the label to remove any limit on duration of use, I would then argue that a longer actual use study is necessary to evaluate consumer use behavior with nonprescription orlistat. The agency has not published any Guidance to Industry regarding the appropriate duration for an actual use study investigating nonprescription therapy of a chronic condition. I note, however, that in the clinical development programs for nonprescription Mevacor and Pravachol, all actual use studies submitted for approval of chronic lipid-altering therapy were of 6 months' duration. These studies also enrolled far greater numbers (3000-6000+ enrolled) than the 3-month actual use study (~700) submitted to the orlistat nonprescription NDA. Consequently, I do not think it is inappropriate to require GSK to conduct an actual use study of the same duration (i.e., 6 months) to evaluate consumer behavior for a drug that has the potential for repeated, if not chronic, use.

Safety

Overall, there are few serious safety concerns associated with orlistat therapy. The majority of adverse events recorded in the prescription and nonprescription studies were gastrointestinal in nature and nonserious. The safety concerns discussed at length by the advisory committee members related to malabsorption of fat-soluble vitamins and the need for multivitamin supplementation and drug-drug interactions.

Table 7.1.7.3.1.1.A from Dr. Golden's review summarizes the frequency of two consecutive measures of vitamins A, D, or E that fall below the lower limit of the reference range in 7 studies conducted under the prescription NDA. There is evidence of decreased levels of fat-soluble vitamins associated with orlistat use, particularly at the 120 mg tid dose which is also recommended in the nonprescription label. The label comprehension study results, as reviewed by Dr. Susanna Weiss, suggest that consumers do not understand the need to take a daily MVI and to separate the MVI intake from the dosing of orlistat. Both review divisions are in agreement that the label should better convey these instructions to consumers and test the changed labeling. Several members of the advisory committee entertained the possibility of co-packaging nonprescription orlistat with a multivitamin. I would also encourage the applicant to consider this recommendation.

Although drug-drug interaction studies between orlistat and warfarin were negative and no clinically relevant changes in prothrombin time have been noted in the clinical studies, decreases in vitamin K levels observed with orlistat use remain a concern in patients taking warfarin. The Drug Facts label used in the label comprehension study recommended that the consumer consult a doctor or pharmacist before orlistat use if he/she is on warfarin. The label comprehension study revealed that 93 to 94% of study participants provided a correct or acceptable response regarding whether the drug should be used with warfarin. The actual use study employed a different Drug Facts label which stated *Do not use* if on warfarin. The correct self-selection in this setting was only 50%. Dr. Feibus noted in her review that the applicant submitted a specific warfarin self-selection study after the advisory committee meeting. The results of this study need to be considered in a revision to the Drug Facts label and tested in another actual use study.

A pharmacokinetic interaction between orlistat and cyclosporine has been established with cyclosporine levels clearly decreased when co-administered with orlistat. The clinical consequence of this interaction may be serious for patients taking cyclosporine to prevent organ transplant rejection. The concern is not a theoretical one. In her review, Dr. Golden has summarized AERS reports of reduced cyclosporine levels and two cases of acute organ rejection resulting from orlistat and cyclosporine co-administration. Similar to the consumer comprehension findings for warfarin, the results from the actual use study did not support

the findings from the label comprehension study for cyclosporine use. Of two patients who were on cyclosporine who reviewed the materials in the actual use study, one inappropriately responded that he/she could use this product despite the Drug Facts label stating "*Do not use* if you are taking cyclosporine (a drug given after organ transplant surgery)". Based on these results, the rate of incorrect self-selection for cyclosporine was 50%, albeit from only a sample size of 2 subjects. The applicant conducted a label comprehension study directed specifically at organ transplant patients taking cyclosporine. This study was not submitted with the NDA for nonprescription orlistat but was presented at the advisory committee. In this study, 89% were able to correctly self-select. Given the dire consequence of incorrect label comprehension for use with cyclosporine (i.e., risk of transplant organ rejection), I find these self-selection results unacceptable. ONP does not have established guidelines for what constitutes appropriate self-selection but judges results based on the circumstance (e.g., reasons provided for decision made by the consumer; healthcare provider advised it was appropriate to use despite labeled exclusion) and potential outcomes (e.g., any harm in making the wrong decision). For this issue I would expect no less than 100% correct self-selection. The consequence of incorrect self-selection far outweighs the efficacy provided with orlistat. The label must be modified and tested with a 100% goal of correct self-selection.

Other safety concerns arising from the review of the actual use study were related to inappropriate self-selection by consumers despite the presence of a labeled exclusion. There were only 681 patients eligible for analysis in the actual use study. Of these, 465 had a labeled exclusion and 358 (77%) made an incorrect decision regarding the use or purchase or orlistat. In addition to the low correct self-selection rates for warfarin and cyclosporine, the results from the actual use study also showed low correct self-selection rates for use of anti-diabetic medicines, anti-hypertensives, gallbladder problems, or malabsorption. The consequence of inappropriate use of orlistat under these circumstances is less certain; however, the applicant should make better effort at improving consumer comprehension of these exclusion criteria.

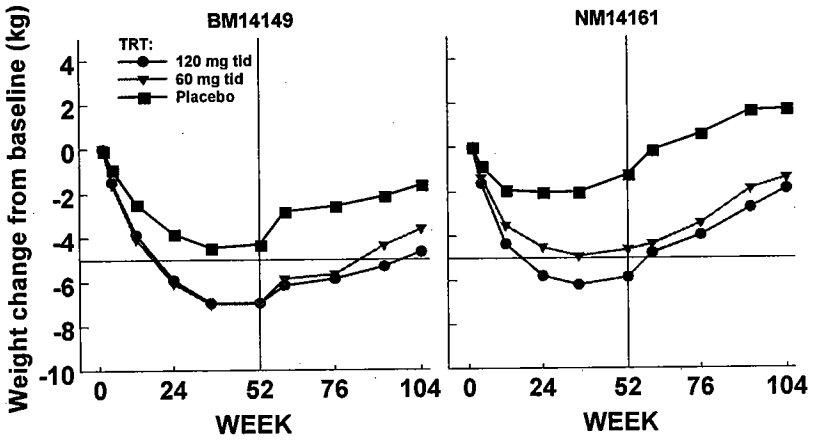
Finally, gallstones and pancreatitis have been raised by DMEP as additional safety matters requiring closer investigation. Both Drs. Golden and Colman have extensively discussed these issues in their reviews. I will only add that I agree with Dr. Colman that should a decision be made to approve orlistat for nonprescription use, the safety signal for pancreatitis will need further consideration.

Educational Program

The applicant is proposing the availability of nonprescription orlistat with educational materials on lifestyle modifications (diet/exercise/behavioral) to assist consumers in losing weight. The significant role of lifestyle modification programs in any weight-loss program is well-argued in Dr. Golden's review. In Section 6 of her review, Dr. Golden outlines the different degrees of lifestyle modification programs employed in the 3 clinical efficacy studies and the impact each had on the efficacy of orlistat. All patients enrolled in studies BM14149, NM14161, and NM17247 were placed on a hypocaloric diet and had scheduled study-site visits with objective weight measures. The more intensive lifestyle intervention program (BM14149) utilized dietitians and included food intake records which were reviewed by the dietitian and discussed with the patient throughout the study. Less intensive programs (NM14161 and NM17247) utilized self-instructional materials or videos, and while food intake records may have been completed by patients and reviewed by study site personnel, no feedback was provided to the patients. The absolute efficacy of orlistat was greater in the intense lifestyle intervention program compared to the less intensive program.

Lifestyle modification programs contribute to weight-loss efficacy across all treatment groups, including placebo. As Dr. Golden points out, liberalizing the dietary intervention results in loss of efficacy as summarized in the following graph generated by FDA statistical reviewer, Ms. Joy Mele. In this graph, patients in the two pivotal NDA prescription trials were switched from a low-caloric diet to a eucaloric

diet after 52 weeks but were maintained on drug treatment. After this period of time, weight regain is observed in all treatment groups.



Dr. Golden also cites landmark studies employing lifestyle/behavioral modification other than weight-loss drug studies to support her argument on the importance of lifestyle modification. The Diabetes Prevention Program, published in February 2002, showed that after an average follow-up period of 2.8 years, patients randomized to intensive lifestyle intervention and exercise (~150 minutes moderate intensity activity per week) with a goal of achieving and maintaining a weight reduction of at least 7% of initial body weight had a statistically significantly lower incidence of developing type 2 diabetes mellitus over metformin therapy or a less intensive lifestyle/exercise program.[3] Even in the absence of pharmacotherapy, intense lifestyle/behavioral modification is an effective and powerful tool that can achieve significant clinical results.

In all, Dr. Golden has presented strong scientific arguments supporting lifestyle intervention as the cornerstone of any weight-loss program. The applicant proposes to market nonprescription orlistat with an OTC starter pack that includes: supplementary support materials; a companion guide; QuickFacts card; a Healthy Eating Guide; a daily journal; a calorie and fat counter; and a Welcome Card that introduces the consumer to the behavioral support program. These materials are considered part of the Alli® Weight Loss Program but were designed after the conduct of the actual use study. At the advisory committee, the applicant also raised the possibility of making a web-based program available to assist consumers on lifestyle and behavioral modifications. All these proposals sound appealing but in truth, have not been tested rigorously to determine if the method of use of nonprescription orlistat along with these educational materials will be an effective weight-loss program. Indeed, the FDA withdrew its question to the advisory committee regarding the effectiveness of the proposed educational materials because these materials were NOT evaluated in the actual use program.

In her review, Dr. Golden expressed concern that in the nonprescription setting, without a learned intermediary, adherence to lifestyle interventions would diminish. She states, "*However, given the degree of interaction with healthcare provider, the above studies do not address how well individuals, without interaction with a healthcare provider, will comply with and benefit from the written educational materials on lifestyle changes that accompany nonprescription orlistat.*" Both she and Dr. Colman have recommended a placebo-controlled efficacy study in the actual use setting to assess the impact of these educational materials on weight loss.

---

[3] Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002; 346:393-403.

In considering her concerns, I must note that a placebo-controlled efficacy study in the actual use setting will not address whether nonprescription orlistat with its educational program but no healthcare provider is as effective as prescription orlistat because these two treatment paradigms are not compared directly to one another. However, the study design that both Drs. Golden and Colman are proposing will inform us whether drug will add any additional benefit to the educational materials proposed for nonprescription marketing of orlistat. Their proposal does have merit. If we are to assume that the approval of nonprescription orlistat includes the educational materials as "collateral measures necessary for the effective use of the drug product", I would concur with Drs. Golden and Colman that such a study is necessary for its approval.

We should also be reminded that the educational materials we approve with nonprescription orlistat serve as the standard under Waxman-Hatch Amendments to the Federal Food, Drug, and Cosmetic Act for labeling of generic nonprescription orlistat products.[4] If these materials become the standard tools for orlistat's weight-loss efficacy, should we not know how well they work before mandating all other generic orlistat nonprescription products adopt them in their program?

I have further discussed Drs. Golden's and Colman's recommendations with Ms. Mele and Dr. Todd Sahlroot from the Office of Biometrics. Interpretable data from such a study would require near complete collection of objective weight measures of study participants. Given the low rate of return from Day 60 to 90 for objective weight measure in the 3-month pilot actual use study (only 25%), complete end-of-study data collection must be the goal targeted by GSK. Such a requirement is not an insurmountable hurdle, as drug companies have been able to conduct 5-year mortality studies with data ascertainment in almost all patients randomized to therapy. I note that in the 5-year, placebo-controlled cardiovascular mortality and morbidity study for simvastatin (Heart Protection Study), over 20,000 patients were randomized to treatment or placebo. Endpoint data were missing in only 7 patients who moved out of the country.

As I am recommending a more definitive actual use study to address aforementioned deficiencies, I would also stipulate that the definitive actual use study be one which includes a control group with one of the objectives being ascertainment of final weight at the retail pharmacy in all patients randomized.

OTHER ADMINISTRATIVE/REGULATORY ISSUES

Financial Disclosure

This was reviewed under Section 4.6 of Dr. Golden's review. No concerns were raised regarding the financial disclosure information submitted that would affect the integrity/reliability of the data.

Pediatrics

Xenical® 120 mg tid was evaluated in a one-year study in pediatric patients ages 12 to 16 years under the prescription NDA. These study results are discussed under the Clinical Studies section of the prescription package insert. The nonprescription program is not proposing marketing in the pediatric population. A label comprehension study has been conducted specifically in teenagers; the results were submitted to the nonprescription NDA after the advisory committee meeting and were not reviewed during this review cycle.

The Division of Pediatric Drug Development was consulted regarding the appropriateness of nonprescription orlistat in the pediatric population. Dr. Lisa Mathis, acting director of DPDD, has recommended against the availability of nonprescription orlistat for pediatric use. I concur with her

[4] United States Court of Appeals for the Second Circuit. SmithKline Beecham Consumer Healthcare, LP vs Watson Pharmaceuticals, Inc., Watson Laboratories, Inc., and Circa Pharmaceuticals, Inc. Docket No. 99-9501.

recommendation, as I agree that overweight and obesity in pediatric patients require a multi-disciplinary approach with intensive behavioral and education intervention to ensure lifelong success at maintaining healthy weight. The importance of good nutrition and exercise is particularly important in children as such programs will surely impact growth and development. I also believe that the concerns regarding fat-soluble vitamin malabsorption may have a greater impact on the growing child and would therefore recommend against the unprescribed use of orlistat in the pediatric population.

RECOMMENDATIONS

Under 21 CFR 310.200(b), a drug can be exempted from prescription-dispensing requirements outlined under section 503(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (i.e., be available as non-prescription therapy) if the agency deems that safety of a drug, the method of use, or the "collateral measures necessary to its use" are no longer necessary for the safe and effective use of the product in self-medication as directed in the proposed label.

Although I believe the overall safety profile of orlistat makes it a favorable candidate for nonprescription availability, the applicant has not demonstrated that the method of its use by consumers will ensure its safety or that the "collateral measures necessary to its use" will ensure that it will be effective in the nonprescription setting.

The deficiencies of this program can be summarized as follows:

Method of Use

The deficiencies under *method of use* relate primarily to the findings from the pilot actual use study and the label comprehension study. The applicant must improve label comprehension and test for appropriate self-selection/comprehension in an actual use study of longer duration for the following:

- reinforce that patients taking cyclosporine not take orlistat
- reinforce that patients taking warfarin not take orlistat
- better instruct patients who are taking anti-diabetic medications on whether orlistat is appropriate
- better instruct patients regarding daily use of a multivitamin and timing of the MVI with orlistat dosing

For reasons already discussed under the *Target Population* section of my memo, I am also recommending that the label specifically target overweight and obese adult patients based on BMI criteria established for the prescription orlistat label. The actual use study should also test whether adolescents will use the product if available in a nonprescription setting.

Collateral Measures

As this NDA is not limited to orlistat alone, but also includes the educational materials to assist consumers in the nonprescription setting to lose weight, I recommend that these *collateral measures* necessary for the effectiveness of nonprescription orlistat be studied in a clinical trial. As I am recommending an actual use study to address the deficiencies under *method of use*, I believe the efficacy of the educational materials can also be evaluated in an actual use study. I believe a 6-month study, if appropriately designed, can address these deficiencies to provide the agency with valuable safety and efficacy information that will allow me to confidently endorse this new treatment paradigm of treating chronic conditions in an over-the-counter setting. I would encourage the applicant and my colleagues in the agency to, at a minimum, discuss the feasibility of such a study and move away from what has been standard practice for the approval of Rx-to-OTC applications.

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

/s/

Mary Parks
3/22/2006 04:14:33 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: **March 21, 2006**

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

Subject: **NDA 21-887**
Orlistat 60 mg capsules

Sponsor: **GlaxoSmithKline**

BACKGROUND:
Orlistat is a pancreatic lipase inhibitor that blocks hydrolysis of triglyceride in the stomach and small intestine, thus inhibiting dietary fat absorption. Orlistat 120 mg (Xenical®, NDA 20-766) was approved as a prescription product in April, 1999. The product is indicated for weight loss and maintenance for obese patients with a BMI $\geq$ 30 kg/m^2 or for a subset of overweight patients with a BMI $\geq$ 27 kg/m^2 plus co-morbid conditions when used with a reduced calorie diet. Orlistat is also approved to reduce the risk for weight gain after prior weight loss. The duration of therapy is not limited by labeling. The sponsor is Roche Laboratories. The prescription labeling does not state that Xenical® must be used only in conjunction with a specific behavioral modification program. It simply states that the patient should be on a nutritionally balanced, reduced-calorie diet that contains approximately 30% of the calories from fat and that the daily intake of fat, carbohydrate, and protein should be distributed over three main meals. The prescription label states that patients should be counseled to take a multivitamin at least 2 hours before or after the administration of Xenical®.

The target population for Xenical® is consistent with the National Institutes of Health's (NIH) *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 1998*, the NIH 2000 *Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*, and the 1996 FDA *Guidance for the Clinical Evaluation of Weight-Control Drugs*. The guidelines state that because overweight and obesity tend to be chronic, relapsing conditions, the indefinite treatment of the target population with drug therapy is warranted. That the Xenical® prescription labeling does not recommend a limitation in duration of therapy reflects this philosophy of treatment.

The FDA's Guidance uses a mean $\geq$ 5% of weight loss as the benchmark for prescription weight loss drug approval because this amount of weight loss is clinically meaningful from a cardiovascular risk factor perspective. The Guidance recommends one year of data to assess the long term efficacy and safety of prescription weight loss drugs.

GlaxoSmithKline Consumer Healthcare, L.P. (GSK), submitted NDA 21-887 for nonprescription orlistat 60 mg capsules (Alli) to promote weight loss in overweight adults, age 18 years and older, when used along with a reduced calorie, low-fat diet. The proposed dosing regimen is 1 – 2 capsules (60 – 120 mg) with each fat-containing meal, up to three times per day. The proposed labeled duration of use is up to six months at which point, if the weight goal has not been met, the consumer is directed to a physician. The sponsor proposes to include a variety of informational materials with the product that address how to properly use the drug, calories and the fat content of food, portion sizes, meal planning, exercise, and how to eat when dining out. A food diary is also among the informational materials.

An Advanced Notice of Proposed Rulemaking was published on February 26, 1982 (47 FR 8466) that addressed over-the-counter (OTC) weight control products. The Advisory Review Panel on OTC Miscellaneous Internal Drug Products, (the Panel), recommended temporary use (which they defined as three months) of OTC weight control drug products, for assistance in weight reduction, in an obese population, in conjunction with a diet. The Panel recognized that behavioral changes were important components of weight control.

In comments and recommendations to GSK dated 5/3/05, FDA stated that treatment exceeding six months for obesity management and treatment of co-morbidities should remain prescription indications and that the OTC population could include a wide range of BMIs ranging from slightly overweight to obese. We told the sponsor that the "overweight" population is acceptable for OTC.

REVIEW:

Chemistry

Refer to the reviews by Dr. Blair A. Fraser and by Dr. Martin Haber. From a CMC perspective, both chemists recommend approval of this NDA

Pharmacology/Toxicology

No new data was submitted for this NDA.

Clinical Pharmacology/Biopharmaceutics

No new data was submitted for this NDA, however, Dr. Golden summarized the biopharmacology data from the Xenical® application.

Orlistat is minimally absorbed and is primarily metabolized within the gastrointestinal wall. Fecal excretion of unabsorbed drug is the major route of elimination. The 1% – 3% of orlistat that is absorbed is excreted through the biliary tree and < 2 % via the kidneys. Approximately 25% of dietary fat absorption is blocked by 60 mg of orlistat and

approximately 30% is blocked by 120 mg. Based upon limited data, the half life of orlistat is 1 – 2 hours.

A single dose of two 60 mg capsules is bioequivalent to one 120 mg capsule.

Clinical:

Efficacy:

See the review by Dr. Julie Golden and the statistics review by Joy Mele. Dr. Golden comments that the efficacy benchmark of 5% used for prescription weight-loss drugs is based on evidence that, in obese patients, this degree of weight loss can result in clinically meaningful improvements in cardiovascular-related co-morbidities. For the purposes of the OTC application for 60 mg – 120 mg of orlistat per dose, Dr. Golden reviewed the data from the first year of two 2-year trials from the Xenical® NDA. One study (study BM 14149) enrolled subjects in Europe in special obesity and nutrition centers with BMIs ranging from 28 – 43 kg/m^2 and the other (study NM 14161) enrolled subjects in the United States with BMIs ranging from 30 – 43 kg/m^2 who saw primary care doctors. In one of the studies (BM 14149) patients received intensive dietary counseling; in the other (NM14161) they did not but they did receive informational material in the form of behavior modification pamphlets and were encouraged to exercise. In study BM 14149, diet diaries were monitored and in the other (NM 14161) they were analyzed but the patients were not given feedback.

Because the sponsor proposed to market nonprescription orlistat for 6 months of use, the FDA reviewers chose the 6-month time point as the efficacy endpoint of interest from the two Xenical® efficacy studies. The pooled data from these two studies demonstrated that at 6 months the orlistat 120 mg group and the orlistat 60 mg group achieved a weight loss $\geq$ 5% that was statistically significantly better than weight loss achieved in the placebo group ($p > 0.001$).

There was an additional 4-month clinical efficacy study of orlistat 60 mg (NM17247) in patients with a BMI of 25 to < 28 kg/m^2 submitted with the GSK NDA. Participants received dietary counseling at each visit. Thirty-six percent of subjects taking orlistat 60 mg versus 28% of placebo-treated subjects lost at least 5% of their weight at four months. This difference was not statistically significant. The percent of orlistat-treated subjects achieving a 3% weight loss was statistically significantly greater compared to placebo after 4 months of treatment (57% versus 42%, $p = 0.004$). Ten percent of the orlistat group lost at least 10% of their weight, but although this group was twice the size of the placebo group with that amount of weight loss, the results were not statistically significant. It is not known what the weight loss would have been at 6 months. Joy Mele notes that the treatment effect seen in study NM 17247 at Month 4 is similar to the treatment effect seen in study BM 14149. She states that the treatment effect was the largest in study 14161 where there was no dietary counseling and that the observed mean weight loss was 3.6 kg. She also notes that after 6 months of treatment, the largest mean decrease that could be expected in future trials with the 60 mg dose is about 5 kg for the 60 mg dose and about 5.5 kg for the 120 mg dose. With the proposed OTC dosing, the

OTC consumer would have the opportunity to titrate their orlistat dose according to their weight loss needs. They could take 60 mg per dose, or they could take 120 mg per dose.

Efficacy was not an endpoint of the 3-month actual use study and the methodology for the study did not lend itself to a meaningful conclusion about efficacy. All that one can surmise about efficacy from this study is that it appears that 75% of subjects lost some weight and that 40-45% may have lost $\geq$ 5% of their body weight by the end of the study. The mean objective weight loss was 3.3 kg at the end of the study (based upon 45% of orlistat users). Among those who lost weight, the mean self-reported weight loss was 4.8 kg.

In the prescription population, people who stop using drug tend to regain weight. Dr. Golden expresses her concern about the likelihood of a similar tendency toward weight regain in the nonprescription user population. Golden also expresses her view that the efficacy data for nonprescription use is lacking because a one year, placebo-controlled trial was not done in that setting. She recommends such a study in "Actual Use."

Safety:
See Dr. Julie Golden's review.
Orlistat is minimally absorbed and the most common adverse events are gastrointestinal. The prolonged use of orlistat without vitamin supplementation has the potential to lead to clinically relevant fat-soluble vitamin malabsorption. If vitamin K is not supplemented while on orlistat, there is the potential, over time, for warfarin users to require a decrease in warfarin dose or they may be at increased risk for bleeding. However, as stated in Dr. Eric Colman's review or orlistat safety for NDA 20-766, long term treatment does not appear to cause frank vitamin K deficiency as assessed by prothrombin time. The potential for change in the International Normalized Ratio (INR) is also possible if warfarin users modify their diet without being on concomitant drugs. Since warfarin users are frequently monitored for changes in their INR (as confirmed in the self-selection study below), in practicality, this potential orlistat Vitamin K deficiency may not be a worry of great concern. This concern is eliminated if consumers follow instructions to take a multivitamin. Orlistat can decrease the absorption of cyclosporine if given concomitantly and has the potential in the worst case scenario to result in rejection of a transplanted organ. This has been reported with the prescription medication. Drug-drug interactions with orlistat and amiodarone have also been recognized. The impact of the possible 25% reduction in serum level of amiodarone on its efficacy is unknown.

The causative role of orlistat in nephrolithiasis, cholethithiasis, hepatitis, and pancreatitis remains inconclusive. A consultation provided by Drs. Cynthia Kornegay and Mark Avigan from the Office of Drug Safety indicates that it is possible that there is a pancreatitis safety signal (albeit rare) for orlistat and they are recommending a warning under *postmarketing surveillance* in the prescription label. There were no cases of pancreatitis in the controlled studies or in the Actual Use Study.

Behavioral Studies:
See the reviews by Dr. Karen Feibus and Dr. Susanna Weiss.

GSK provided:

- Roche's Actual Use Study (AUS) Data
- GSK's Label Comprehension Study (LCS) Data from a label comprehension study conducted following the Actual Use Study and using a label that was different from that used in the AUS. The label comprehension study label was identical to the proposed NDA label except that the "Do not use if you are not overweight" warning was added after the LCS.
- GSK's Three Self-Selection studies (SSS): one testing teenagers, one testing warfarin users and one testing cyclosporine users. These studies were performed using the proposed NDA label.

AUS:
The AUS was designed to evaluate self-selection, compliance with dosing and other label directions for use, and adverse events. The study population was skewed in that it was predominantly female, Caucasian, and of normal literacy. The study demonstrated that subjects could self-diagnose that they were overweight; only eight percent who were normal weight self-selected to use the drug and no one who was underweight self-selected to use the drug. This is consistent with the advisory panel's view that obesity/overweight is an acceptable OTC indication. Study participants dosed orlistat correctly based on label directions and most reported following low fat/reduced calorie dietary recommendations.

Consumers made many self-selection errors based upon the label warnings. The following self-selection outcomes are most concerning from a clinical standpoint:

- Cyclosporine users (50% correct)
- Diabetes medicine users (35% correct)
- Warfarin users (50% correct)
- Taking another weight loss medicine (12% correct)
- Gall bladder problems (40% correct)

The safety profile in the actual use study was similar to that seen in the controlled clinical trials.

LCS:
The well-conducted label comprehension study demonstrated excellent comprehension of these label warnings (cyclosporine, diabetes medicines, warfarin, taking another weight loss medicine, gall bladder problems). There was a low literacy cohort of good size and this cohort also demonstrated excellent comprehension of these warnings. Comprehension was also excellent for how to dose orlistat. However, the label comprehension study showed that 73 % of consumers understood the multivitamin messages and 79% understood that it is not appropriate to use orlistat if a person is underweight. It would be of value to improve upon comprehension in these areas.

The diabetes medication warning was changed for the LCS and comprehension was 97%. This new language was not tested in a self-selection study. Since there is a theoretical potential for hypoglycemic episodes in diabetics on medication who might incorrectly

self-select to use orlistat without asking their doctor, a SSS on this element would be worthwhile.

SSS:
As Dr. Feibus points out, in the cyclosporine self-selection study, among 46 cyclosporine users, 44 had an organ transplant. Overall, 89% made a correct self-selection decision and 92% of these individuals made their decision based on using cyclosporine or having an organ transplant. If the self-selection rate is calculated only for cyclosporine users with a transplant and the data on the participant who was probably erroneously classified as "male, pregnant, and breastfeeding" is excluded, 40 out of 43 (93%) participants made a correct self-selection decision.

Three of the five participants who made an incorrect self-selection decision did not see the cyclosporine warning when they reviewed the orlistat label. When presented with the label and warning for a second time, two of the three stated that orlistat was not appropriate to use. It is not clear whether or not the participant who self-selected incorrectly the second time had an organ transplant. As is true for all nonprescription drug products, some individuals who read and understand the cyclosporine warning may choose to disregard it. (This quirk of human behavior that leads medication users to disregard important professional advice can also apply to the doctor-patient setting.) I agree with Dr. Feibus that strengthening labeling language and enhancing the appearance of the cyclosporine warning on the orlistat label may still improve self-selection decisions among consumers.

In the warfarin self-selection study, 59% of the 54 warfarin users made a correct self-selection decision. It is interesting, that as Dr. Feibus points out, among warfarin users with no other labeled contraindications to orlistat use, self-selection decisions were correct 89% of the time. However, warfarin users with other labeled contraindications self-selected correctly only 31% of the time.

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

Warfarin users enrolled in the study were able to self-diagnose overweight. All reported having coagulation studies done at least four times per year and most reported having coagulation studies at least monthly.

In the AUS, only 14 subjects were warfarin users and 50% made correct self-selection decisions. It is difficult to compare this data to that from the warfarin SSS. This is because the warfarin warning on the AUS label was a "Do not use" warning, and the warfarin warning on the proposed NDA label used in the SSS was an "Ask before use"

warning. In the LC study, 94% of subjects demonstrated comprehension of the warfarin warning used in the SSS.

The teenager SSS enrolled 147 teenagers ages 14 – 17 and showed that 59% of teens made the correct self-selection decision and that those who made an incorrect decision were motivated to do so by the urge to lose weight. Dr. Weiss points out that teenagers who were either at risk of being overweight or who were overweight according to their BMIs were more inclined to want to purchase orlistat (60%) compared to those who were either underweight of normal weight (29%). It appeared from this study that price deterred teens from pursuing purchasing orlistat because the percentage of incorrect self-selectors who wished to purchase dropped precipitously after hearing the price. Overall, only 13% of the entire study population wished to buy orlistat.

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.

Advisory Committee Meeting
At the January 23, 2006 joint meeting of the Nonprescription Drug Advisory Committee and the Endocrinologic and Metabolic Drug Advisory Committee on January 23, 2006, the committee members assessed that efficacy of orlistat had been demonstrated for both the 60 mg and 120 mg dose in the nonprescription setting for overweight and obese individuals. They determined that the safety profile of the drug was acceptable for an OTC drug. The committee recommended stronger labeling to discourage use in people less than 18 years of age. The committee voted that the label was adequately understood and that consumers complied with the dosing directions. The consensus was that the potential benefit of orlistat availability without a prescription outweighed the risk and they voted that the NDA should be approved for nonprescription use. The committee was mixed as to the adequacy of self-selection decision making on the part of the consumer and many members wanted to see stronger labeling to improve self-selection.

DISCUSSION
Consistent with the Advisory Committee's and the Panel's view, "overweight" is a self-diagnosable condition. For NDA 21-887 GSK relied upon the efficacy data from the Roche NDA for Xenical®. This approach to supporting product efficacy is typical for Rx-to-OTC switch applications when the OTC product is intended for the same indication as its prescription counterpart. GSK performed an additional placebo-controlled efficacy study at the 60 mg dose in an overweight population that was not covered by the original efficacy studies but who might use orlistat OTC. This approach to supporting product efficacy is typical for Rx-to-OTC switch applications when the OTC product is intended for a different indication.

Dr. Golden suggests that we do not have adequate efficacy data for Orlistat 60 mg for the nonprescription population. We have 2-year data for both orlistat doses in overweight and obese individuals and 4 months of data at the low dose in overweight individuals. We have data when the drug is used in the setting of intensive behavioral modification

and in settings where minimal dietary assistance was provided. It would be reasonable, looking at the totality of the data, to conclude that subjects who use orlistat (whether 60 mg or 120 mg, with and without physician oversight, with and without substantial behavioral modification) lose more weight over time than subjects who do not. How much weight loss is clinically relevant and represents a favorable benefit/risk ratio can be interpreted differently by different observers. It is clear from the Xenical® efficacy studies that orlistat in both 60 mg and 120 mg doses can cause a significant weight loss in users with and without active behavioral modification therapy. The prescription Xenical® label only recommends following a diet in addition to using the drug. The behavior modification materials the sponsor is including in the proposed Alli package contain elements that inform about appropriate diets to follow while on orlistat. The information is consistent with the dietary recommendations in the Xenical® prescription labeling and, in many ways, more complete. I disagree with Dr. Golden that more efficacy data is needed.

Dr. Golden comments that no data exists to support the clinical benefits of weight loss in subjects who are mildly overweight. She must be referring only to cardiovascular-related clinical benefits as defined by improvement in co-morbidities and as written in the FDA guidance. I do not agree with the guidance limitations on target population. For instance, it does not make clinical sense to me that someone with a BMI of 27 kg/m^2 with hypertension and hyperglycemia should be able to take a safe medicine to help lose weight, but someone with a BMI of 26 kg/m^2 who has those same co-morbidities should not. Nor does it make clinical sense to me that someone with a BMI of 26 kg/m^2 should be denied a safe medication until he/she gains the 5 or 6 additional pounds that lift him/her into the 27 kg/m^2 BMI category at which point hypertension and hyperglycemia might develop.

Thinking in terms of just cardiovascular co-morbidities as a trigger for drug therapy in the overweight population overlooks many other medical reasons for this population to lose weight, for the medical literature is replete with articles demonstrating non-cardiovascular risks of being overweight and obese. For example, it is well-recognized that overweight is related to osteoarthritis of the knees. Overweight persons are at high risk of osteoarthritis in the knee and probably also in the hips and hands. The mechanism by which being overweight causes osteoarthritis is poorly understood; a contribution from both an increased local force across the joint and systemic factors is likely.[1] The 1995 American College of Rheumatology Osteoarthritis Guidelines recommended that overweight patients with hip and knee osteoarthritis have a significant improvement in their symptoms if they lose weight and this was reiterated in the updated 2000 Guidelines[2]. Weight loss reduces the risk for symptomatic knee osteoarthritis in women.[3] In this article, Felson showed that a decrease in body mass index of 2 units or more (weight loss, approximately 5.1 kg) over the 10 years before the current examination decreased the odds for developing osteoarthritis by over 50% (odds ratio, 0.46; 95% CI, 0.24 to 0.86; P = 0.02). Among women with a high risk for osteoarthritis due to elevated baseline body mass index (greater than or equal to 25), weight loss also decreased the risk (for 2 units of body mass index, odds ratio, 0.41; P = 0.02). Data suggests that even a moderate increase in BMI within the normal weight range (BMI 23 to < 25 kg/m^2

compared to a BMI ,23 kg/m^2) is significantly related to increased risk of developing osteoarthritis of the knee in men[4]. To improve the symptoms of osteoarthritis, even a small amount of weight loss helps. It is important to remember that arthritis begets physical inactivity and the NIH Guide mentioned above states that regular physical activity can independently reduce the risk for cardiovascular disease. In adult life, a shift from normal to overweight may carry a higher risk for knee OA requiring arthroplasty than does constant overweight.[5] Overweight can be damaging in other ways. End stage renal disease risk had recently been linked to being overweight.[6] Psychological benefits that weight loss can offer should be considered, as well.

Orlistat appears to be a safe drug. It is barely absorbed at all. The predominant adverse events are gastrointestinal ones. Ironically, these gastrointestinal adverse events in some ways have the potential to be a silver lining with regard to dietary compliance. By modifying eating behavior to reduce dietary fat the orlistat user can prevent objectionable events like fecal leakage and attendant adverse "social consequences." After seven years of prescription use it is unclear whether the drug plays a causative role in nephrolithiasis, gall bladder disease, pancreatitis, or hepatitis. If the drug is, indeed, associated with pancreatitis, the incidence is quite rare and, in my opinion, insufficient to keep the drug out of the nonprescription marketplace. I do not see this possible rare incidence as a significant shift in risk/benefit ratio. I note that this would not be the first time that a drug rarely associated with pancreatitis (e.g., cimetidine, omeprazole, raniditine) would be available without a prescription.

In the July 17, 2002 End-of-Phase 2 meeting with Roche when they were exploring the prescription to OTC switch for orlistat, the Agency recommended that Roche "address in the OTC label the issue of vitamin supplementation" and that the "potential drug-drug interaction (e.g., cyclosporine-orlistat) be addressed in this population." What the sponsor was told is consistent with the way the Agency has addressed other drug-drug interaction issues for OTC drugs. The Agency did not state to the sponsor that a particular threshold of comprehension and self-selection needed to be met and did not say that any error in comprehension or self-selection for drug-drug interactions would make this drug a "no starter" for an OTC switch. Thus, the sponsor could assume that there would be some tolerance for error in these areas, but that the degree of tolerance was yet to be determined.

The actual use study data suggests that the risk of abuse would be low for orlistat since no one self-selected to use orlistat who was underweight. If a subset population were to abuse orlistat, the safety issues related to abuse are likely to be minimal. The drug is not absorbed and is not addictive. As Dr. Feibus points out, it exerts a physiological effect only when fat is present in the diet. Among individuals with anorexia nervosa who practice severe dietary restriction and consume little fat, the drug would not exert an effect. She notes that half of anorectics do binge and purge but the binges are small. Individuals with bulimia often induce vomiting or use cathartics following binging. Because of the way orlistat works, the bulemics would be unlikely to achieve the immediate or substantial weight loss with orlistat use that they seek and sometimes achieve with other purging methods. In Dr. Feibus' review she referenced the four

published cases of bingers using orlistat. She also referenced two published studies that suggest that orlistat is effective for weight loss in individuals with binge eating disorder when combined with behavioral therapy. One could anticipate that the primary safety issue for inappropriate orlistat users who have anorexia or a binge eating disorder would be the same risk of vitamin deficiency that could develop over time with chronic use in the orlistat targeted population.

As with other OTC drugs that have the potential for drug-drug interactions, I think this issue can be addressed with labeling. My opinion is the same for the multivitamin messages. The Advisory Committee shared these views. It is interesting that compliance with multivitamin use was not an endpoint of the Xenical® clinical studies. Thus, it is unclear how use in the prescription setting would compare to use in the nonprescription setting.

The approval of Xenical® did not appear to have hinged on whether patients were exercising or motivated. As such, in her comments on pages 7 and 9 of her review, Dr. Golden seems to hold orlistat to a higher standard OTC than as an Rx drug. She seems to be of the view that weight loss can only be properly approached in a monitored healthcare environment. This was not the consensus of the members of the joint Advisory Committee that met two months ago to consider this issue. I agree with the Advisory Committee recommendations and the Panel's perspective and, as a physician, think that the opposite view is excessively paternalistic.

With regard to the labeling, the reasons for disconnect between the label comprehension study and the self-selection decisions of consumers are probably multifactorial and may never be completely bridged. We see this disconnect commonly when we assess label comprehension and actual use study data. When people understand a warning, but choose to ignore it further attempts at strengthening the warning may make a difference, but they may not. The most important thing is that consumers make an informed choice.

The orlistat label directs consumers to check with their doctor if they still need to lose more weight at the end of 6 months. This is reasonable. The message should also direct users to the doctor if they are not losing weight. I think that it would be reasonable to consider labeling the product without a limit on duration of use if the sponsor achieves better comprehension of the multivitamin directions. Less motivated people in the OTC setting will tend to regain weight after they stop taking medication (as they do in the prescription setting) but highly motivated people will not. It is my view that if someone has reached his target weight, for example, after 4 months of use and is able to maintain the weight loss then he should not be mandated to continue to take medication. The product label could remind consumers that if they regain weight they should seek the advice of a healthcare professional about going back on orlistat. This would address Dr. Golden's concern about weight regain, which we know occurs even in the prescription setting.

As Dr. Weiss suggests, it may be helpful for the sponsor to provide guidance about what it means to be "overweight" on the exterior of the product container. Also, the messages

about the need to take a multivitamin and how to dose it relative to orlistat should be strengthened.

It is reassuring that warfarin users are in fact getting monitored frequently by their healthcare providers. This is especially good to see since many nonprescription products already carry a warfarin warning and frequent International Normalized Ratio monitoring adds to their protection if they make a self-selection error. Frequent monitoring alone helps allay concerns about the potential for vitamin K deficiency and its theoretical influence on bleeding risk in warfarin users. However, better compliance with the multivitamin should be sought and could most likely be accomplished through label modifications. Language advising warfarin users that before embarking upon any change in their diet they should talk to their doctors may help to strengthen the warfarin message further.

It is striking that concomitant orlistat and cyclosporine use has occurred in the prescription setting, so the prescription setting is not perfectly safe in avoiding this potential interaction. The cyclosporine warning on the OTC label could possibly be strengthened even more than it already is to achieve even better consumer self-selection, although 93% correct self-selection among transplant recipients is about as good a correct self-selection number as we ever see in actual use studies with regards to a label warning. The degree of tolerance for error among cyclosporine users will ultimately come down to an issue of judgment about benefit/risk for the entire potential user population compared to the cyclosporine user population.

Improved labeling with regard to the use of diabetes medication would also be worthwhile. Also, labeling should be strengthened to increase correct self-selection among teenagers. If a generic version of orlistat were eventually to become available OTC, the price deterrent for adolescents may disappear.

CONCLUSION:
Orlistat is a safe and effective drug for weight loss. With stronger labeling that leads to more accurate self-selection decisions on the part of the consumers (especially with regard to teenage self-selection and not using if not overweight) orlistat could offer a favorable benefit/risk ratio for the nonprescription population of overweight and obese adults. It is unclear if self-selection can be improved for the cyclosporine user since comprehension of the warning is so high. It would be beneficial to see a more effective diabetes medication warning. Duration of use could be made indefinite if comprehension of the directions for multivitamin use improves. In any case, attempts at improving comprehension of the directions for multivitamin use would be worthwhile. Consumers need to be directed to a doctor if they do not lose weight or if they cannot reach their weight loss goal.

RECOMMENDATIONS
This NDA should be approvable. I do not think that further efficacy data is needed. The sponsor should do additional work to strengthen the label. The sponsor should investigate other label wording both on the outside of the product box and in a package

insert and/or other ancillary materials that may enhance the messages about cyclosporine, multivitamin use, and only to use if overweight. Testing the diabetes medication element in a SSS would be useful. The labeling could emphasize that if weight lost is regained, to seek professional assistance before re-starting orlistat. The label should clearly state that the product is not for people less than 18 years old. The sponsor should provide guidance about what it means to be "overweight" on the exterior of the product container. The sponsor could revise the duration of use to an unlimited one if consumers better comprehend the message about taking a multivitamin and if the label contains directions to see a physician if not losing weight or if the weight loss goal is unmet.

REFERENCES:

1. Felson, DT: Weight and osteoarthritis. Am J Clin Nutr 1996 Mar;63(3 Suppl):430S-432S.

2. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines: Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee. Arthritis Rheum 2000;43(9):1905-1915.

3. Felson DT, et al: Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med. 1992;116:535-9.

4. Holmberg A, Thelin A, Thelin N: Knee osteoarthritis and body mass index: a population-based case-control study. Scand J Rheumatol 2005;34:59-64.

5. Manninen P, et al: Weight changes and the risk of knee osteoarthritis requiring arthroplasty. Ann Rheum Dis. 2004 Nov;63(11):1434-7

6. Hsu C et al: Body Mass Index and Risk for End Stage Renal Disease. Ann Intern Med 2006;144:21-28

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

/s/

Andrea Segal
3/21/2006 04:06:32 PM
MEDICAL OFFICER

MEMORANDUM
MEDICAL TEAM LEADER
NONPRESCRIPTION ORLISTAT NDA

NDA: 21-887

DRUG: Orlistat

INDICATION: Weight loss in the nonprescription setting

COMPANY: GlaxoSmithKline

PRIMARY REVIEWER: Julie Golden, MD

DATE OF MEMO: March 16, 2006

I. PRIMARY MEDICAL REVIEWER'S RECOMMENDATION

Dr. Golden recommends that this application not be approved. A principal reason for her recommendation is the fact that GlaxoSmithKline (GSK) has not demonstrated that overweight and obese individuals lose a clinically and statistically greater amount of weight on orlistat vs. placebo when using the company's to-be-marketed lifestyle modification program in the nonprescription setting.

Additional reasons Dr. Golden believes that this NDA should not be approved include the lack of evidence that having access to a nonprescription weight-loss drug has any impact on motivation, dietary or exercise compliance, or long-term health or weight loss outcomes; that individuals derive a health benefit from having orlistat, or any other weight-loss drug, as a nonprescription agent; and that any cosmetic benefit achieved with orlistat being available as a nonprescription weigh-loss drug outweighs actual or theoretical risks of orlistat; in particular, interactions with fat-soluble nutrients and drugs.

Dr. Golden acknowledges that a long-term, placebo-controlled, actual-use trial could be conducted to test the hypothesis that the sponsor's proposed nonprescription orlistat – lifestyle modification program is effective (and safe) in overweight and obese consumers, but she does not believe that the deficiencies outlined in the second paragraph above can be remedied through additional study.

I agree in general with Dr. Golden's overall assessment of the data submitted in this NDA. However, since the Agency did not require Roche to demonstrate that prescription orlistat had an impact on motivation, or compliance with dietary or exercise, or that it

favorably influenced long-term health or weight-loss outcomes, there is no reason to hold the sponsor of nonprescription orlistat to these pre-approval standards.

As acknowledged by Dr. Golden, a principal deficiency of this application could be addressed through conduct of a long-term study conducted under actual use conditions that examined the ability of to-be-marketed labeling to direct effective and safe use of the nonprescription orlistat-lifestyle modification program (when compared with placebo plus the lifestyle modification program) in high overweight subjects with weight-related comorbidies and obese subjects with or without comorbid conditions.

I favor conduct of a long-term, controlled actual-use study as a path forward for the nonprescription orlistat application.

II. REGULATORY BACKGROUND

Orlistat's Approval as a Prescription Weight-Loss Drug

In 1996 FDA approved dexfenfluramine for the treatment of obesity. Unlike all of the previously approved weight-loss drugs, which were indicated for a few weeks use only, dexfenfluramine was developed and approved for long-term therapy. This reflected a growing awareness that obesity is not simply the result of weak willpower that could be corrected with short-term anorectic therapy, but rather a chronic, multifactorial condition that requires long-term or indefinite treatment.

Prescription orlistat 120 mg TID was approved in April, 1999, for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. The target population included individuals with BMIs $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 when accompanied by weight-related comorbidies such as hypertension, type 2 diabetes, or dyslipidemia.

In pre-approval randomized, double-blind, placebo-controlled studies, in which all subjects received standard of care lifestyle modification (diet/exercise/behavior therapy) from investigative sites specialized in treating obesity, 43 – 55% of high overweight and obese individuals treated with orlistat vs. 21 – 27% of subjects treated with placebo, lost $\geq$ 5% of their baseline body weight ($p<0.001$) during one year of treatment. In a study in which patients received less intensive standard of care lifestyle modification from primary care physicians not experienced in the care of obese patients, 37% of orlistat-treated subjects compared with 16% of placebo-treated subjects lost $\geq$ 5% of baseline body weight during one year of therapy ($p<0.001$). The absolute efficacy of orlistat was reduced in subjects who received a "lower dose" of lifestyle modification.

The statistically significant differences between the orlistat and placebo groups in the proportions of patients who lost $\geq$ 5% of their baseline weight satisfied one of the efficacy criterion established in the Agency's 1996 draft *Guidance on the Clinical Evaluation of Weight-Control Drugs*.

Pre-Submission Interactions between FDA and Roche and GlaxoSmithKline

On June 14, 2001, Roche opened an IND with the Division of Metabolic and Endocrine Drug Products to investigate the feasibility of developing orlistat as an over-the-counter (OTC) product. The initial IND submission included a protocol entitled, "A Study to Evaluate the Effect of Orlistat Plus Diet Administered for up to 12 Weeks in a Naturalistic Setting."

On July 17, 2002, The Division of Metabolic and Endocrine Drug Products and the Division of Nonprescription Drug Products met with Roche to further discuss development of orlistat as an OTC drug. Among other things, the Agency informed Roche that they may need to conduct "an actual-use study that can demonstrate the consumer's ability to understand and follow a reduced-calorie diet without the intervention of a dietician and the outcomes on safety and effectiveness for orlistat patients who do not make appropriate diet and exercise modifications."

On December 8, 2004, the two FDA review divisions had a pre-NDA meeting with GlaxoSmithKline (GSK), the company that purchased ownership of the orlistat nonprescription IND from Roche. The Agency informed GSK that the efficacy of an OTC weight-loss drug should be judged by the same criteria used to evaluate the efficacy of a prescription weight-loss drug (e.g., greater proportion of drug vs placebo patients losing $\geq$ 5% of baseline weight following one year of treatment). Furthermore, the Agency explicitly stated that GSK should perform a label-comprehension study prior to conduct of a 12-month, placebo-controlled actual-use study.

On June 6, 2005, GSK submitted NDA 21-887 seeking approval of nonprescription orlistat 60 – 120 mg TID to promote weight loss for up to 6 months in overweight adults when used along with a reduced calorie and low fat diet. The NDA did not include data from a 12-month, placebo-controlled, actual-use trial.

III. CLINICAL DATA

Efficacy

Data from three controlled studies were submitted in support of the nonprescription orlistat NDA. Studies BM14149 and NM14161 were randomized, double-blind, placebo-controlled 2-year trials of 60 mg and 120 mg TID orlistat conducted to support registration of prescription orlistat. Study NM17247 was a randomized, double-blind, placebo-controlled 16-week trial of 60 mg TID orlistat conducted specifically for the nonprescription NDA.

The results of a pilot actual-use trial and a label-comprehension study were also submitted in support of the nonprescription orlistat NDA.

Below I provide brief synopses of the efficacy findings from the three controlled trials and the pilot actual-use study. I also briefly summarize the results of a label-comprehension study.

Studies BM14149 and NM14161

Dr. Julie Golden from the Division of Metabolism and Endocrine Products was the primary reviewer of studies BM14149 and NM14161.

Study BM14149 included subjects with BMIs of 28 – 43 kg/m^2, whereas study NM14161 included individuals with BMIs of 30 – 43 kg/m^2. Study BM14149 was conducted outside of the United States at centers that specialized in the treatment of obesity. Study NM14161 was conducted at United States primary care outpatient sites where there was no particular expertise in the treatment of obese patients.

Participants from both studies were placed on hypocaloric diets and instructed to adhere to a diet that contained approximately 30% fat calories. Subjects from BM14149 received monthly counseling sessions from dietitians, whereas there was no dietary intervention from study personnel in NM14161. However, subjects from NM14161 viewed videos on behavior modification and were encouraged to increase physical activity by walking.

Subjects completed food diaries on 15 occasions during BM14149 and on 7 occasions during NM14161. Subjects from both studies met with study personnel on a regular basis, if only to have their body weight measured.

Because studies BM14149 and NM14161 were similar in design, GSK pooled the data from these trials (hereafter pooled studies). In the pooled studies, a total of 448 patients were randomized to placebo TID with meals, 452 to 60 mg TID with meal, and 451 to 120 mg TID with meals. Seventy-five to 81% of the subjects in each treatment group completed one year of study. The majority of the patients were women and Caucasian. The mean age was 43 years. The average BMI at baseline was 35 kg/m^2 with roughly 10% of patients having a BMI in the range of 28 to 30 kg/m^2.

At Month 6 in BM14149, approximately 28% of placebo patients, 46% of 60 mg patients, and 49% of 120 mg patients lost $\geq$ 5% of baseline body weight ($p<0.05$).

At Month 6 in NM14161, approximately 17% of placebo patients, 35% of 60 mg patients, and 40% of 120 mg patients lost $\geq$ 5% of baseline body weight ($p<0.05$).

At Month 6 in the pooled studies, approximately 23% of placebo patients, 42% of 60 mg patients, and 45% of 120 mg patients lost $\geq$ 5% of their baseline body weight ($p<0.001$, both orlistat groups vs. placebo). Placebo-subtracted weight loss at Month 6 was 2.4% and 3.1% for the 60 mg and 120 mg groups, respectively.

At Month 12 in BM14149, approximately 33% of placebo patients, 52% of 60 mg patients, and 60% of 120 mg patients lost $\geq$ 5% of baseline weight ($p<0.01$ both orlistat groups vs. placebo).

At Month 12 in NM14161, approximately 25% of placebo patients, 36% of 60 mg patients, and 47% of 120 mg patients lost $\geq$ 5% of baseline body weight ($p<0.01$ both orlistat groups vs. placebo).

While the efficacy of orlistat relative to placebo was similar in studies BM14149 and NM14161, the absolute efficacy of the drug was greater in study BM14149 than NM14161, a finding attributable to the more intensive lifestyle modification program in BM14149.

Study NM17247

Dr. Julie Golden from the Division of Metabolism and Endocrine Products was the primary reviewer of study NM17247.

This was a randomized, double-blind, placebo-controlled 16-week trial of 60 mg orlistat TID in low overweight subjects (BMI 25 – 28 kg/m^2). The trial was conducted by Roche for the nonprescription orlistat NDA. Unlike studies BM14149 and NM14161, there was no 4-week, placebo lead-in phase in study NM17247. At baseline all subjects were prescribed a reduced-calorie diet: subjects < 90 kg = 1200 kcal daily for females and 1400 kcal daily for males; and subjects $\geq$ 90 kg = 1400 kcal daily for females and 1600 kcal daily for males. Subjects were also instructed to adhere to a diet that contained approximately 30% of calories from fat, 50% as carbohydrate, and 20% as protein. Self-instructional materials on diet/exercise/behavior modification were provided to all study participants. Body weight was measured and dietary and lifestyle instructions provided at baseline and Days 15, 29, 57, and 85.

A total of 194 subjects were randomized to 60 mg orlistat and 184 to placebo. Seventy-eight percent of the orlistat-treated subjects vs. 72% of placebo-treated subjects completed the four-month study. The majority of the study subjects were female, 89% were Caucasian, and the average age was 46 years. The mean baseline BMI was 27 kg/m^2 (range 24 – 29 kg/m^2).

The mean placebo-subtracted weight loss in the orlistat group was 1.1 kg ($p<0.01$). Approximately 36% of orlistat subjects compared with 28% of placebo subjects lost $\geq$ 5% of baseline body weight by Month 4 ($p=0.10$). Even if the difference in the proportion of patients who lost $\geq$ 5% of baseline weight was of nominal statistical significance, the clinical significance of a drug effect in 8% of the study population is questionable.

The orlistat group lost an average of 3.0 kg of body weight from baseline to Month 4 and the placebo group lost an average of 1.9 kg during this time period ($p<0.001$). Again, the clinical significance of a 1.1 kg difference in weight loss is questionable.

Study NM17285

Dr. Karen Feibus from the Office of Nonprescription Products was the primary reviewer of this pilot actual-use trial.

The primary objectives of this pharmacy-based, open-label, 3-month pilot actual-use study were to evaluate the ability of consumers to correctly self-select orlistat for personal use based on labeling directions; to provide initial information regarding how consumers use and dose orlistat without physician supervision; and to evaluate the adverse event profile in the actual-use setting. A secondary objective was to evaluate the consumer educational materials and website. Weight loss was not a pre-specified endpoint.

The consumer education material included 1) a 12-page booklet containing information about how to correctly use orlistat and encouraged patients to eat three balanced meals a day; 2) a food diary; 3) a fat counter; 4) a fat wheel; 5) a portion card; and 6) a diet success planner that included information about setting eating and activity goals, planning meals and food shopping lists, etc.

After potential study subjects read the proposed drug facts label (see appendix), they were asked by a pharmacy staff member if they thought the medication was appropriate for them to use. It should be noted that the labeling stated that the drug was for mild-to-moderately (up to 30 pounds) overweight adults. Patient demographic and medical history information was then obtained. Body weight was measured. Informed consent was obtained and subjects were then asked if they would like to buy the product.

Of 681 eligible subjects, 80% thought that orlistat was appropriate for them to use, based on the information from the Drug Facts panel. Four hundred sixty-five subjects had labeled exclusions. Of these, 107 self-selected correctly and 358 incorrectly. Two hundred sixteen subjects had no labeled exclusions. Of these, 209 self-selected correctly and 7 incorrectly. Subjects taking cyclosporine, warfarin, or diabetes medication were instructed in the Drug Facts panel not to use this product. Nonetheless, one of two patients on cyclosporine, seven of 14 patients on warfarin, and approximately 30 of 46 patients on anti-diabetic medication self-selected for orlistat use.

Approximately 80% of the subjects were female and Caucasian. The average age was 45 years and the mean BMI was 32 kg/m^2 (range 21 – 53 kg/m^2).

When queried, 80% of the subjects said they followed some kind of diet during the early phases of the study. This declined to roughly 60% by the end of the trial. Thirteen percent of subjects said they used the referenced website.

Objectively measured weights from Day 60 and beyond were obtained in 25% of the study participants. Forty-two percent of these subjects reportedly lost > 5% of baseline body weight.

Below are some of Dr. Feibus's conclusions (bolded font mine):

- Subjects appeared to lose some weight using orlistat 60 – 120 mg TID and the supportive educational materials. **However, due to the lack of objective weight assessments, it is not possible to make evidence-based conclusions regarding weight loss achieved during the actual use study.**
- Only 237 subjects became orlistat users. **This population may be too small and not diverse enough to accurately reflect consumer behavior decisions and weight loss patterns among consumers likely to use this product**.
- Subjects' self-selection decisions suggest either a problem with label-comprehension or extensive disregard for label warnings.
- This study does no demonstrate consumer use decisions beyond 90 days of drug use. There [are] no data to support labeling for six-month duration of use for this product. Results from placebo-controlled orlistat studies of longer duration suggest that weight loss continues beyond three months of use; however, **the decrease in adherence to diet seen during this three month study suggest that weight loss might plateau, especially with the lack of a learned intermediary to reinforce lifestyle changes.**
- During the first two weeks of the study, nearly 80% of subjects reported following some type of diet. However, the number of subjects using orlistat and following a diet plan declined during the study to about 60% by study's end.

Label-Comprehension Study

Dr. Susanna Weiss from the Office of Nonprescription Products was the primary reviewer of this label-comprehension study.

This was a multi-site, mall-intercept study conducted from 31 January 2005 to 11 February 2005.

The objectives of the study were to measure consumers' understanding of the key aspects of nonprescription labeling and to assess consumers' understanding of where to locate additional information included in the nonprescription orlistat package. A copy of the Drug Facts Label used in this study is provided in the appendix of this memo.

Male and female consumers 18 year of age or older who expressed an interest in weight loss were eligible to take part in this label-comprehension study. A total of 410 interviews were conducted in two general groups of subjects: general population and low literacy.

Seventy-five percent of the participants in the general population group were Caucasian whereas 39% of the participants in the low literacy group were Caucasian. Approximately 60% of the subjects in both populations were female.

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

The overall results of the study, as shown in Dr. Weiss's review, are provided below.

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

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

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

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

There were three areas in which I believe consumers' label comprehension was inadequate.

First, 10% of the low-literacy group responded incorrectly to the warning about cyclosporine use with orlistat. Because concomitant use of orlistat with cyclosporine may in the worse case scenario lead to organ rejection, a 10% failure rate is unacceptable.

Second, 50% of the low-literacy group responded incorrectly on the question stating that a multivitamin should be taken once a day. Furthermore, only 34% of the low-literacy group understood that in order to ensure adequate vitamin absorption, the vitamin must be taken 2 hours before or 2 hours after taking orlistat.

Third, 22% of the low-literacy group responded incorrectly that it is not okay to use orlistat if a person is not overweight. As Dr. Weiss noted in her review, the sponsor should include a BMI chart or BMI-calculating wheel in the nonprescription package. The consumer should have the ability to calculate their BMI prior to making a decision to purchase the product.

The sponsor should be asked to address the above three deficiencies and then examine whether modifications to the labeling satisfactorily improve consumer comprehension in these areas.

IV. ADVISORY COMMITTEE MEETING

A joint meeting of the Nonprescription Drugs and the Endocrinologic and Metabolic Drugs Advisory Committees was held on 23 January 2006. Three areas of interest are discussed below.

A). Eleven of 14 committee members endorsed approval of nonprescription orlistat. However, a number of caveats accompanied the favorable votes. Two of these caveats are provided below (excerpted from the meeting transcript.)

Dr. Benowitz: "....I thought for an actual use study this was really a not very satisfying study. There wasn't the right label. There wasn't the right duration to make any sense of

it. There were not proper outcome data. The educational package which they touted as being so wonderful, which I don't doubt, wasn't tested."

Dr. Griffin: "I guess I just want to second some of those opinions about the relatively small actual use study. If the market is potentially five million people I would really like to see a much bigger study of actual use with long-term follow-up data on persistence of weight loss."

B). Based on findings from the pilot actual-use and label comprehension studies, many committee members expressed concern about the potential for inappropriate use of orlistat in transplant patients taking cyclosporine. Committee members' comments about cyclosporine are provided below.

Dr. Patten: "I think that in my mind there are some profound safety concerns regarding cyclosporine (and warfarin). I think that the labeling needs to be very explicit and very conspicuous to inform people about these possible safety hazards. What I saw on the label that is part of the NDA did not assure me that that was the case. I was not reassured by the fact that people of warfarin and people on cyclosporine incorrectly selected themselves into the group to use so I have concerns."

The following is an exchange about cyclosporine between Dr. Wood (the meeting Chair) and Drs. Benowitz and Carpenter.

Dr. Benowitz: "I just would say that one consequence of not paying attention [regarding the adverse interaction between orlistat and cyclosporine) is that you may have organ rejection. I think it [the labeling] should be very frank; not just say see your doctor but say what the consequences may be."

Dr. Wood: "you may lose your kidney."

Dr. Benowtiz: "Yes."

Dr. Carpenter: "Given the seriousness of what could happen with decreased cyclosporine levels and rejection, shouldn't this just be an exclusion?"

Dr. Wood: "It is."

Dr. Carpenter: "An enforced exclusion."

Dr. Wood: "Well, how do you enforce it?"

Dr. Carpenter: "Point of sale check."

Dr. Wood: "But that is not OTC."

C). FDA's Question 1 to the committee asked: Has clinical effectiveness been demonstrated with orlistat 60 mg TID and 120 mg TID in the nonprescription setting. For each of these doses, please comment on the following:

a. A 6-month duration of us
b. Repeated use or chronic use
c. Use in the overweight individual
d. Use in the obese individual
e. Use with the proposed educational materials

Part "e" of this question was withdrawn by FDA, so no specific comments from the committee were made regarding whether the proposed orlistat plus lifestyle modification program was effective in the OTC setting. This is an important question that I believe needs to be answered.

Although a majority of the advisory committee was in favor of approving the application, as noted above, the committee clearly believed that additional work needed to be done by GSK before nonprescription orlistat was allowed into the market place. I believe the committee's concerns are captured in the deficiencies listed at the end of this memorandum.

V. DISCUSSION

Efficacy

Data from the prescription orlistat NDA indicate that in patients with BMIs $\geq$ 27 kg/m^2 with comorbidities or $\geq$ 30 kg/m^2 with or without comorbidities, orlistat 60 mg and 120 mg TID in conjunction with a reduced-calorie diet vs. placebo with a reduced-calorie diet alone, significantly increases the chances of losing $\geq$ 5% of baseline body weight during one year of treatment – one of the criterion used by the Agency to judge the efficacy of weight-loss drugs.

Data from the nonprescription NDA indicated that patients with BMIs of 25 – 28 kg/m^2 lost 1.1 kg more weight when treated with orlistat 60 mg TID plus a reduced-calorie diet vs. placebo plus a reduced calorie-diet during four months of treatment. Although of statistical significance, it would be difficult to classify a 1.1 kg difference in weight loss as clinically meaningful. The proportion of subjects who lost $\geq$ 5% of baseline weight was not statistically or clinically significantly different between the orlistat and placebo groups.

Safety

Due to its low bioavailability, orlistat is considered a relatively safe drug. Gastrointestinal adverse events such as fecal urgency, oily spotting, and flatus with discharge are common and expected given the drug's mechanism of action increasing fecal fat content . While

perhaps of significant inconvenience or embarrassment to patients, these events are not true safety concerns.

Decreased absorption of some fat-soluble vitamins and some lipophilic drugs were identified as true safety issues at the time of orlistat's approval as a prescription weight-loss drug in 1999. These remain safety issues with prescription orlistat today and would apply to nonprescription orlistat, particularly if approved for long-term use. The risks for fat-soluble vitamin insufficiency or deficiency are most likely reduced if patients adhere to the labeled recommendation to take a daily multivitamin 2 hours before or after ingestion of orlistat. Given that less than half of the orlistat users in the pilot actual-use trial took their multivitamin as directed, GSK should address this deficiency through enhanced labeling. Consideration should also be given to co-packaging orlistat with multivitamins.

As demonstrated in a drug-drug interaction study, co-administration of orlistat with cyclosporine reduces absorption of the latter. That this represents a true clinical risk in the prescription setting has been verified in numerous reports from the literature and FDA's Adverse Event Reporting System (AERS). Patients have co-administered these drugs and developed subtherapeutic cyclosporine levels. Two case of acute rejection have been reported.

Concern for inappropriate use of orlistat by transplant patients in the nonprescription setting is heightened by the fact that one of two subjects taking cyclosporine who participated in the pilot actual-use study self-selected for orlistat. These results, albeit involving only two patients, are at apparent odds with the results of the label-comprehension study in which approximately 90% of respondents correctly answered that it was not appropriate to take orlistat if taking cyclosporine. Nonetheless, a case can be made that it is unacceptable for even 10% of patients on cyclosporine to self-selecting for orlistat use. What level of inappropriate self-selection is acceptable is difficult to say, but ideally, prior to approval, GSK should demonstrate that far fewer than 10% of patients on cyclosporine would purchase orlistat in the nonprescription setting.

If orlistat is approved as a nonprescription weight-loss drug, it is inevitable, despite implementation of a risk minimization plan, that some transplant patients on cyclosporine will purchase orlistat, will co-administer the two drugs, will develop subtherapeutic cyclosporine levels, and will reject their transplanted organ. This does not necessarily preclude approval of nonprescription orlistat, but it does stress the need for convincing counterbalancing evidence that GSK's orlistat – lifestyle modification program is effective and provides benefit in the OTC setting.

Based on orlistat's mechanism of action it was assumed prior to its approval as a prescription drug that it would increase intestinal absorption of oxalates, particularly in patients on high-fat diets, and in turn increase the risk for nephrolithiasis. Seven years post-approval, there is little-to-no evidence from controlled trials or spontaneous reports that orlistat significantly increases the risk of developing kidney stones.

The same cannot be said for gallstones. In XENDOS, a trial of more than 3000 obese patients treated with orlistat 120 mg or placebo TID for up to 4 years, 2.9% of drug-treated vs. 1.8% of placebo-treated subjects developed symptomatic cholelithiasis. Because weight loss itself increases the risk for gallstones, it is difficult to separate the role orlistat and weight loss alone play in the risk for this adverse event.

The rates of cholelithiasis from XENDOS provide a framework from which to evaluate reports of pancreatitis associated with use of orlistat, as gallstones are a common cause of pancreatitis. Based on spontaneous reports, drug regulators from Europe and Canada were the first to inquire about a possible connection between orlistat and pancreatitis. In 2002, European regulators requested that Roche add pancreatitis to orlistat's labeling.

In response, Roche reviewed data from their controlled trials, the company's global drug safety database, a general epidemiological database from the UK, preclinical studies, and published literature. Based on this review, the company concluded that there was no evidence for a causal relationship. Apparently the European regulators agreed, as pancreatitis was not included as an adverse event in the overseas orlistat labeling.

Given that an over-the-counter drug carries a greater burden of safety than a prescription agent, reviewers from the Division of Metabolism and Endocrinology Products (DMEP) and the Office of Drug Safety (ODS) initiated a detailed investigation of the relationship between orlistat and pancreatitis.

From the time of its approval in 1999 through January 2006, there were a total of 99 unique reports (29 domestic) of acute pancreatitis in orlistat users submitted to AERS. Because weight loss is a risk factor for gallstone formation, which is a risk factor for pancreatitis, we evaluated the number of reports of pancreatitis submitted for sibutramine, the only other prescription drug approved for long-term treatment of obesity. From the time of its approval in 1997, there were a total of 8 unique reports (1 domestic) of acute pancreatitis in sibutramine users submitted to AERS. The number of U.S. prescriptions for orlistat has been approximately 1.5 to 1.7 times greater than that for sibutramine. Dr. Golden reviewed the individual reports and found that a sizable portion of them seemed credible – that is, many of the patients had objective evidence of pancreatitis.

If not for the markedly lower reporting rate of pancreatitis for sibutramine compared with orlistat, there would be little basis for concern regarding orlistat's relationship with pancreatitis. However, given the notable imbalance in reports of this adverse event between orlistat and sibutramine, and ODS's proportional reporting rate analysis, which indicates a small but statistically significant signal for pancreatitis in orlistat users, I believe this issue requires further investigation and discussion before serious thought is given to approving orlistat as a nonprescription weight-loss drug.

VI. CONCLUSIONS

GSK is seeking approval of nonprescription orlistat for weight loss in overweight individuals. The recommended duration of use is not to exceed 6 months. In the pilot actual-use trial, where the drug was promoted for weight loss in mild-to-moderately overweight adults, the majority of consumers who self-selected for orlistat had a BMI in the obese range (i.e., > 30 kg/m^2). Moreover, a sizable number of these subjects reportedly had common weight-related comorbidities such as high blood pressure, high cholesterol, and/or type 2 diabetes.

These findings are telling and support the position that, if approved for OTC sale, orlistat should be indicated for the same population as that targeted for prescription orlistat: individuals with a BMI of $\geq$ 27 kg/m^2 when accompanied by a weight-related comorbidity or $\geq$ 30 kg/m^2 regardless of the presence of comorbid conditions.

This population is clearly at increased risk for weight-related illness and stands to gain more from treatment with a weight-loss drug, including orlistat, than mildly overweight individuals. I am not in favor of approving orlistat for use in individuals with BMIs of 25 - 27 kg/m^2, because the short-term risk for weight-related disease is low in this population. At the population level, I doubt that the benefits of orlistat in mildly overweight subjects would outweigh the risks of fat-soluble vitamin insufficiency or deficiency or adverse drug-drug interactions.

Since it is now widely accepted that obesity is a chronic condition that requires chronic treatment, I also don't agree with GSK's proposal to limit use of nonprescription orlistat to 6 months. Placing a limit on its duration of use would be tantamount to approving orlistat for cosmetic weight loss. The duration of pharmacologic treatment of overweight and obesity should be the same regardless of whether the medication is prescription or nonprescription: long-term or indefinite.

Lifestyle modification is the cornerstone and standard of care in the treatment of obesity and overweight. Given the critical role lifestyle modification plays in determining the efficacy of weight-loss drugs, one cannot assume that the results of the trials conducted in support of approval of prescription orlistat can be extrapolated to orlistat when used with GSK's proposed lifestyle modification program in the over-the-counter setting.

In prescription orlistat study BM14149, in which all patients received intensive lifestyle modification, 28% of placebo patients and 46% of orlistat 60 mg subjects lost $\geq$ 5% of baseline body weight at Month 6. In study NM14161, in which subjects received less intensive lifestyle modification, 17% of placebo patients and 35% of orlistat 60 mg subjects lost $\geq$ 5% of baseline body weight at Month 6.

In the nonprescription setting, where patients would not receive feedback or encouragement from healthcare professionals to enhance compliance with lifestyle modification, there is a reasonable chance that orlistat would not produce efficacy sufficient to support approval (e.g., the proportion of orlistat-treated subjects who lose $\geq$

5% of baseline weight is at least 25%, is double the proportion of placebo patients, and the difference between groups is statistically significant).

For this reason, I believe GSK should conduct a controlled efficacy trial under actual-use conditions to demonstrate that their proposed orlistat-lifestyle modification program is indeed more effective than placebo-lifestyle modification in the nonprescription setting. This study would also examine the ability of labeling to direct appropriate self-selection of subjects with BMIs of 27 to 29 kg/m^2 who have at least one comorbidity and subjects with BMIs $\geq$ 30 kg/m^2 regardless of comorbid status. A BMI calculator should be incorporated into the nonprescription program to allow consumers to appropriately self-select for orlistat use.

VII. REGULATORY RECOMMENDATION

If the below deficiencies can be adequately addressed, I would consider orlistat's risk-benefit profile favorable in the nonprescription setting and support its approval for long-term weight loss in subjects with a BMI $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 in the presence of other risk factors such as hypertension, type 2 diabetes, or dyslipidemia.

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.

Eric Colman, MD
Medical Team Leader
Acting Deputy Division Director

2 Page(s) Withheld

_____ Trade Secret / Confidential

__✓__ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2

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

/s/

Eric Colman
3/21/2006 04:39:59 PM
MEDICAL OFFICER

Mary Parks
3/21/2006 05:13:27 PM
MEDICAL OFFICER

OTC MEDICAL OFFICER'S REVIEW

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

NDA # / Serial Number: 21-887
Type of Submission: Final study reports
Product/Ingredient Name: Alli/ orlistat
Proposed Indication: Overweight
Dosage Form/Route of Administration: Oral capsules
Sponsor: GlaxoSmithKline Consumer Healthcare, L.P.
Date Submitted: January 17, 2006
Date Received: January 24, 2006
Date Reviewed: March 14, 2006
Reviewer: Karen B. Feibus, M.D.

Introduction

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

Background

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

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