FDA Advisory Committee Briefing Document

Orlistat 60 mg Capsules

NDA 21-887

Joint Meeting of the

Nonprescription Drugs Advisory Committee

and

Endocrinologic and Metabolic Drugs Advisory Committee

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1. Executive Summary

1.1 Introduction

This briefing document provides an overview of the safety, efficacy, consumer understanding and usage data which, collectively, demonstrates the appropriateness of orlistat 60mg capsules for use as an over-the-counter (OTC) weight loss aid in overweight adults. FDA recognizes weight loss as an acceptable OTC indication, but to-date, has not approved (NDA or Final Monograph) any weight loss agents for use in an OTC setting. Conversely, FDA has approved several Rx drugs for obesity management and has a guidance delineating the clinical development recommendations for approval of an Rx weight control agent. It is in the context of this regulatory environment that the data supporting orlistat as an OTC weight loss aid is provided.

Orlistat, developed by Hoffmann-La Roche (Roche), was approved Rx by the FDA in April 1999 as 120 mg capsules (Xenical®) tid for obesity management and to reduce the risk of weight regain in obese and overweight patients with risk factors.

Roche initiated a program to switch orlistat 60 mg OTC in 2001. In 2004, GlaxoSmithKline (GSK) licensed the right to OTC orlistat and assumed ownership for the OTC development program.

A comparison of the proposed positioning of the OTC and Rx products is provided for reference at the end of this section, in Table 1.1.

1.2. Public Health Rationale

The prevalence of obesity and overweight in the United States has reached epidemic proportions. Greater than 120 million adults (nearly two-thirds of adults) in the United States are affected and these numbers are increasing.

Overweight and obesity (clinically defined as BMI > 25 kg/m^2 and >30 kg/m^2, respectively) substantially raise the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, and endometrial, breast, prostate, and colon cancers.[1,2]

The total economic cost of obesity in the United States is over $100 billion per year. This includes more than $50 billion in avoidable medical costs.[3] Obesity is linked to

very high rates of chronic illnesses and higher health care costs than is smoking or drinking.[4]

Even a modest 5% weight loss, can have considerable medical benefits in terms of ameliorating the weight-related medical complications. [5,6,7,8] However, although most Americans recognize the benefits of losing weight, accomplishing this goal is extremely difficult.

One in three American adults is engaging in a weight loss attempt.[9] However; most do not consult a health care professional, but instead turn to self-help measures. In addition to diet and exercise this may include use of one or more of the widely available herbals and other dietary supplements, many of which have not been the subject of rigorous clinical study and scientific review.

Availability of an approved OTC product for weight loss would provide an important addition to the self-help measures available to consumers.

1.3. OTC Indication

This application seeks approval for Orlistat 60 mg indicated as a weight loss aid, to promote weight loss in overweight adults when used with a reduced calorie (hypocaloric), low fat diet. The proposed dose is 1-2 capsules with each meal containing fat, up to six capsules a day, for up to six months.

Weight loss has been long-recognized as an acceptable OTC indication as evidenced by the establishment of a proposed OTC monograph for Weight Control Drugs. Although no specific criteria were established for OTC weight loss agents, in 1982 the Miscellaneous Internal Drugs Panel categorized two ingredients as safe and effective weight control agents (benzocaine and phenylpropanolamine HCL). A final monograph for OTC weight control drugs has not been published, subsequently phenylpropanolamine was the subject of voluntary withdrawal.

1.4. Pharmacology of Orlistat

Orlistat is a reversible inhibitor of lipases, key enzymes needed for the hydrolysis and subsequent absorption of dietary triglycerides. The drug is minimally absorbed (<2% bioavailable) and has a non-systemic mode of action. It exerts its therapeutic activity locally in the lumen of the stomach and small intestine to reduce the breakdown (and thereby, absorption) of dietary fat.

The relationship of dose to pharmacological effect (fecal fat excretion) in a Phase II study showed that orlistat 60 mg and 120 mg resulted in excretion of approximately 25% and 30% ingested fat, respectively. Fecal fat excretion at a 30 mg dose was approximately 15%. Doses beyond 120 mg resulted in little increased fat excretion.

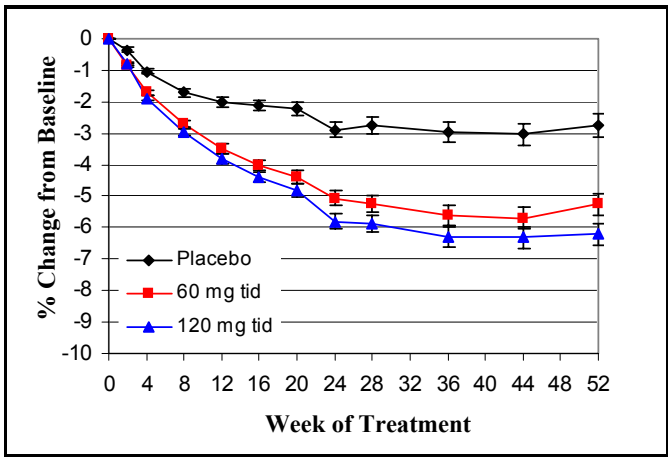
1.5. Efficacy

For Rx weight control drugs, the FDA published a draft standard of efficacy, in the 1996 ***Guidance for the Clinical Evaluation of Weight-Control Drugs***.[10]

Orlistat 60 mg (1-2 capsules) meets the same efficacy criteria used in the evaluation and approval of the Rx product. Orlistat 60mg is an effective weight loss aid.

In two placebo controlled clinical trials involving a total "Intent to Treat" (ITT) population of 1351 obese (BMI $\geq$30 kg/m^2) patients, orlistat 60 mg resulted in statistically more patients losing >5% of their body weight at six months compared to placebo. Pooled data from the two studies are shown below.

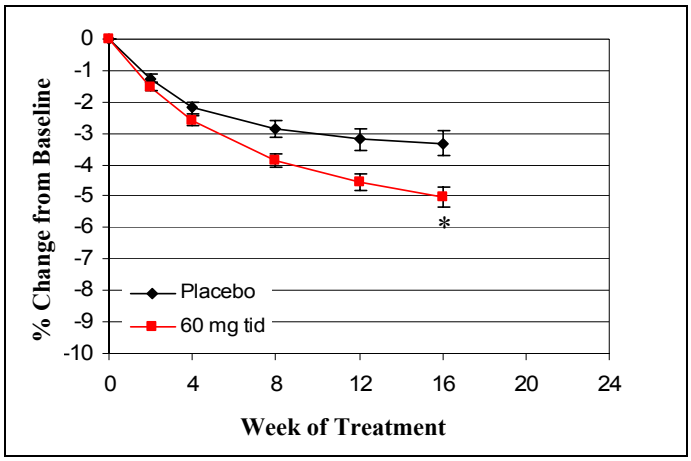
Figure 1-1
Relative Change from Baseline Weight: Pooled Long-Term Studies



ITT population, observed data; mean +/- SE

A four month trial of 60 mg orlistat in overweight (but not obese) subjects (BMI $\geq$ 25 - 28 kg/m^2), produced a statistically significant reduction in weight compared to placebo.

Figure 1-2
Relative Change from Baseline Weight: 4m Study



ITT population, observed data; mean +/- SE

* Relative weight change at 4 months for 60 mg vs. placebo; p< 0.001.

1.6. Safety

Orlistat's safety is supported by extensive clinical experience and post marketing surveillance. It has been evaluated in over 100 clinical trials[11] in over 30,000 subjects, including a 4 year controlled clinical trial in non-diabetic obese subjects.[12] Orlistat 120 mg tid is currently approved in over 145 countries including 6 in which the product has been reclassified to over-the-counter ('pharmacy-only') status. The adverse event profile is primarily characterized by non-serious, transient and predictable gastrointestinal effects that are manageable by following a diet reduced in fat, as recommended in the product labeling.

There are few known drug-drug interactions with orlistat. The only known direct interaction of potential concern is cyclosporine where concomitant administration reduces cyclosporine levels by approximately 30%. Orlistat should not be taken with cyclosporine (the Rx label recommends a two-hour dosing gap).

Unlike a number of Rx and OTC drugs, orlistat does not directly affect the pharmacokinetics or pharmacodynamics of warfarin. However, through a potential effect on vitamin K, orlistat may alter the coagulation parameters of warfarin. The proposed OTC label instructs individuals taking warfarin to ask their doctor or pharmacist before use.

Although remaining within the normal range, reduced blood levels of fat soluble vitamins have been observed with orlistat use. This has not been a cause for clinical concern; however, vitamin supplementation is recommended as part of the proposed label.

There has been no evidence of central nervous system effects indicative of abuse potential. However, as with any weight loss agent, of potential concern are people (e.g. teens) with eating disorders who are not overweight, but might consider using the drug. Four cases of misuse in patients with a long-term history of eating disorders have been identified post-marketing in the literature. There were no clinically significant safety concerns reported in these case studies.

1.7 Labeling and Consumer Use

The label for OTC orlistat has been extensively researched in a series of label comprehension and self selection studies, and in an actual use trial. In general, label comprehension was excellent in both the general- and low-literacy populations. The actual use study revealed a number of issues which led to label changes, which were explored further.

The cumulative data from all labeling studies support that consumers:

- Can identify the condition of overweight and are looking for tools to help them treat it
- Understand the label and make self-selection decisions based on their need to lose weight
- Use orlistat according to the labelled directions for use, and do so safely and effectively in the absence of physician intervention

The label submitted in the NDA follows and is presented also in section 3.2.1 of this briefing packet.

Figure 1-3
OTC Drug Facts Label in NDA 21-887

Drug Facts

Active ingredient (in each sealed capsule)……Purpose
Orlistat 60 mg…….Weight Loss Aid

Use
promote weight loss in overweight adults when used along with a reduced calorie and low fat diet

Warnings
Do not use
- if you are taking cyclosporine (a drug given after organ transplant)
- if you have been diagnosed with problems absorbing food
- if you are allergic to any of the ingredients in orlistat capsules
- if you are not overweight

Ask a doctor before use if you have
gallbladder problems or kidney stones

Ask a doctor or pharmacist before use if you are
- taking medicine for diabetes. Your medication dose may need to be adjusted during weight loss.
- taking warfarin (blood thinning medicine)
- taking other weight loss drugs

When using this product
- you should follow a well-balanced diet that is reduced in calories and contains 30% fat or less. Try starting this diet before you begin taking orlistat capsules. See enclosed Companion Guide for information and tips on how to follow a well-balanced diet that is low in calories and fat.
- orlistat capsules work by preventing the absorption of about 25% to 30% of the fat you eat. Instead of turning into calories, the fat passes out of your body.
- as a result of undigested fat passing through the body, you may experience bowel changes. Examples include fat in your stools and loose and more frequent stools, particularly after meals containing more fat than recommended.
- these bowel changes are related to how the product works and usually subside in a few weeks. You can decrease the likelihood of these effects by reducing the fat in your diet.
- you should start to lose weight within the first two weeks. How much weight you lose will depend on how closely you follow the recommended diet and the orlistat program.

If pregnant or breast-feeding, do not use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

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

Other information
- store at 20 – 25ºC (68 – 77ºF)
- avoid exposure to excessive light, humidity and temperatures over 30ºC (86ºF)

Inactive ingredients
FD&C Blue No. 2, edible ink, gelatin, iron oxide, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium starch glycolate, talc, titanium dioxide

Questions or comments? Call 1-800-123-1234 weekdays (10:00am – 4:30pm EST)
Llame a este numbero para obtener una copia de la etiqueta del producto en Espanol

1.8. Risk Benefit Profile

The potential risks of OTC orlistat are related to drug interactions involving cyclosporine and warfarin and a concern about the potential for misuse (e g, by teens). Proposals to mitigate these risks include labelling, behavioural support and education programs, together with comprehensive monitoring post-launch (including media and internet).

Although many diet products exist in the consumer environment, none have been FDA-approved. Availability of orlistat OTC would provide consumers with a safe, effective weight loss aid. With the inclusion of education and support materials with the product, the sponsor believes the potential benefit to consumers will be maximised and enhance their ability to lose weight over diet and exercise alone, improving their health.

1.9. Overall Summary and Conclusions

- The efficacy of orlistat at a dose of 60 mg for up to 6 months continuous use has been demonstrated in two placebo-controlled weight loss trials in obese subjects. The efficacy data from these trials at 6 months meets the approvability criterion proposed in the 1996 draft guidance for prescription weight loss drugs at 1 year.

- A 4-month study in subjects with a BMI range of 25 to 28 kg/m^2 supports and confirms results from studies carried out in a more obese population.

- The safety profile of orlistat is well established and suitable for the OTC setting. Orlistat is minimally absorbed, has no medically significant systemic effects and is well tolerated based on Phase III clinical trials and post-marketing experience.

- With respect to drug-drug interactions, cyclosporine is the only direct interaction of potential clinical consequence. We believe the risks posed by this interaction, as well as those posed by the indirect interaction with warfarin, can be effectively managed in an OTC setting via the warnings that appear in the proposed OTC label, in-pack materials, and proposed programs for both consumers and healthcare professionals.

- Weight loss as an OTC indication is both well-established and clearly understood by consumers. The consumer labelling and usage studies demonstrate that consumers can understand the proposed OTC label and use

the product in the correct manner that allows them to achieve weight loss in a real-world setting.

- Lastly, GSK recognizes that the efficacy of any weight loss therapy is inherently tied to lifestyle changes and; therefore, commits to providing educational in-package materials and behavioral support tools tailored to meet this challenge.

Table 1-1
Comparison of orlistat OTC and Rx

	Proposed OTC	Current Rx
Dosage Form	60 mg capsule (banded)	120 mg capsule (unbanded)
Indication	Promotion of weight loss when used in conjunction with a reduced calorie and low fat diet	Obesity management including weight loss, weight maintenance, and prevention of weight regain when used in conjunction with a reduced calorie meal
Clinical Benefit	Weight loss	Long term use for weight management also results in clinical benefits for patients with selected co-morbidities, including type 2 diabetes, dyslipidemia and high blood pressure
Age	18 years and over	18 years and over (Data available in patients 12 years and over)
Population	Overweight	Obese patients or overweight at risk BMI $\geq$30kg/m^2 BMI $\geq$27kg/m^2 with other risk factors
Duration of Use	Up to 6 months continuous use	Up to 4 years continuous use data available (labeling does not limit duration of use)
Directions for Use	One to two capsules (60 mg/capsule) with each meal containing fat up to 6 capsules per day.	One capsule (120 mg) three times daily with each meal containing fat
Sponsor	GlaxoSmithKline	Roche

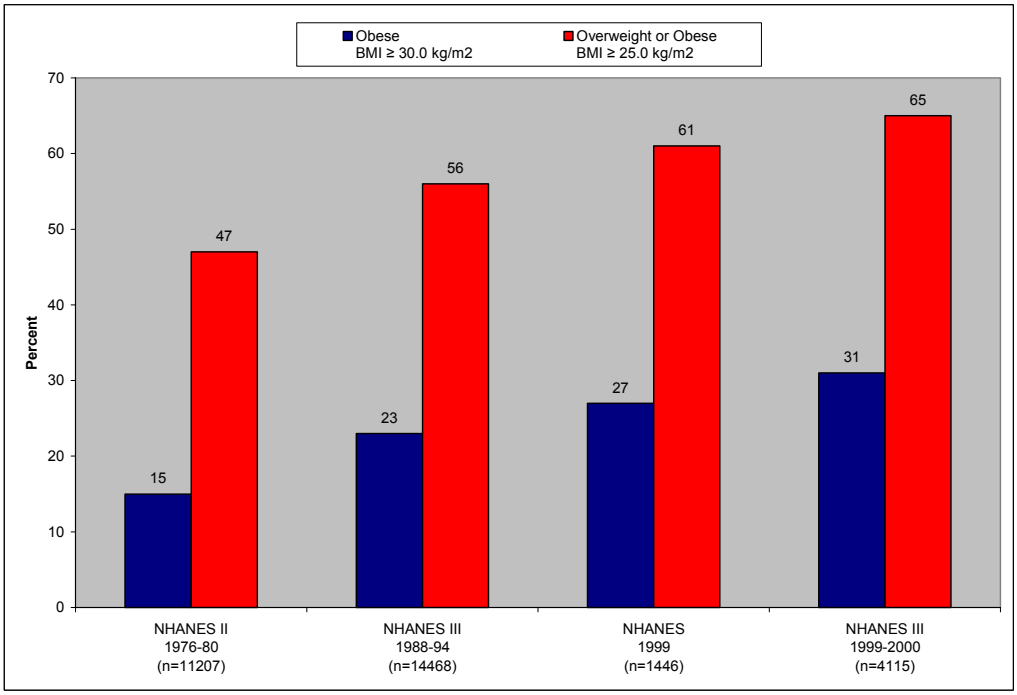
2. Introduction and Public Health Rationale

2.1 Overweight as a Public Health Crisis

2.1.1 The Growing Prevalence of Obesity and Overweight

The prevalence of obesity and overweight in the United States has reached epidemic proportions. Greater than 120 million adults (nearly two-thirds of adults) in the United States are affected and overweight and obesity are increasing (Figure 2-1).

Figure 2-1
Age Adjusted Prevalence of Overweight and Obesity among U.S. adults, aged 20 - 74 yrs



NHANES = National Health and Nutrition Examination Survey

2.1.2 The Negative Health Consequences of Obesity and Overweight

Overweight and obesity (clinically defined as BMI ≥25 kg/m^2 and ≥30 kg/m^2, respectively) substantially raise the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease,

osteoarthritis, sleep apnea, respiratory problems, and endometrial, breast, prostate, and colon cancers.[1,2]

The long-term impact of this trend on life expectancy and quality of life pose concern. Life expectancy trends during the past thousand years have shown a slow, steady increase.[13] However, within 50 years, obesity will most likely shorten the average US life span of 77.6 years by at least two to five years. This is more than the impact of cancer or heart disease described in a recent paper supported by the NIH.[13] The FDA's Working Group on Obesity stated, "If it is not reversed, the gains in life expectancy and quality of life resulting from modern medicine's advances on disease will erode, and more health-related costs will burden the nation's healthcare system."[3]

2.1.3 The Harmful Economic Impact of Obesity and Overweight

The total economic cost of obesity in the United States is over $100 billion per year. This includes more than $50 billion in avoidable medical costs.[3] Obesity is linked to very high rates of chronic illnesses and higher health care costs than is smoking or drinking.[4] When compared with 100 normal-weight individuals of the same age and sex having similar backgrounds, 100 obese people would be expected to suffer 67 additional chronic conditions. In contrast, the increase associated with smoking is about 25 additional conditions per 100 smokers and 12 additional conditions for problem drinkers.[4] Obesity is associated with rising disability levels nationwide. The added health care costs for obesity-related conditions among those who will be age 50-69 in the year 2020 could account for as much as 1 in 5 health care dollars.[4]

2.2 The Unmet Medical Need in the Treatment of Overweight

Even a modest 5% weight loss can have considerable medical benefits in terms of ameliorating the weight-related medical complications described above. Significant improvements in cholesterol, blood pressure, triglycerides and HbA1c are seen with weight losses in this 5% range.[5,6,7,8] Effective weight loss therapy that reduces the progression of overweight to obesity can thus have a beneficial effect on health and health care costs.

2.2.1 Treatment is Primarily Self-Driven

Although one in three American adults is engaging in a weight loss attempt,[9] most do not consult a health care professional. Further, during routine patient evaluation, healthcare professional advice to overweight individuals regarding weight loss is limited. In a recently published evaluation of weight loss counseling prevalence by health providers in 100 US cities[14], the Centers of Disease Control (CDC) found that

only 12-35% of overweight and obese individuals recalled receiving weight loss/maintenance advice. While it is recognized that there are a number of barriers to physician's assessment and management (e.g. lack of time and reimbursement, low training in counseling) the result is that, treatment of overweight and obesity is primarily patient-driven with most individuals turning to self-help measures.

2.2.2 Limitations of Current Consumer Weight Loss Offerings

While there are no FDA-approved OTC pharmacotherapies available for weight loss, there has been a proliferation of diet products whose claims and support for safety and efficacy are not subject to premarket review and approval by the FDA. This includes widely distributed herbals and other dietary supplements. Many of these products have not been the subject of rigorous clinical study and scientific review. Some are promoted aggressively and irresponsibly (from 2003 through to October 2005 there have been over 700 compliance actions taken by regulatory agencies in Mexico, Canada and the United States in response to inappropriate advertising and promotion).[15] Sales of these products reflect consumer desire; therefore, there is a need to provide consumers with access to proven alternatives that can safely and effectively assist in weight loss.

2.2.3 More Alternatives are Needed

Many different factors have contributed to the current weight gain epidemic in the United States, including unhealthy diets, inadequate physical activity, poor eating habits, and limited education about the importance of proper diet and nutrition. Government and industry have recognized that more than one approach will be required to slow down and/or reverse these trends as illustrated in the "Nutrition and Overweight" component of the Healthy People 2010 initiative led by both the Food and Drug Administration (FDA) and the National Institutes of Health (NIH). NIH recommends use of multiple techniques and strategies to achieve effective weight control since no one technique will guarantee an individual will achieve a healthy weight.[1]

Having a safe and effective pharmacotherapy for weight loss available as an Over-the-Counter product would provide an important addition in the fight against this growing epidemic.

2.3 Weight Loss is an Accepted OTC Indication

The FDA has long recognized weight loss as an indication for OTC products (Advisory Review Panel report of 1979, the February 26, 1982 advance notice of

proposed rulemaking and October 30, 1990 Proposed Rulemaking). In 1982 the Miscellaneous Internal Drugs Panel categorized two ingredients as safe and effective, benzocaine and phenylpropanolamine HCL. The latter has since been subject to voluntary withdrawal. Although a final monograph for OTC weight control drugs has yet to be published, FDA discussions concerning this NDA has reaffirmed that a weight loss indication is appropriate for the OTC environment.

3. Description of Orlistat OTC

Orlistat (60 mg capsules) is one component of a comprehensive program of drug product, consumer education and behavioral support, described below.

3.1 The Product

Orlistat (60 mg capsules) is proposed as an OTC weight loss aid to promote weight loss in overweight adults, when used in conjunction with a reduced calorie and low fat diet. The proposed label restricts usage to adults 18 years of age and older.

The proposed dose is 60 mg (1 to 2 capsules) with each meal containing fat (maximum 6 capsules per day) for up to 6 months. The increased tolerability of the one 60 mg capsule dose makes it an appropriate starting dose, with flexibility to increase to 2 capsules. Dosing flexibility is well-established in an OTC environment (e.g. directions for analgesics; take 1 to 2 tablets) where consumers can self-recognize and self-treat their condition.

Efficacy is supported by Phase III pivotal efficacy trials. Measurable weight loss is shown after 15 days use and continues for approximately 6 months. After 6 months the rate of weight loss declines and plateaus due to a lesser energy expenditure at the lower weight.[1] The proposed 6 month duration of use reflects the timeframe in which the majority of consumers will experience near-maximum weight loss.

Consumers who do not reach their weight loss goal within the 6 months are advised to check with their doctor to evaluate treatment options.

3.2 Consumer Education

3.2.1 Labelling

The labelling for orlistat 60 mg capsules as an OTC weight loss aid has been designed to educate consumers about the use of the product and about how to modify their diet. The labelling has been tested and reviewed by experts in weight control, nutrition and behavioral change.

As with all OTC drug products, the **Drug Facts** section contains the proposed key information for safe and effective use of the product for its intended indication, formatted in accordance with 21 CFR 201.66 (see Figure 3-1).

Figure 3-1
OTC Drug Facts Label in NDA 21-887

Drug Facts

Active ingredient (in each sealed capsule)……Purpose
Orlistat 60 mg…….Weight Loss Aid

Use
promote weight loss in overweight adults when used along with a reduced calorie and low fat diet

Warnings
Do not use
- if you are taking cyclosporine (a drug given after organ transplant)
- if you have been diagnosed with problems absorbing food
- if you are allergic to any of the ingredients in orlistat capsules
- if you are not overweight

Ask a doctor before use if you have
gallbladder problems or kidney stones

Ask a doctor or pharmacist before use if you are
- taking medicine for diabetes. Your medication dose may need to be adjusted during weight loss.
- taking warfarin (blood thinning medicine)
- taking other weight loss drugs

When using this product
- you should follow a well-balanced diet that is reduced in calories and contains 30% fat or less. Try starting this diet before you begin taking orlistat capsules. See enclosed Companion Guide for information and tips on how to follow a well-balanced diet that is low in calories and fat.
- orlistat capsules work by preventing the absorption of about 25% to 30% of the fat you eat. Instead of turning into calories, the fat passes out of your body.
- as a result of undigested fat passing through the body, you may experience bowel changes. Examples include fat in your stools and loose and more frequent stools, particularly after meals containing more fat than recommended.
- these bowel changes are related to how the product works and usually subside in a few weeks. You can decrease the likelihood of these effects by reducing the fat in your diet.
- you should start to lose weight within the first two weeks. How much weight you lose will depend on how closely you follow the recommended diet and the orlistat program.

If pregnant or breast-feeding, do not use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

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

Other information
- store at 20 – 25ºC (68 – 77ºF)
- avoid exposure to excessive light, humidity and temperatures over 30ºC (86ºF)

Inactive ingredients
FD&C Blue No. 2, edible ink, gelatin, iron oxide, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium starch glycolate, talc, titanium dioxide

Questions or comments? Call 1-800-123-1234 weekdays (10:00am – 4:30pm EST)
Llame a este numbero para obtener una copia de la etiqueta del producto en Espanol

In addition to the label, several dietary and behavioral support **Reference Guides** have been developed, with input and expertise of dieticians and illustrators from the consumer education field. These reference guides are pocket-sized; contain over 250 pages of material, including all of the key messages tested in the actual use trial (NM17285) as well as the placebo-controlled Phase III study using self-help materials (NM17247). Please refer to Table 5-1 for a brief summary of all studies supporting the safety, efficacy and actual use of orlistat 60 mg.

The orlistat OTC **Starter Pack** contains a complete set of dietary reference guides and tools (Welcome Card, Companion Guide, Healthy Eating Guide, Calorie and Fat Counter, Daily Journal, QuickFacts Card) plus a temporary carrying case. After beginning the program with their purchase of the OTC Starter Pack, users are expected to purchase the orlistat OTC **Refill Pack.** The orlistat OTC **Refill Pack** contains the Companion Guide which serves as a basic "users guide" providing instructions for use and an overview of the program.

Reference Guides

- **Welcome Card**

This short pamphlet is designed to be first and provides an overview of the program and access to a free optional Behavioral Support Program. Topics include: "Program at a Glance" and "Six Steps to a Quick Start". This pamphlet covers a high level view of the critical concepts, including establishing realistic expectations for gradual weight loss, highlighting the importance of adopting a low fat diet, and proactively alerting consumers to the treatment effects that can result from non-compliance.

- **Companion Guide**

This contains the essentials of the program and reflects input from experts who suggest "staged" disclosure of content (from general and essential to the more detailed and comprehensive) is a strategy to reinforce the most important concepts. Topics include: expectations and goals, dosage and product use, basic diet guidelines, treatment effects, and encouragement to increase physical activity.

- **Healthy Eating Guide**

This provides practical suggestions for healthy eating. Topics include: "Eating at Home", "Eating Out", "Menu Planning", "Shopping", and "Preparing Meals".

- **Calorie and Fat Counter**

This guide is to help users make the right food choices, both at home and at a restaurant. Topics include: "Calorie Counter", "Fat Counter" and "Food Exchanges".

- **Daily Journal**

This journal is designed to make it easy for users to record their meals. This self-monitoring has been shown to increase successful weight loss. Topics include: "Keeping a Journal", and "Calorie Counting and Fat Tracking".

- **QuickFacts Cards**

These are portable cards that provide basic information on dosage and diet tips and support compliance to adopting a low fat eating plan and awareness of foods likely to lead to treatment effects unless consumed in moderation. Information includes "Best Choices", "Foods to Avoid", and "Portion Size".

3.2.2 Consumer Communication

The sponsor recognizes the difference between OTC drugs that provide symptom relief of temporary ailments and those that involve both a drug effect plus a behavioural change. GSK's smoking cessation products (Nicorette®, NicoDerm®), approved for over-the-counter use in 1996, are examples of the latter. Steps were taken to ensure that increased access via OTC distribution was not accompanied by inappropriate use. Similar steps are proposed for OTC orlistat, namely, compliance with communication principles that help reinforce label messages for appropriate use:

- Advertising that targets those overweight adults sufficiently motivated to adopt a reduced calorie, low fat diet.

- Avoidance of exaggerated claims prevalent in the current weight loss landscape of unapproved dietary supplements. GSK will ensure that communications will appropriately convey expectations of effectiveness (weight loss will be modest and gradual) and some users may encounter gastrointestinal (GI) side effects that could limit acceptability (a risk minimized by compliance with a diet containing no more than 30% of calories from fat).

- Inclusion of reference guides, consumer access to in-pack educational materials and out-of-pack behavioral support materials.

- Message consistency that effective weight loss can only be achieved by combining OTC orlistat use with appropriate diet and behavior change.

3.3 Behavioral Support Program

To supplement the in-pack materials, whose content was included with and tested in the actual use trial (study NM17285) and the 4 month efficacy study (study NM17247) in adults with lower BMIs, GSK will encourage the use of additional tools and resources to help users of OTC orlistat adopt and maintain a healthy eating plan and physical activity. GSK will offer a free, 12 month, web-based behavioral support program personalized to each user's profile, such as their weight loss goals, and provide relevant advice and motivational support via weekly contacts over the first six months. The content evolves based on feedback from enrollees and focuses during the first six months on strategies that:

- Promote compliance with a reduced caloric diet containing no more than 30% of calories from fat.
- Staying motivated and committed to other lifestyle changes, e.g. physical activity.
- Recognizing and better understanding why problems may/did occur and how to modify and adopt appropriate behaviors.
- Knowing where and/or who they can turn to for further assistance.

Based on labeling which advises users not to continue drug therapy beyond six months, content during the second 6 month phase of the program focuses on increased physical activity as a strategy to maintain weight loss, continues to provide dietary advice, and reinforces the labeling directions to seek the advice of a health care professional if they have not met their weight loss goals.

Behavioral modification is recognized as an important component for successful weight loss. Although some individuals are self motivated and can modify behavior on their own, others may benefit from a behavior support program. Research with Rx orlistat showed that patients who enrolled in a support program achieved higher rates of compliance, significant weight loss, and high rates of satisfaction.[16] GSK's experience in smoking cessation also highlights the ability of a personalized behavioral support program (Committed Quitters®) to improve compliance and outcomes (i.e., quit rates) incrementally to cessation rates achieved with a product and generic self-help materials alone.[17,18,19]

The availability of the behavioral support program will be promoted with all starter and refill packages, as well as within other consumer communication. The behavioral support program will also provide reminders that orlistat users can contact a consumer support center through a toll free telephone number for further assistance. A direct mail version of the behavioral support program will also be available for those with limited access to the internet.

4. Pharmacology of Orlistat

4.1 Extent of Absorption

Unlike other currently available prescription weight loss medications, orlistat has a non-systemic mechanism of action. Absorption of orlistat is minimal (<2% bioavailable). Fecal excretion of the unabsorbed drug is found to be the major route of elimination with 97% of the ingested dose excreted in the feces. Orlistat has two inactive metabolites that are considered pharmacologically inconsequential and this metabolism further limits systemic absorption. Based on limited data, the half-life of absorbed orlistat is in the range of 1 to 2 hours. There is no evidence of accumulation in any tissues.

4.2 Mechanism of Action

Pancreatic lipase and, to a lesser extent, gastric lipase are the key enzymes for the hydrolysis and subsequent absorption of dietary triglycerides. These lipases act by breaking down ingested triglycerides into free fatty acids and monoglycerides, which are ultimately absorbed via the small intestine into the peripheral circulation. Intact non-hydrolyzed triglycerides are not absorbed from the intestinal lumen, but are excreted in the feces.

Orlistat acts locally within the gastrointestinal (GI) tract to inhibit pancreatic and gastric lipase. An increase in fecal fat is generally seen within 24-48 hours and diminishes in an equivalent timeframe after discontinuation of treatment. Inhibition has been shown to be potent, selective, and reversible, blocking the absorption of 25 to 30% of dietary fat. As a result, roughly one-quarter to one-third of ingested fat passes through the GI tract and is eliminated.

Importantly, orlistat's mechanism of action produces the same pharmacologic effect in all individuals, regardless of overweight status. Obese and overweight individuals may differ in the relative amounts of total weight loss experienced within a similar timeframe, however, the mechanism by which orlistat induces weight loss is the same in both groups.

4.2.1 How Orlistat Affects the Gastrointestinal System

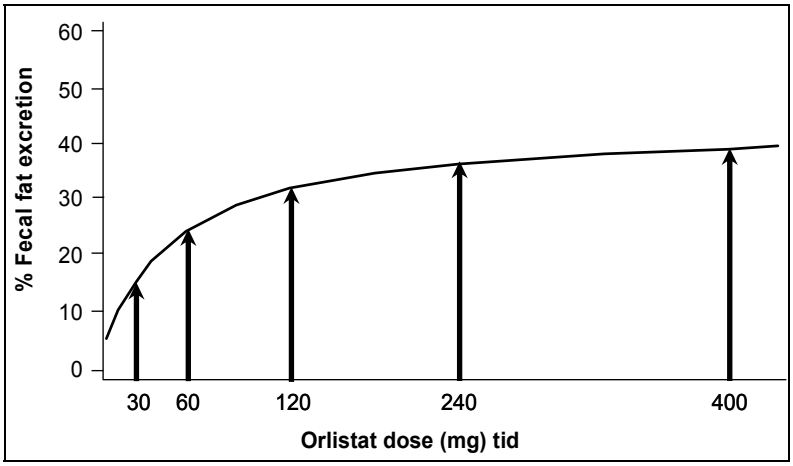
The mechanism of action can lead to treatment-related GI effects. These are predictable, experienced mostly at the beginning of treatment and can be managed and mitigated through dietary means.

Orlistat does not change the proliferation status of the colonic epithelium or the histopathology of the colon. Also, there is no meaningful change in small bowel transit time, gall bladder function or pancreatic functions.

4.3 Dose Response

The relationship of orlistat dose to pharmacologic effect was explored in 11 double-blind, placebo-controlled, parallel-group randomized studies.[20] The daily mean fecal fat excretion as a percentage of ingested fat was correlated to the orlistat daily dose. A simple maximum effect (Emax) was used to define the dose-response curve as illustrated in Figure 4-1.

Figure 4-1
Orlistat Dose Response



Administration of orlistat at doses of 60-120 mg results in the excretion of approximately 25%-30% of ingested fat, respectively. These results demonstrate 60 mg as the minimum effective dose. Increasing the dose beyond 120 mg results in little increased fat excretion. Further, these data provide reassurance that consumers who exceed label directions will not experience an increased drug effect.

4.4 Drug-Drug Interactions

Drug interaction studies were conducted as part of the original Rx clinical development program and continued subsequent to Xenical® approval. The results of

these studies have been incorporated into the current approved prescription label as it appears in Appendix 1 of this document.

Of the many drugs studied, two orlistat drug interactions raise potential concerns in an OTC setting; namely cyclosporine (direct interaction) and warfarin (indirect interaction). These interactions are discussed in the context of drug safety in Section 7.14.

5. Overview of the Clinical Development Program

Orlistat was approved Rx by the FDA in April 1999 as Xenical® (orlistat) 120 mg capsules tid for obesity management and the reduction of weight regain. The safety and efficacy of orlistat was firmly established during Roche's clinical development program which included seven long-term (1 to 2 years) multicenter, double-blind, placebo-controlled clinical trials. Subsequent to Xenical® approval, a 4-year study was conducted (XENDOS), providing additional long-term safety and efficacy data.

Several of these trials also evaluated orlistat at a dose of 60 mg tid, and provide substantial evidence of orlistat's safety and efficacy at the proposed OTC dose of 60 mg (1 to 2 capsules). These data and the results of studies conducted specifically in support of the OTC development program (clinical and actual use) are briefly described below and in greater detail in the sections to follow.

The effectiveness of orlistat 60 mg in terms of weight loss was first demonstrated in a short term Phase II dose-ranging study which evaluated strengths ranging from 30 to 240 mg tid. The results of this study showed that 60 mg orlistat administered three time a day with meals containing fat produced clinically meaningful and statistically significant weight loss at 6 months. Further, these data supported the exploration of both 60 and 120 mg doses as part of the Rx clinical development program. Two long term (2 year) pivotal Phase III studies evaluated the use of orlistat for weight loss at a dose of 60 mg tid in patients whose BMI was ≥ 28 kg/m^2 and firmly established the safety and efficacy in this population. In discussions with the FDA, an additional clinical study was conducted in support of the OTC clinical development program to confirm the safety and efficacy of orlistat 60 mg in an overweight population whose BMI was 25 - 28 kg/m^2.

Adverse event data from the pivotal Phase III clinical studies discussed above provide strong evidence of orlistat's safety. In addition to these weight loss studies, a clinical trial was conducted to evaluate orlistat for the purpose of assessing weight maintenance following 6 months of conventional dieting. The results of this study are considered further support of orlistat safety.

Lastly, two studies were conducted to evaluate orlistat 60 mg under naturalistic OTC-like conditions of use: a 1 month home use market research study and a 3 month actual use trial. The results of the actual use trial provide more comprehensive information as to the use of orlistat 60 mg in an OTC setting are reviewed in the current briefing document. These data are considered supportive to the safety and effectiveness demonstrated in the pivotal trials described above.

Notably, although these studies were conducted in different settings, with varying levels of dietary intervention and behavioral support, they consistently demonstrated significant weight loss across the range of BMIs studied and similar safety profiles.

These studies contain either pivotal or supportive information about a 60 to 120 mg tid dose of orlistat. Collectively, they demonstrate the safety and efficacy in a representative OTC target population and support the appropriateness of the product in an OTC environment. These studies are briefly summarized in Table 5-1 and described in greater detail in the sections to follow.

Table 5-1
Studies Supporting the Safety, Efficacy and Use of Orlistat (60 mg)

Study No.	Type of Study	Role in OTC NDA	Duration	BMI (kg/m^2)	Dose (mg tid)
BM14150	Phase II Dose-ranging study	Dose selection, Supportive Safety & Efficacy	6 mos	28-43	Placebo 30 mg 60 mg 120 mg 240 mg
BM14149	Phase III Weight loss study [a]	Pivotal Safety & Efficacy	2 yrs	28-43	Placebo 60 mg 120 mg
NM14161	Phase III Weight loss study using primary care providers [a]	Pivotal Safety & Efficacy	2 yrs	30-43	Placebo 60 mg 120 mg
NM17247	Phase III Weight loss study in overweight subjects in a primary care setting	Confirmatory Safety & Efficacy	4 mos	25-28	Placebo 60 mg
NM14302	Phase III Weight maintenance [b]	Safety	18 mos [b]	28-38	Placebo 30 mg 60 mg 120 mg
NM17285	Phase IV actual use trial	Supportive; Actual Use in OTC setting	3 mos	--- [c]	60 mg
RCH-ORL-002[d]	Home use market research study	Supportive; Actual Use in OTC setting	1-month	≥27	60 mg

a. Weight loss evaluated in 1st year; weight maintenance in 2nd year.
b. 6 months conventional dieting without drug followed by 12 months of drug treatment
c. This study was intended to simulate an OTC environment; no BMI restriction was imposed.
d. Included in Table 5-1 for completeness, but not discussed in this briefing document.

6. Summary of Orlistat Efficacy

6.1 Introduction and Overview of Clinical Efficacy Program

The breadth of the clinical program supporting the efficacy of orlistat 60 mg (1 to 2 capsules) to promote weight loss was introduced in Section 5. Section 6 presents the results of this comprehensive program showing statistically significant and clinically meaningful weight loss with the use of orlistat 60 mg capsules.

There are established criteria by which the efficacy of long-term prescription weight control drugs (including Xenical®) is assessed. Importantly, although weight control drugs have been long-recognized as appropriate for OTC use, there are no guidelines in place for the determination of efficacy in an OTC environment. To provide context in which to review the efficacy data for orlistat 60 mg (1 to 2 capsules), the current Rx criteria and relevant OTC experience with monograph weight control products is discussed below.

6.1.1 Rx Efficacy Criterion

The standard of efficacy used to support the approval of Xenical® 120 mg was consistent with the efficacy criteria for the approval of prescription weight control drugs intended for long term use as described in the 1996 draft FDA guidance entitled, "***Guidance for the Clinical Evaluation of Weight-Control Drugs***".[10] The content of this draft guidance has been discussed in more than one Endocrinologic and Metabolic Drugs Advisory Committee meeting, as recently as September 2004. Importantly, these Rx criteria apply to a study population with a BMI $\geq$27 kg/m^2 and treatment lasting for one year in duration. The drug treatment group must demonstrate a weight loss greater than that observed in the control group at the end of one year of treatment based on one of two weight loss criteria[21]:

1. absolute mean weight loss difference from placebo of 5%, **OR**

2. statistically significantly greater percentage of patients achieving a $\geq$ 5% weight loss in subjects on drug in comparison to placebo (referred to as categorical or 'responder' analysis)

Efficacy criterion #2 formed the basis of the approval of Rx Xenical® (120 mg) in 1999. Although these clinical criteria apply to prescription weight control drugs at 1 year, they provide a framework for evaluating the effectiveness of orlistat 60 mg for up to 6 months continuous use.

Specifically, weight loss data from two well-controlled long-term trials whose population is consistent with that outlined in the guidance are presented in Section 6.4 of this briefing document and clearly demonstrate that 60 mg orlistat meets the FDA's established categorical weight loss criteria for subjects with BMI ≥27 kg/m^2 at the one year timeframe as well as at 6 months.

6.1.2 Efficacy Criteria for an OTC Weight Loss Aid

Although weight loss has been recognized as an appropriate indication in an OTC environment, standards of efficacy do not currently exist. Presently, no efficacy criteria have been established in a public forum for OTC weight loss agents intended for shorter term use in a potentially lower weight population (BMI ≥25 kg/m^2). Some guidance exists in the form of evaluations conducted as part of the OTC drug review.

In the Federal Register of Feb 26,1982 (47 FR 8466), FDA published an advance notice of proposed rulemaking to establish a monograph for OTC weight control products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (responsible for reviewing data on active ingredients in this class of drugs). The Miscellaneous Internal Drugs Panel reviewed a total of 113 OTC weight control drugs and categorized only two ingredients as safe and effective weight control agents (benzocaine and phenylpropanolamine HCL). A final monograph for OTC weight control drugs has not been published and phenylpropanolamine has subsequently been the subject of voluntary withdrawal due to issues of safety; however it is important to understand the basis by which the Panel determined the effectiveness of these two ingredients.

- benzocaine in the form of gum, lozenges or candy was considered an effective OTC product for weight control based on the demonstration of approximatley 1.5 - 2 pounds per week of weight loss in short term studies. (ANPR Vol 47, No 39 Feb 26, 1982)

- phenylpropanolamine HCL was considered effective based on the results of supportive studies and two adequate, well-controlled trials (12 week) which showed statistically significant weight loss in the active group compared to placebo. No specific weight loss target was required (FR 13295, Vol 56, No 62, Apr 1, 1991).

6.1.3 Summary of Clinical Efficacy Program

As mentioned in Section 5, the clinical efficacy program conducted in support of orlistat 60 mg as a weight loss aid is composed of an initial dose-ranging study and 3

weight loss efficacy trials. These four studies are discussed in detail in the following sections.

6.2 Phase II Dose Ranging Study (Study BM14150)

6.2.1 Study Design and Clinical Methods

As a prelude to the Phase III program, a confirmatory dose ranging study of 6 months' duration was carried out to establish the target dose. Study BM14150 had a multicenter, placebo-controlled, double-blind, double-dummy parallel group design. Eligible patients were 18 years of age or older and had an entry BMI of 28-43 kg/m^2.

Enrolled patients entered a 4-week placebo lead-in period and were placed on a nutritionally balanced weight loss diet (600 kcal/day deficit). Following placebo lead-in, patients continued on a hypocaloric diet and were randomized to receive placebo or orlistat (30, 60, 120 or 240 mg) for 24 weeks 3 times per day (tid) with meals.

6.2.2 Dietary Intervention

Throughout the study patients received dietary counseling and instructions. During the first month of the study, patients visited the clinic every two weeks for assessment of tolerability, efficacy and dietary monitoring. Thereafter, patients were seen monthly until the conclusion of the trial.

6.2.3 Efficacy Results

The efficacy results are presented in Table 6-1 in terms of differences from baseline (BL) body weight. Only the 30 mg dose was not significantly different ($p=0.106$) from placebo. The 60 mg, 120 mg, and 240 mg doses were all significantly ($p \leq 0.002$) different from placebo.

Table 6-1
Effect of Orlistat Dose on Weight Loss Efficacy at 6 Months

Treatment Group	N	Adjusted Mean Change from BL (kg)	Difference from Placebo (Least Squares Mean Difference)		
			Adjusted Mean (kg) ± SE	95% Confidence Interval	P-Value
Placebo	123	-1.78	---	----	---
30 mg tid	122	-2.74	-0.95 ± 0.59	-2.11, 0.20	0.106
60 mg tid	123	-3.64	-1.86 ± 0.59	-3.00, -0.71	0.002
120 mg tid	120	-4.34	-2.55 ± 0.60	-3.73, -1.37	<0.001
240 mg tid	117	-4.59	-2.81 ± 0.59	-3.97, -1.64	<0.001

Intent-to-treat (ITT) Population; Means adjusted for center, lead-in weight loss (≤2 kg, >2 kg), center by lead-in weight loss interaction, center by treatment interaction, and treatment by lead-in weight loss interaction.

6.2.4 Conclusions Related to Therapeutic Dose

In conclusion, the results of dose-ranging study BM14150 demonstrate that the 60 mg tid dose is the lowest dose that yields a clinically meaningful and statistically significant weight loss at 6 months. Further, doses greater than 120 mg tid do not produce significantly greater benefit in terms of weight loss.

Thus, the ideal dosing range for weight loss over 6 months duration is 60 - 120 mg, and forms the basis of the proposed OTC dose. The proposed OTC label directs consumers to take 1 to 2 (60 mg) capsules with meals containing fat. Additional recommendations for starting with 60 mg are based on the desire to balance efficacy and tolerability as discussed within Safety Section 7 of this briefing document.

6.3 Description of Phase III Controlled Clinical Efficacy Studies

The efficacy of orlistat 60 mg tid for weight loss was demonstrated in three randomized, controlled clinical studies (BM14149, NM14161, and NM17247) in which subjects were initially randomized to a 60 mg orlistat tid dosing regimen.

Studies NM14161 and BM14149 were long-term studies (2 years) that assessed weight loss over 12 months in obese subjects.* Study NM17247 was a short-term study that evaluated weight loss in overweight subjects over a four-month period.

6.3.1 Study Designs

These were double-blind, randomized, parallel-group, placebo-controlled, multicenter studies conducted in both non-US (BM14149) and US sites (NM14161, NM17247).

In studies BM14149 and NM14161, subjects were stratified according to the amount of weight lost (≤ 2 kg, >2 kg) during a 4 week lead-in period with a hypocaloric diet and placebo prior to being randomized to diet and treatment (placebo tid, 60 mg orlistat tid, or 120 mg orlistat tid). A hypocaloric diet is defined as 30% of calories from fat, 50% of calories from carbohydrates, 20% of calories from protein and a maximum of 300mg/day of cholesterol.)

In contrast, study NM17247 had no placebo lead-in period or stratification. Subjects were randomized to a 16-week treatment period with 60 mg orlistat tid, or placebo tid. Both groups were placed on a hypocaloric diet.

6.3.2 Description of Diet, Behavior Modification, and Exercise

It is important to understand the range of dietary intervention and behavioral modification that was experienced in the different studies; especially in the context of evaluating comparative efficacy and predicting effectiveness in an OTC environment with low intervention. In all three studies, a hypocaloric diet containing approximately 30% of calories from fat was recommended for the weight loss portions of the studies. The level of dietary intervention differed among the clinical studies as outlined in Table 6-2.

* Weight maintenance and prevention of weight regain were evaluated during the second year of treatment; these data are not presented as they are beyond the scope of the desired weight loss indication for OTC.

Table 6-2
Level of Intervention and Dietary Guidance in Controlled Clinical Studies

Study	Dietary Instruction and Intervention	Behavioral Modification	Exercise
BM14149 (non-US)	Dietitians on site Dietary counseling 12 times during 1 yr weight loss phase Multiple calorie levels assigned	No formal behavioral modification Dietary counseling by dietitian	No formal exercise counseling
NM14161	No dietitians on site No specific staff training in nutrition or weight management techniques Assignment to 1 of 2 calorie levels	Subjects could view 4 videos on their own during the weight loss phase. No group meetings or counseling sessions held.	No formal exercise counseling; subjects encouraged to increase physical activity by walking
NM17247	No dietitians on site No specific staff training in nutrition or weight management Assignment to 1 of 2 calorie levels Self-instructional materials	No group meetings or counseling sessions held Self-instructional materials	Self-instructional

6.3.3 Description of Efficacy Parameters & Methods of Analysis

Primary Efficacy Parameter

The primary efficacy parameter was change in body weight. Weight loss was evaluated in terms of:

- the relative change from baseline body weight over time (where baseline corresponds to the start of the double-blind treatment period)
- the adjusted mean difference in weight loss between active treatment group and placebo (treatment group comparison)
- the percentage of patients who lost at least 5% of baseline body weight (responder analysis)

Other Efficacy Parameters

Secondary efficacy parameters included anthropometrics such as waist circumference and waist to hip ratio. Since waist circumference is currently considered a more relevant risk factor in overweight and obesity than waist to hip ratio, these data are presented herein.[1]

The clinical trial design also included measurements of lipids, glucose levels and blood pressure. Although outside the scope of the 6 month OTC indication to promote weight loss, orlistat has a demonstrated positive impact on these parameters.

Therefore, these important data and impact on co-morbidities are presented in the context of the overall risk-benefit profile for orlistat OTC.

6.3.4 Pooling Strategy

To illustrate the consistent efficacy observed in each of the weight loss trials, analyses of the primary efficacy variable (weight loss) is presented separately for studies BM14149, NM14161 and NM17247. For analyses of demographics, baseline characteristics, and other efficacy parameters, data are presented together to simplify presentation and facilitate review.

6.3.5 Statistical Methods

Continuous variables were summarized by treatment group and time point using the mean, standard deviation, median, and range. Categorical variables were summarized using frequency distributions.

Studies BM14149 and NM14161

Analysis of covariance was used to compare change in weight from baseline to 6 months among treatment groups. Least squares means were computed for the treatment groups and each of the orlistat treatment groups was compared to the placebo group. A 95% confidence interval was computed for the adjusted mean difference between each orlistat-treated group and the placebo group. Least squares means were adjusted for center, lead-in period weight loss (≤2 kg, >2 kg), baseline weight and site by baseline weight interaction, where necessary. Comparisons of responder rates between each orlistat group and the placebo group were conducted using Fisher's exact tests.

Study NM17247

Analysis of covariance was used to compare change in weight from baseline to 4 months. Factors in the model were site and baseline weight. Least squares means were computed and compared for the 60 mg orlistat and placebo group.

6.3.6 Analysis Populations

Populations for analysis of weight loss are defined below and presented in Table 6- 3.

The *intent-to-treat (ITT) population* comprised all randomized subjects who received at least one dose of study medication and had body weight measurements before and after randomization.

In each study the *completers population* was defined as follows:

- Studies BM14149 and NM14161 - all subjects who did not have any protocol violations thought to affect efficacy and completed at least 22 weeks of treatment and had efficacy measurements between 154 and 182 days.
- Study NM17247 - all subjects who were randomized and completed 113 days of treatment.

Table 6- 3
Overview of Analysis Population

Population	Pooled Studies (NM14161 and BM14149) N	Study BM14149 N	Study NM14161 N	Study NM17247 N
Enrolled	1579	783	796	498
Randomized	1371	729	642	391
Intent to Treat				
Placebo	448	236	212	184
60 mg tid	452	239	213	194
120 mg tid	451	241	210	N/A
Completers*				
Placebo	341	185	156	140
60 mg tid	367	198	169	152
120 mg tid	373	202	171	N/A

Source: NDA 21-887; Item 11, Table 1

*Completers were defined as all subjects without protocol violations thought to affect efficacy who completed (a) at least 22 weeks of treatment and had efficacy measurements between 154 and 182 days in studies NM14161 and BM14149 and (b) all subjects who were randomized and completed 113 days of treatment in study NM17247.

Analyses were conducted in the ITT population using observed data (no imputation of missing values); in the ITT population using last observation carried forward (LOCF) imputation of missing values; and in completers using observed data. Results for ITT observed are presented throughout this document, except where noted. Similar results, however, were obtained for ITT LOCF and completers.

6.3.7 Demographics and Baseline Characteristics

As outlined in Table 6-4, the demographic data of the ITT population were similar in studies BM14149, NM14161 and NM17247. The majority of subjects were female and Caucasian, with a mean age of 44 -46 years. Baseline characteristics were consistent in the two long term studies (BM14149 and NM14161), while the baseline characteristics of participants in NM17247 reflected the different target population of that study in terms of initial weight status.

Table 6-4
Demographics and Baseline Characteristics

	BM14149 and NM14161						NM17247			
	Placebo (N=448)		Orlistat 60 mg tid (N=452)		Orlistat 120 mg tid (N=451)		Placebo (N=184)		Orlistat 60 mg tid (N=194)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Sex										
Male	78	(17.4)	103	(22.8)	84	(18.6)	9	(4.9)	12	(6.2)
Female	370	(82.6)	349	(77.2)	367	(81.4)	175	(95.1)	182	(93.8)
Age										
< 65 years	438	(97.8)	442	(97.8)	439	(97.3)	176	(95.7)	182	(93.8)
≥ 65 years	10	(2.2)	10	(2.2)	12	(2.7)	8	(4.3)	12	(6.2)
Race										
Caucasian	428	(95.5)	436	(96.5)	423	(93.8)	165	(89.7)	172	(88.7)
Black	16	(3.6)	11	(2.4)	20	(4.4)	12	(6.5)	18	(9.3)
Hispanic	4	(0.9)	2	(0.4)	6	(1.3)	0		1	(0.5)
Other	0	0	3	(0.7)	2	(0.4)	7	(3.8)	3	(1.5)
BMI at Baseline (kg/m^2)										
< 25	0	0	0	0	0	0	4	(2.2)	5	(2.6)
≥ 25 to 28	8	(1.8)	6	(1.3)	4	(0.9)	161	(87.5)	167	(86.1)
≥ 28 to 30	49	(10.9)	41	(9.1)	51	(11.3)	19	(10.3)	22	(11.3)
≥ 30 to 35	178	(39.7)	211	(46.7)	198	(43.9)	0	0	0	0
≥ 35	213	(47.5)	194	(42.9)	198	(43.9)	0	0	0	0
Mean ± SD (min,max)	34.82 ± 4.010 (26.7, 45.9)		34.59 ± 3.788 (26.7, 42.7)		34.42 ± 3.611 (27.1, 42.8)		26.84 ± 0.944 (23.7, 28.6)		26.82 ± 0.960 (24.5, 29.0)	
Age (years)										
Mean ± SD (min,max)	43.1 ± 10.33 (18, 71)		43.7 ± 10.87 (20, 72)		43.4 ± 10.80 (18, 78)		46.6 ± 10.91 (19, 72)		45.8 ± 11.89 (20, 80)	
Initial Weight (kg)										
Mean ± SD	99.64 ± 14.750		99.69 ± 14.475		98.51 ± 14.126		72.64 ± 6.601		72.60 ± 6.867	
(min,max)	(67.4, 155.5)		(68.9, 152.0)		(68.4, 147.3)		(56.0, 89.8)		(58.3, 103.0)	

ITT Population; Source: NDA 21-887; Item 11, Table 3.1 and Table 16

6.4 Primary Efficacy Results

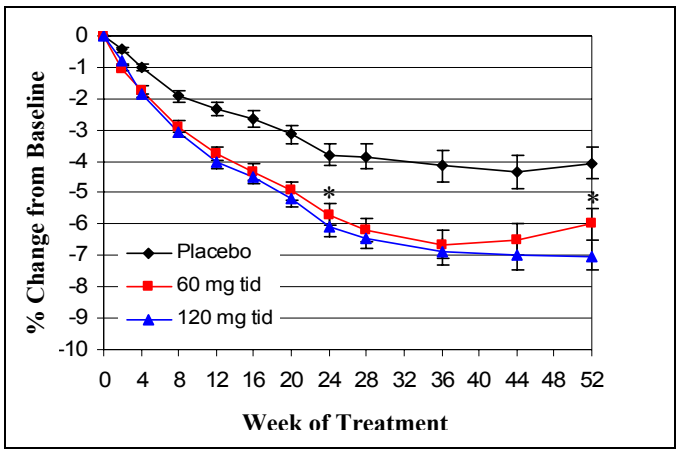
6.4.1 Relative Change from Baseline Body Weight Over Time

In studies NM14161 and BM14149 that included a 4-week placebo lead-in period, all treatment groups lost similar amounts of weight during this time. Recall that all treatment groups, including placebo, were prescribed the same hypocaloric diet. In all studies, the orlistat plus diet groups showed significantly greater weight loss than placebo plus diet. Additionally, all three weight loss studies showed significant and consistent weight loss of approximately 5% from baseline body weight with orlistat 60 mg tid. These data are presented in Figure 6-1, Figure 6-2 and Figure 6-3 for studies BM14149, NM14161 and NM17247, respectively.

Examination of the data from the two longer-term trials which evaluated both the 60 and 120 mg dose, reveals that most of the weight loss occurs in the first 6 months of treatment, the proposed duration of use for OTC orlistat (Figure 6-1 and Figure 6-2).

Additionally, these figures illustrate that the efficacy of 60 mg tid and 120 mg tid is generally comparable within this timeframe, with the 120 mg dose providing a numerically greater weight loss that 60 mg.

Figure 6-1
Relative Change From Baseline Weight - Study BM14149

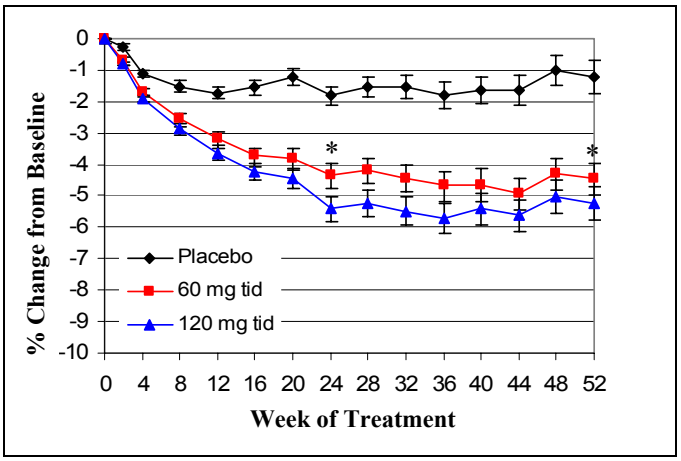


ITT population, observed data; mean +/- SE

* Relative weight change at 6 mos and 1 yr; 60 mg vs. placebo and 120 mg vs. placebo; p< 0.001.

Importantly, Figure 6-2 demonstrates that similar efficacy results were achieved in Study NM14161 where there was a lower level of dietary intervention.

Figure 6-2
Relative Change From Baseline Weight - Study NM14161

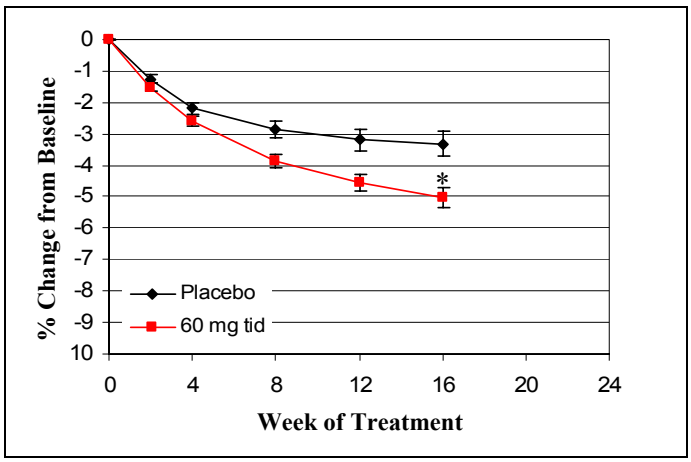


ITT population, observed data; mean +/- SE

* Relative weight change at 6 mos and 1 yr; 60 mg vs. placebo and 120 mg vs. placebo; $p < 0.001$.

The results of study NM17247 evaluating weight loss in a lower BMI population with minimal dietary guidance and intervention are shown in Figure 6-3. These data confirm that orlistat provides significantly greater weight loss across all clinical studies regardless of degree of overweight or level of dietary intervention.

Figure 6-3
Relative Change From Baseline Weight - Study NM17247



ITT population, observed data; mean +/- SE

* Relative weight change at 4 months for 60 mg vs. placebo; p< 0.001.

6.4.2 Treatment Group Comparison for Efficacy Trials

Table 6-5 demonstates that there was a statistically significant difference in weight loss between the active treatment groups and placebo in all clinical studies, including study NM17247:

- in all populations analyzed (observed ITT, LOCF ITT, and completers)
- in obese and overweight individuals,
- evaluated at 6 months (BM14149 and NM14161) and 4 months (NM17247)

It is important to note that consistent results in weight loss were found with orlistat in all studies, despite the lower baseline body weight in study NM17247. In addition, the mean relative reduction in body weight from baseline was approximately 5% across all studies, including the short term study NM17247.

Table 6-5
Adjusted Mean Differences from Placebo after 6 Months of Treatment

Study	Treatment Group	Adjusted Mean Change from BL (kg ± SE)	Difference from Placebo: Adjusted Mean (kg ± SE)	Difference from Placebo: 95% Confidence Interval	Difference from Placebo: P-Value
BM14149	Placebo	-3.07 ± 0.344			
	Orlistat 60 mg	-5.27 ± 0.327	-2.19 ± 0.456	(-3.09, -1.30)	<0.001
	Orlistat 120 mg	-5.59 ± 0.325	-2.52 ± 0.450	(-3.40, -1.63)	<0.001
NM14161	Placebo	-1.11 ± 0.352			
	Orlistat 60 mg	-3.82 ± 0.338	-2.72 ± 0.478	(-3.65, -1.78)	<0.001
	Orlistat 120 mg	-4.63 ± 0.341	-3.52 ± 0.482	(-4.47, -2.58)	<0.001
Pooled Studies	Placebo	-2.12 ± 0.247			
	Orlistat 60 mg	-4.56 ± 0.235	-2.43 ± 0.330	(-3.08, -1.79)	<0.001
	Orlistat 120 mg	-5.09 ± 0.236	-2.97 ± 0.329	(-3.61, -2.32)	<0.001
NM17247*	Placebo	-2.36 ± 0.278			
	Orlistat 60 mg	-3.56 ± 0.257	-1.20 ± 0.37	(-1.92, -0.48)	0.001

*Applies to weight change at the end of 4 months of therapy.
BM14149, NM14161: means adjusted for site, lead-in weight loss category, baseline weight, and baseline weight by site interaction.
Pooled studies: means adjusted for study, site nested in study, lead-in weight loss category, baseline weight, and baseline weight by site interaction.
NM17247: means adjusted for site and baseline value.
Observed data, ITT Population

6.4.3 Responder Analysis

An overall assessment of weight loss efficacy is illustrated by an analysis of the responder rate as a function of treatment. Recall that one of the criterion by which the FDA assesses the efficacy of prescription weight loss drugs is that a statistically significantly greater proportion of subjects on treatment achieve a 5% weight loss ***after 1 year***, in comparison to placebo.

Data from the two long-term studies show that both the 60 and 120 mg orlistat doses meet this efficacy criterion (data presented in the NDA). Of greater relevance to OTC orlistat proposed for up to 6 months of use, Table 6-6 shows significantly ($p<0.001$) more subjects using orlistat 60 mg lost more than 5% of their body weight compared to placebo ***at 6 months*** for study BM14149 and study NM14161 individually and pooled. In addition, orlistat at doses of 60 mg and 120 mg produced very similar results. These data firmly establish the efficacy of the 60 mg tid dose to achieve weight loss in a 6 month timeframe.

Table 6-6
Responder Analysis:
Subjects who Lost ≥5% of Baseline Body Weight at 6 Months

Study	Placebo		Orlistat 60 mg tid		Orlistat 120 mg tid	
	%	n	%	n	%	n
BM14149	30.9	[63/204]	54.6*	[118/216]	54.8*	[121/221]
NM 14161	21.3	[39/183]	37.7*	[72/191]	42.8*	[80/187]
Pooled studies	26.4	[102/387]	46.7*	[190/407]	49.3*	[201/408]

Observed data, ITT Population
* Significant difference with respect to placebo ($p<0.001$)

Additional data from the long-term studies BM14149 and NM14161 demonstrates orlistat efficacy after 6 months:

- substantially greater percentage of subjects lost at least 10% of their body weight at 6 months; 16.2% and 18.9% on orlistat 60 mg and 120 mg, respectively, compared to placebo (6.5%).

- approximately 2 to 3 times the number of subjects gained weight in the placebo group (31.8%) compared to orlistat 60 mg (15.5%) and 120 mg (10.8%) groups.

Short-term efficacy study NM17247 in lower BMI subjects was not designed or powered to apply the 1 year efficacy criterion. However, the percentage of subjects achieving a ≥5% weight loss in the orlistat 60 mg group was greater than the placebo group at 4 months (43.5% vs. 36.2%) and similar to the long-term studies in terms of the percentage of subjects achieving ≥5% weight loss with orlistat 60 mg group.

6.5 Other Efficacy Parameters

Although weight loss was the primary measure of efficacy assessed in the controlled clinical trials, consistent with the proposed indication for use as a weight loss aid, other positive effects were associated with the use of orlistat 60 mg capsules.

Changes in anthropometric measurements over time were evaluated as secondary efficacy parameters during 6 months of treatment using the ITT population.

These parameters included waist circumference (a measure of upper body obesity); hip circumference (a measure of lower body obesity) and waist to hip ratio. Although waist-hip ratio was also measured, its effect is often obscured by simultaneous changes which are similar in magnitude for both waist and hip circumference. Therefore, this measure is of limited utility as a sensitive indicator of change in overweight/obese status. Since waist circumference is currently considered the most relevant anthropometric risk factor in overweight and obesity, only these data are described herein.[1]

The effect of orlistat 60 mg capsules tid on serum lipids concentrations and blood pressure was also assessed. Although the treatment of co-morbid conditions is outside the scope of the 6 month OTC indication to promote weight loss, these data are presented in the context of evaluating the overall benefit to the consumer.

6.5.1 Waist Circumference

In pooled studies, mean waist circumference at baseline was similar in placebo, 60 mg, and 120 mg treatment groups: 103.48, 103.71, and 102.59 cm, respectively. After 6 months of treatment, there was a significant, though modest, reduction in waist circumference with both 60 and 120 mg groups (-4.54 cm ± 0.281; p=0.013 and -4.85 cm ± 0.276; p<0.001) compared to placebo (-3.58 cm ± 0.299).

In study NM17247, mean waist circumference at baseline was 85.61 and 84.90 cm in placebo and 60 mg groups, respectively. After 4 months of treatment, waist circumference decreased to a greater extent with 60 mg orlistat (-4.27 cm ± 0.360) compared to placebo (-3.68 cm ± 0.418).

6.5.2 Lipids and Blood Pressure

At the prescription dose of 120 mg tid, orlistat has consistently been shown to significantly improve risk factors for up to 4 years. In the Phase III trials evaluating orlistat 60 mg tid, it's use has been associated with a favorable profile in terms of co-morbidities. In contrast to centrally-acting weight loss drugs, Orlistat does not raise

blood pressure and has a consistent beneficial effect on LDL cholesterol. Importantly, consistent results were observed in 4-month clinical study NM17247 in overweight subjects. These data appear in this briefing document in the discussion of safety (Section 7.11) and overall risk-benefit profile (Section 9.14).

6.6 Efficacy Conclusions

- The results from the long-term controlled clinical studies on orlistat 60 mg show that when used as an adjunct to diet, subjects taking orlistat 60 mg consistently lost significantly more weight and had greater reductions in waist circumference compared to the placebo group.

- These differences between treatments were statistically significant and clinically meaningful. A significantly greater ($p<0.001$) number of subjects lost ≥5% of baseline body weight on orlistat 60 mg compared to placebo. Therefore, these findings meet the criterion used by the FDA for the approval of Rx weight loss drugs.

- The results from the 4-month trial in overweight subjects also confirm weight loss in this population of lower weight individuals.

- A weight loss of ≥5% from baseline body weight has been shown to provide significant health benefits.

- These data provide strong support for the use of orlistat at a dose of 60-120 mg as an OTC weight loss aid. The proposed OTC label directs consumers to take 1 to 2 (60 mg) capsules with meals containing fat. Additional recommendations for starting with 60 mg are based on the desire to balance efficacy and tolerability as discussed within Safety Section 7 of this briefing document.

7. Summary of the Safety of Orlistat

7.1 Introduction and Overview of Safety Program

This Safety Summary provides a comprehensive review of safety data from clinical trials and extensive global post-marketing experience.

7.1.1 Clinical Data

The safety of orlistat has been studied extensively in over 100 clinical trials[11], including four 2-year and one 4-year double-blind placebo-controlled studies. The safety of Xenical® (orlistat) 120 mg capsules was established in comprehensive preclinical, clinical pharmacology and long-term, placebo-controlled clinical trials. These extensive data form the basis of the approved prescription labeling (provided as reference in Appendix 1).

As previously described in the Overview of Clinical Development (Section 5), this briefing document focuses on those clinical studies which evaluated orlistat at a dose of 60 mg tid. Information related to the Phase II dose-ranging study, consumer use studies evaluating orlistat 60 mg, and other Roche clinical trials evaluating Xenical® 120 mg is presented in terms of the extent of exposure to orlistat as an active ingredient. These studies may provide supportive safety information; however, the data from Phase III clinical trials evaluating 60 and 120 mg orlistat are considered most relevant to the assessment of the safety of orlistat OTC and are; therefore, discussed in detail in the current section.

The data presented in this Safety Summary are consistent with the well-established safety profile reflected in the approved Rx labeling and provide strong evidence of the safety and tolerability of the proposed OTC dose of 60 mg (1 to 2 capsules).

7.1.2 Post-Marketing Safety Data

Xenical® (orlistat) 120 mg capsules was approved by the FDA for US marketing in 1999 and is currently approved and marketed in over 145 countries, with over 22 million patients treated. This foreign marketing experience includes 6 countries where Xenical® (120 mg) has recently been reclassified to OTC status as a 'pharmacy-only' medicine. Although the 'pharmacy-only' designation affords some level of pharmacist intervention at the initial point of sale, the experience provides some perspective on the drug's safety profile in a consumer-driven OTC environment.

Hoffmann-La Roche maintains a database of all adverse experiences spontaneously reported to the company for its products worldwide (Roche World Wide Safety

Database) and shares this information with GSK as it pertains to orlistat. Review of the postmarketing data has not revealed any new safety findings or areas of concern. Further, as recently shared with the FDA in our Safety Update Report, post-marketing data from two major markets, Australia and New Zealand, where orlistat has recently been switched to OTC status suggests that the well-established safety profile of the drug has not been affected by this reclassification.

7.2. Description of Clinical Studies and Study Design

The study designs of Phase III clinical studies BM14149, NM14161 and NM17247 were previously described in Efficacy Section 6. One additional study (NM14302) is described in the current section.

Study NM14302 was a Phase III multicenter, double-blind, randomized, parallel-group, double-dummy, placebo-controlled study with a 24-week lead-in period during which subjects were prescribed a hypocaloric diet with behavior modification and dietary counseling followed by 52 weeks of active treatment. The BMI entry criterion was 28 to 38 kg/m^2.

Subjects were randomized into two strata based on their weight loss (≤10%, >10% of initial weight) during the 24 week weight loss period (analogous to other Phase III study lead-in periods) prior to randomization to placebo or 30, 60, or 120 mg orlistat tid. The 52 week treatment period assessed the prevention of weight regain.

7.2.1 Pooling Strategy

Safety data from the three placebo-controlled, Phase III trials where subjects had their first exposure to orlistat as a 60 mg dose (BM14149, NM14161, and NM14302) were pooled to facilitate review and detection of safety signals. These studies had a similar duration of treatment (1 to 2 years) and BMI entry criteria (≥28 kg/m^2).

Data from study NM17247 were not pooled with the studies discussed above due to differences in study design and duration; these data are analyzed separately.

7.2.2 Vitamin Supplementation

For studies BM14149 and NM14161, patients were not routinely administered vitamin supplements. During the course of the study, plasma levels of vitamin A, 25-OH vitamin D, vitamin E, and beta-carotene were measured. Vitamin K activity was assessed indirectly by measuring prothrombin time. Supplementation only occurred if, during the double-blind treatment period, the fat soluble vitamin or beta-carotene levels measured below the reference range on two consecutive measurements.

Study NM14302 was unique in that all subjects in this study were supplemented with one Centrum® multivitamin daily throughout the course of the study, including the six month diet lead-in period. Supplementation was increased if vitamin levels were found to be below the reference range during the study. Vitamin levels were measured as in the other 2 studies.

In study NM17247, all subjects in this study were provided Centrum® multivitamins and instructed to take daily throughout the study period at least two hours before or after taking orlistat. Vitamin levels were not measured in this study.

7.2.3 Variables to be Analyzed for Safety

The data in this section which demonstrate orlistat's clinical safety include:

1. Extent of Exposure
2. Demographic Information and Subject Characteristics
3. Analysis of Adverse Event (AEs): characterized in terms of degree of seriousness, incidence, intensity and relation to discontinuation.
4. Analysis of Clinical Laboratory Parameters:
    - Hematology – hemoglobin, hematocrit, platelet count, RBC count, WBC count, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.
    - Serum chemistry – total protein, albumin, creatinine, BUN, total bilirubin, calcium, sodium, potassium, chloride, phosphorus, glucose, total cholesterol (TC), HDL, LDL, LDL:HDL ratio, TG, alkaline phosphatase, creatine phosphokinase, GGT, AST, ALT,TSH, amylase, uric acid, and free thyroxine.
    - Fat soluble vitamin levels (vitamin A, 25-OH vitamin D, vitamin E, and beta-carotene and vitamin K via measurement of prothrombin time)
5. Analysis of Vital Signs
6. Analysis of ECG, Renal and Gallbladder Ultrasounds
7. Possible Drug Interactions
8. Other Safety-Related Issues such as use by pregnant/breast-feeding women and misuse potential are discussed in Section 9 (Risk Benefit Profile)

7.3 Extent of Exposure to Orlistat in Controlled Clinical Trials

The extent of exposure of subjects to orlistat 60 mg was adequate and appropriate to evaluate orlistat's long-term safety. In total, over 1300 subjects were exposed to orlistat 60 mg tid for up to 1 year. Specifically, in the Phase III clinical program, over 800 subjects received orlistat 60 mg tid; over 600 subjects were exposed for up to 1 year and approximately 200 subjects, with a lower BMI at entry, were exposed for 4 months. There were over 100 subjects enrolled in a Phase II study who received orlistat 60 mg tid for up to 6 months, and there were at least 400 subjects exposed to orlistat 60 mg tid for 4 to 12 weeks in two Phase IV consumer use studies (details of the Sponsor's Actual Use trial are provided in Section 8). For comparative purposes, there were approximately 700 subjects exposed to orlistat 120 mg tid and 900 subjects exposed to placebo in the trials described above. Additionally, when one considers the extent of exposure to orlistat 120 mg (Xenical®) from the Rx clinical development program, the support of long-term safety is even more extensive: over 2800 patients in 1 to 2 year trials and over 1640 patients in the 4-year XENDOS study have been treated with Xenical® 120 mg capsules (see approved Rx label in Appendix 1).

7.4 Demographics and Subject Characteristics

A summary of the demographic characteristics of patients in the Phase III studies is provided in Table 7-1 (next page). The distribution of subjects by demographic characteristics was comparable among the three treatment groups.

Table 7-1
Demographic Characteristics Placebo-Controlled Phase III Studies

	Pooled Phase III Studies (Studies BM14149, NM14161, NM14302)						4-Month Phase III Study Study NM17247			
	Placebo (N=634)		Orlistat 60 mg tid (N=623)		Orlistat 120 mg tid (N=632)		Placebo (N=195)		Orlistat 60 mg tid (N=196)	
	n	(%)	n	(%)	n	%)	n	(%)	n	(%)
Sex										
Male	106	(16.7)	138	(22.2)	107	(16.9)	11	(5.6)	12	(6.1)
Female	528	(83.3)	485	(77.8)	525	(83.1)	184	(94.4)	184	(93.9)
Race										
Caucasian	594	(93.7)	591	(94.9)	578	(91.5)	174	(89.2)	174	(88.8)
Black	25	(3.9)	21	(3.4)	29	(4.6)	14	(7.2)	18	(9.2)
Hispanic	12	(1.9)	7	(1.1)	23	(3.6)	0	0.0	0	0
Other Race	3	(0.5)	4	(0.6)	2	(0.3)	7	(3.6)	4	(2.0)
Age (years)										
Mean ± SD	44.0 ± 10.33		44.3 ± 10.51		44.2 ± 10.64		46.5 ± 10.97		45.8 ± 11.87	
(Min, Max)	(18, 72)		(20, 72)		(18, 78)		(19, 72)		(20, 80)	
Weight (kg)										
Mean ± SD	97.1 ± 14.60		97.7 ± 14.27		96.0 ± 14.00		72.9 ± 6.94		72.7 ± 6.95	
(Min, Max)	(62.3, 155.5)		(67.3, 152.0)		(63.5, 147.3)		(56.2, 106.6)		(57.4, 102.5)	
BMI (kg/m^2)										
Mean ± SD	34.8 ± 3.89		34.8 ± 3.72		34.6 ± 3.59		26.8 ± 0.95		26.8 ± 0.96	
(Min, Max)	(27.0, 45.8)		(28.0, 44.0)		(27.4, 43.4)		(23.7, 28.6)		(24.5, 29.0)	

7.5 Disposition of the Study Population

Placebo-Controlled Studies

In the placebo-controlled Phase III studies (4 studies), a greater proportion of placebo-treated subjects withdrew prematurely from the study for any reason compared to orlistat-treated subjects. The most common reasons for withdrawal from the study for the placebo subjects were lost to follow-up and refusal of treatment. For the orlistat-treated subjects, the most common reasons for withdrawal were adverse events and lost to follow-up.

Table 7-2 reflects the total number of subjects who prematurely withdrew from these studies (for reasons other than adverse events) as well as those who withdrew due to

an adverse event. Generally, the proportion of subjects prematurely discontinuing treatment is less for the 60 mg dose, providing evidence that this lower dose of orlistat may provide a better tolerability profile for use as an OTC product.

Table 7-2
Premature Withdrawal in Safety Population

	Pooled Phase III Studies (Studies BM14149, NM14161, NM14302)						4-Month Phase III Study Study NM17247			
	Placebo		Orlistat 60 mg tid		Orlistat 120 mg tid		Placebo		Orlistat 60 mg tid	
Reason for Withdrawal	(N=634) n	(%)	(N=623) n	(%)	(N=632) n	(%)	(N=195) n	(%)	(N=196) n	(%)
Total subjects withdrawn	220	(34.7)	156	(25.0)	175	(27.7)	55	(28.2)	44	(22.4)
Adverse event (Total)	21	(3.3)	42	(6.7)	56	(8.9)	6	(3.1)	13	(6.6)

For the pooled Phase III studies, withdrawals in the first year are tabulated.

For Study NM17247, withdrawals in the 4-month treatment period are tabulated.

7.6 Adverse Events in 6 Months of Treatment

Orlistat's systemic absorption is minimal (<2%) and does not result in tissue accumulation, making the potential for adverse reactions low. Adverse events are primarily limited to the GI tract where orlistat's lipase inhibition activity is localized.

The overall incidence and intensity of AEs during treatment with 60 mg or 120 mg orlistat tid were reviewed for 6 months and 1 year. Data are presented in the following section and focus on 6 months of treatment, the proposed OTC duration of use.

7.6.1 Incidence of Adverse Events

Phase III pooled studies

A summary of the most frequently reported adverse events (incidence ≥5% in an active treatment group and greater than the placebo group) is shown in Table 7-3 by decreasing order of incidence for the 60 mg orlistat tid group. The most common reported adverse events were headache and influenza syndrome, with similar incidences among treatment groups and placebo. Most of the adverse events reported were related to the gastrointestinal system.

Table 7-3
Adverse Events with Incidence ≥5% during First 6 Months of Treatment
Pooled Phase III Studies (BM14149, NM14161, NM14302)

WHO-ART Preferred Term	Placebo (N=634) n	(%)	Orlistat 60 mg tid (N=623) n	(%)	Orlistat 120 mg tid (N=632) n	(%)
Subjects with ≥1 AE	536	(84.5)	555	(89.1)	581	(91.9)
Gastrointestinal system disorders						
Abdominal pain	83	(13.1)	125	(20.1)	132	(20.9)
Fecal urgency	50	(7.9)	117	(18.8) *	148	(23.4)
Flatulence	114	(18.0)	116	(18.6)	114	(18.0)
Oily spotting	7	(1.1)	110	(17.7)	137	(21.7)
Flatus with discharge	12	(1.9)	108	(17.3)	126	(19.9)
Fatty/oily stool	17	(2.7)	107	(17.2) *	137	(21.7)
Liquid stools	47	(7.4)	74	(11.9)	90	(14.2)
Oily evacuation	4	(0.6)	72	(11.6)	85	(13.4)
Stools soft	37	(5.8)	63	(10.1)	49	(7.8)
Increased defecation	17	(2.7)	44	(7.1)	52	(8.2)
Fecal incontinence	5	(0.8)	29	(4.7) *	49	(7.8)
Nausea	41	(6.5)	29	(4.7)	47	(7.4)
Respiratory system disorders						
Sinusitis	54	(8.5)	66	(10.6)	63	(10.0)
Upper respiratory tract infection	57	(9.0)	61	(9.8)	56	(8.9)
Bronchitis	26	(4.1)	24	(3.9)	37	(5.9)
Pharyngitis	32	(5.0)	23	(3.7)	44	(7.0)
Resistance mechanism disorders						
Influenza syndrome	185	(29.2)	168	(27.0)	188	(29.7)
Central & peripheral nervous system disorders						
Headache	119	(18.8)	116	(18.6)	146	(23.1)
Musculoskeletal system disorders						
Back pain	37	(5.8)	45	(7.2)	51	(8.1)

World Health Organization's Adverse Reaction Terminology (WHO-ART)
Table includes events with incidence in either orlistat group ≥5% and greater than that in the placebo group.
* An analysis of the seven gastrointestinal adverse events associated with orlistat treatment (see Section 7.7) indicates a significant difference between 60 mg and 120 mg; $p<0.05$.

Phase III Study NM17247 (4 month study)

A summary of the most frequently reported adverse events for this study with an incidence of at least 2% in the orlistat group and the incidence greater than that in the placebo control group is presented in Table 7-4. Overall, 54.4% of subjects in the placebo group and 69.9% of subjects in the orlistat 60 mg group reported at least one

AE. As was seen for the pooled Phase III studies, gastrointestinal AEs were the most frequently reported AEs for this study.

Table 7-4
Adverse Events with Incidence ≥2% in 4 Months of Treatment
4-Month Phase III Study

MedDRA Preferred Term	Placebo (N=195) n	(%)	Orlistat 60 mg tid (N=196) n	(%)
Subjects with ≥1 AE	106	(54.4)	137	(69.9)
Gastrointestinal system				
Fatty/oily stool	5	(2.6)	44	(22.4)
Fecal urgency	11	(5.6)	33	(16.8)
Oily spotting	0		22	(11.2)
Flatus with discharge	3	(1.5)	18	(9.2)
Increased defecation	7	(3.6)	17	(8.7)
Stools soft	7	(3.6)	11	(5.6)
Abdominal pain NOS	6	(3.1)	8	(4.1)
Dyspepsia	0		6	(3.1)
Fecal incontinence	0		6	(3.1)
Oily evacuation	0		6	(3.1)
Infections and infestations				
Upper respiratory tract infection NOS	5	(2.6)	11	(5.6)
Nasopharyngitis	5	(2.6)	6	(3.1)
Sinusitis NOS	3	(1.5)	8	(4.1)
Bronchitis NOS	1	(0.5)	5	(2.6)
Nervous system disorders				
Headache NOS	5	(2.6)	9	(4.6)
Dizziness (excl vertigo)	2	(1.0)	4	(2.0)
Musculoskeletal, connective tissue and bone disorders				
Myalgia	3	(1.5)	5	(2.6)

Medical Dictionary for Regulatory Activities (MedDRA)
Table includes events with incidence in the orlistat group ≥2% and greater than that in the placebo group.

7.6.2 Intensity of Adverse Events in Phase III Studies

Phase III pooled studies

A majority of subjects had adverse events that were mild in intensity (71.6% of placebo subjects, 78.3% of subjects in the 60 mg group, and 79.6% of subjects in the

120 mg dose group). At least half the subjects had an adverse event that was moderate in intensity (49.7% of placebo subjects, 55.7% of subjects in the 60 mg group, and 60.3% of subjects in the 120 mg dose group). Few subjects reported adverse events that were severe in intensity (7.9% of placebo subjects, 11.2% of subjects in the 60 mg group, and 10.3% of subjects in the 120 mg dose group).

Among those adverse events considered severe in intensity, most were gastrointestinal in nature, particularly for the active treatment groups: 30% [15/50 total severe events in the placebo group]; 51% [36/70] in the 60 mg group; and 51% [33/65] in the 120 mg dose group. The incidence of any particular severe event was low (<2%) in all treatment groups. A similar pattern was seen for subjects exposed up to 1 year.

Phase III Study NM17247 (4 month study)

As was seen for the pooled Phase III studies, the majority of adverse events for Study NM17247 were mild to moderate in intensity. Overall, 12.3% of placebo-treated and 10.2% of orlistat-treated subjects had at least one severe event. The most frequent severe AEs in both treatment groups were gastrointestinal events (13 subjects in each treatment group).

7.6.3 Demographic Distribution of Adverse Events

The demographic distribution of adverse events (AEs) was examined in the three pooled Phase III studies in terms of age, race and gender.

Age

The distribution of AEs by age (<65 vs ≥65) was examined. The distribution of adverse events across treatment groups was similar in the <65 years group to that of the overall study population. Since most subjects enrolled (97.3%) were less than 65 years of age, there were too few subjects to make meaningful comparisons. In the original review of the Rx NDA for orlistat 120 mg capsules (larger database), the population >65 years of age was found to a have similar safety profile to that of the general population.

Race

The distribution of AEs by race (Caucasian vs non-Caucasian) was examined. Most subjects (92.9%) enrolled were Caucasian; consequently, the distribution of adverse events across treatment groups for this race group was similar to that of the overall study population. Similar to age, there were too few non-Caucasian subjects to make

meaningful comparisons. In a review of published literature, two studies show that the safety profile in Hispanics is similar to that seen in the general population. [22, 23]

Gender

Most subjects enrolled were female (81.7%). In the placebo group, the incidence of the AEs was similar in the two genders with one exception; the incidence of abdominal pain in females was 3 times the incidence in males. In the orlistat groups, there was a greater proportion of female subjects compared to male subjects who experienced fecal urgency, abdominal pain, oily spotting (60 mg dose group), flatus with discharge, liquid stools (120 mg dose group), and oily evacuation compared to male subjects; however, the differences between the genders were small.

7.7 Characterization of Gastrointestinal Adverse Events

The pharmacological action of orlistat results in increases in fecal fat excretion; therefore, gastrointestinal AEs would be expected to occur in orlistat-treated subjects at higher rates than in the placebo treated subjects. The orlistat gastrointestinal AE profile is summarized below.

Description of treatment related effects

Seven gastrointestinal AEs were identified as being related to orlistat treatment (incidence of at least 5% and twice that of placebo): fecal urgency, oily spotting, fatty/oily stool, flatus with discharge, oily evacuation, increased defecation and fecal incontinence. The incidences of these gastrointestinal AEs were lower for the 60 mg orlistat group compared to the 120 mg orlistat group, particularly for fecal urgency, oily spotting, and fatty/oily stool, supportive of improved tolerability with the lower dose.

Number and intensity of episodes

In Phase III pooled studies, the majority of subjects (approximately 80%) reported only single episodes within each adverse event with very few subjects (<4%) reporting 3 or more episodes of a single event. Most gastrointestinal AEs were of mild (39.9% placebo vs. 57% 60 mg group) to moderate (21% placebo vs. 32.3% 60 mg group) intensity and very few were of severe intensity (2.4% placebo vs. 5.8 % 60 mg group). The data for subjects exposed for up to 1 year were similar.

Results were consistent in study NM17247 (4 month Phase III study) in that the majority (82%) of subjects reported single episodes. Most of the gastrointestinal events in study NM17247 were mild to moderate in intensity for both the placebo

group (48.7% mild and 34.2% moderate) and the 60 mg group (55.8% mild and 35.6% moderate). There were comparable numbers of severe gastrointestinal events in both the placebo and the 60 mg dose groups (20 events each).

Time to first occurrence

Time to first occurrence for the gastrointestinal AEs was analyzed for the pivotal pooled Phase III studies. A majority of the subjects had the first occurrence of the gastrointestinal AE within the first 12 weeks with many subjects experiencing gastrointestinal AEs within the first week. In an OTC environment, the consumer's perceptions of the product are greatly affected by their initial treatment experience. Subjects receiving the 60 mg dose of orlistat had incidences approximately one-third less than that of the 120 mg dose group during the first week of treatment.

Duration

For many of the gastrointestinal AEs, most subjects reported that they experienced episodes of these GI AEs for one week or less and most subjects reported that these events generally subside within 4 weeks. Once subjects stopped taking orlistat, there was rapid resolution of the adverse event.

Frequency of gastrointestinal adverse events in the first 6 months

The number of gastrointestinal adverse events (GI AEs) occurring in the first 6 months of treatment is generally less for the 60 mg versus 120 mg dose. Furthermore, in the pooled Phase III studies, a greater proportion of subjects using orlistat 60 mg tid reported having no GI AEs in comparison to those taking 120 mg tid (31.3% vs. 25.3% for 60 and 120 mg, respectively).

7.8 Deaths and Serious Adverse Events in Clinical Trials

7.8.1 Deaths in Clinical Trials

In over 2000 subjects randomized to treatment in the three Phase III studies (NM14302, BM14149 and NM14161; total n=2075), there were 3 deaths reported. None were considered related to study drug by the investigator as described in detail below.

Table 7-5
Description of Deaths in Pooled Phase III Studies

Study	Subject ID	Treatment Group	Subject Description	Description of Death	Relation to Study Medication
NM14302	13144/0083	N/A (diet lead-in)	40 year old white female BMI = 34.6 kg/m^2	Died on Day 107 of the lead-in period due to a closed head trauma resulting from being struck by an automobile	unrelated
BM14149	1283/M019	60 mg tid	61 year old white male BMI = 32.7 kg/m^2	Died on study Day 449 due to a myocardial infarction. Past medical history of ischemic cerebral insult and a myocardial infarction 7 years before the study.	unrelated
NM14161	12329/408	120 mg tid	55 year old white male BMI = 38.8 kg/m^2	Died on study Day 317 of an acute myocardial infarction. Diagnosed with hypertension on Day 122; antihypertensive therapy begun on Day 205.	unrelated

Studies NM14302, BM14149 and NM14161

To provide a wider perspective of orlistat safety, it's important to consider the number of deaths reported during the conduct of the broader orlistat Rx clinical development program. In over 100 clinical studies involving more than 30,000 patients, there were 24 deaths reported in subjects taking orlistat. Of these, 19 were deemed not related to study drug by the study investigator and 1 was considered to be unlikely related. The relation to study medication is unknown for the remaining four cases.

7.8.2 Serious Adverse Events in Clinical Trials

The incidence of serious adverse events during 6 months of treatment was similar across treatment groups (3.5% placebo, 3.4% orlistat 60 mg, and 3.5% orlistat 120 mg). Among the three treatment groups, a total of 6 subjects developed cholecystitis within the 6 month treatment period; however, there was no difference between the placebo or active groups in terms of incidence (0.5% placebo, 0.3% orlistat 60 mg, and 0.2% for 120 mg). Data from the original Rx development program showed that there was no meaningful increase in gallbladder ultrasound abnormalities associated with 2 years of orlistat treatment and orlistat treatment did not appear to increase the risk of gallstones.

The SAEs that occurred in ≥2 of subject in the active treatment groups in the pooled Phase III studies are summarized in Table 7-6.

Table 7-6
Serious Adverse Events Occurring in ≥2 Subjects in Orlistat Treatment Groups in 6 Months of Treatment: Pooled Phase III Studies

WHO-ART Body System Preferred Term	Placebo (N=634) n (%)	Orlistat 60 mg tid (N=623) n (%)	Orlistat 120 mg tid (N=632) n (%)
Subjects with ≥1 SAE	22 (3.5)	21 (3.4)	22 (3.5)
Reproductive disorders, female:			
Neoplasm breast female	0	1 (0.2)	2 (0.3)
Urinary system disorders:			
Urinary incontinence	0	0	2 (0.3)
Gastrointestinal system disorders:			
Hernia inguinal	0	2 (0.3)	0
Liver and biliary system disorders:			
Cholecystitis	3 (0.5)	2 (0.3)	1 (0.2)
Body as a whole - general disorders:			
Surgical procedure	4 (0.6)	3 (0.5)	0

Studies BM14149, NM14161, NM14302

In Study NM17247, a total of two serious adverse events were reported in the orlistat treatment group. These events were repair of hernia and herniated disc re-injury. Both serious adverse events were reported by the investigator as unrelated to orlistat.

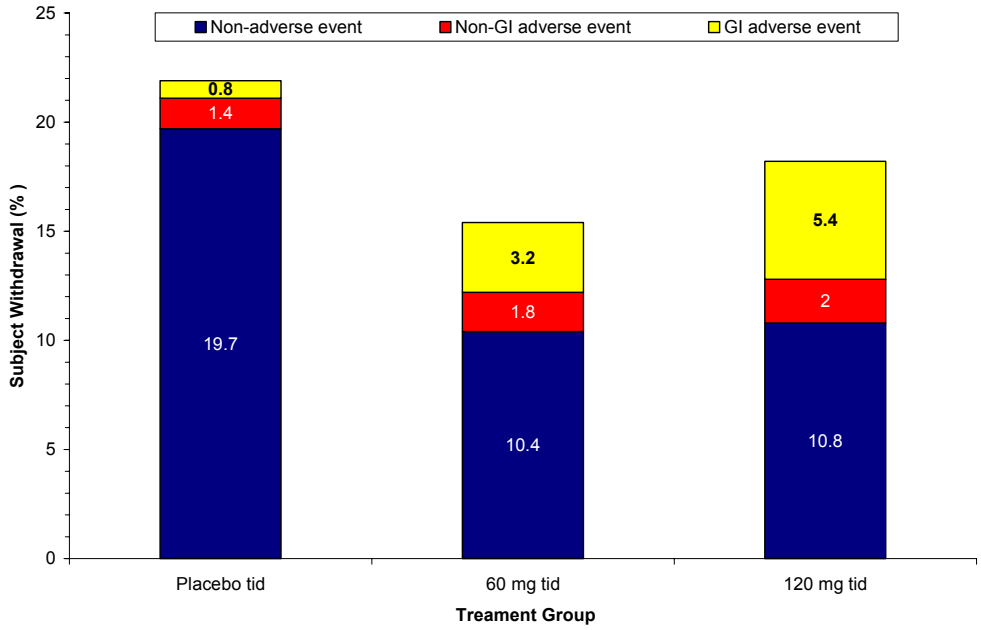
In terms of serious *gastrointestinal* AEs, there was no difference among treatment groups during the first 6 months of treatment. There were two cases of serious abdominal pain (one in the 120 mg group and one the 60 mg group). Both were considered not related to the study drug and subjects recovered. In terms of the seven

GI AEs categorized as 'treatment-related', there were no reported serious adverse events.

7.9 Adverse Events Leading to Discontinuation

From the three pooled Phase III studies, the incidence of adverse events leading to discontinuation during 6 months of treatment was greater for the orlistat treatment groups compared to placebo, but less for the 60 mg dose compared to the 120 mg dose. Most of the events leading to discontinuation were gastrointestinal AEs. More orlistat subjects compared to placebo subjects discontinued due to a GI event however, there were fewer subjects in the 60 mg treatment group discontinued due to orlistat related gastrointestinal AEs. These data are displayed in Figure 7-1.

Figure 7- 1
Relationship of Dose to Discontinuation of Treatment



Similar trends were observed in Study NM17247 in that most events leading to discontinuation were gastrointestinal AEs (six subjects in orlistat 60 mg tid group vs no subjects in placebo group).

7.10 Clinical Laboratory Data

There were no clinically relevant differences between orlistat and placebo with respect to the clinical laboratory data. Orlistat had a beneficial effect on total cholesterol and LDL cholesterol at 6 months and 1 year.

For all four Phase III studies (including study NM17247), there were comparable proportions of subjects among the treatment groups with markedly abnormal laboratory values during treatment and most were transient (Table 7-7).

Table 7-7
Incidence of Markedly Abnormal Lab Values in Pooled Phase III Studies

Treatment	Markedly Abnormal Laboratory Values	
	Incidence	Most Common Type
Placebo	52/829 or 6.4%	elevated CPK (n=14) elevated AST (n=5), elevated ALT (n=7) elevated GGT (n=5) elevated potassium (n=5) low platelets (n=5) low neutrophils (n=5)
60 mg tid	55/819 or 6.7%	elevated CPK (n=15), low neutrophils (n=8) low WBC (n=7) low platelets (n=5) low phosphorus (n=5)
120 mg tid	42/632 or 6.7%	elevated CPK (n=13) elevated GGT (n=5) low WBC (n=6).

Studies BM14149, NM14161, NM14302

7.10.1 Hematology

Phase III Pooled studies

The mean changes from baseline were small and comparable among the treatment groups. There were some values outside the reference range at baseline (Day 1) and during treatment for all treatment groups, including placebo.

Phase III Study NM17247 (4 months)

No clinically meaningful changes were seen between treatment groups for each parameter. The types and percentage of subjects with each marked laboratory

abnormality were similar among treatment groups. Most of the abnormalities were non-specific, isolated changes that returned to baseline.

7.10.2 Serum Chemistry

Pooled Phase III studies

The orlistat 60 mg and 120 mg treatment groups showed decreases in total cholesterol of 3.1% and 4.9%, respectively, as compared to an increase of 2.1% in the placebo group at 6 months. In addition, the orlistat 60 mg and 120 mg treatment groups showed decreases in LDL cholesterol of about 5.2% and 6.4%, respectively, as compared to an increase of 2.7% in the placebo group at 6 months. Overall, there was a decrease in total cholesterol and LDL cholesterol in the orlistat 60 mg and 120 mg groups at weeks 12, 24, and 52 in contrast to an increase seen in the placebo group. A slight increase in HDL cholesterol was seen in all treatment groups with the highest increase seen in the placebo group.

Phase III Study NM17247 (4 months)

The orlistat 60 mg group showed a decrease in total cholesterol of 3.8% as compared to a decrease of 0.09% in the placebo group at 4 months. In addition, orlistat 60 mg showed a decrease in LDL cholesterol of 5.9% compared to a decrease of 0.48% in the placebo group at 4 months. A slight increase in HDL cholesterol was seen with orlistat 60 mg whereas a decrease in HDL cholesterol was seen in the placebo group.

7.11 Special Laboratory Safety Assessments

7.11.1 Vitamins

Not unexpectedly, in view of its pharmacologic effect, treatment with orlistat appears to produce a slight decrease in the absorption of fat-soluble vitamins (A, D, E, K, and beta-carotene) in subjects not receiving any vitamin supplementation. Analysis of 2 year data from the Rx clinical development programs shows no statistically significant difference from placebo in plasma levels of vitamin A but small statistically significant decreases of plasma levels in vitamin D and E and beta-carotene over one or two years of treatment with orlistat (120 mg or 60 mg tid). However, in the cases of vitamin E and beta-carotene, the mean plasma levels remained well within the reference range and the statistical differences were often due to increases in the placebo group with little or no change in the orlistat groups. Vitamin K levels, as assessed indirectly by measurement of prothrombin time, showed no clinically relevant changes in orlistat 60 or 120 mg groups for up to 2 years of treatment.

The effect on these fat soluble vitamins is measurable, whether the dose of orlistat is 60 mg tid or 120 mg tid, although some dosage differences are evident. It should be noted that subjects in the orlistat studies were not routinely supplemented with a multivitamin in contrast to the current prescription label recommendation. Table 7-8 presents the frequency of two consecutive low levels of vitamins A, D, E, and beta-carotene in 6 months of treatment. These values were generally low across all treatment groups and slightly higher for the orlistat groups.

Table 7-8
Frequency of Two Consecutive Plasma Levels of Vitamins Below the Lower Limit of the Reference Range in 6 Months of Treatment

	Placebo		Orlistat 60 mg tid		Orlistat 120 mg tid	
Vitamin	n	(%)	n	(%)	n	(%)
Vitamin A	3/580	(0.5%)	1/203	(0.5%)	15/962	(1.6%)
Vitamin D	13/558	(2.3%)	2/209	(1.0%)*	50/954	(5.2%)
Vitamin E	2/565	(0.4%)	7/196	(3.6%)	29/944	(3.1%)
Beta-carotene	2/576	(0.3%)	3/207	(1.4%)	40/977	(4.1%)

This analysis includes all U.S. Studies (NM14336, NM14161, and NM14185) conducted by Roche of orlistat 60 and 120 mg that did not require routine vitamin supplementation

*Significant difference between 60 mg and 120 mg doses; Fisher's exact test at $p<0.05$.

These data serve to emphasize that the effect of orlistat 60-120 mg on the absorption of vitamins A, D, E, K, and beta carotene at 6 months is limited. The maximum recommended continuous treatment duration will be 6 months at 60-120 mg for OTC use.

Adverse clinical consequences resulting from lack of multivitamin supplementation are not anticipated. Nonetheless, as a precaution, the OTC label will instruct consumers to take a multivitamin, which we believe to be beneficial to all consumers undertaking a weight loss program.

7.12 Vital Signs

7.12.1 Systolic Blood Pressure

Phase III Pooled studies

Overall, the mean change in systolic blood pressure was small for all treatment groups. At 6 months (Week 24), the 60 mg and 120 mg orlistat treatment groups

showed a mean change in systolic blood pressure of -0.7 mmHg compared to no change from baseline in the placebo group.

Phase III Study NM17247 (4 month study)

The mean change from baseline to the end of treatment at 4 months for systolic blood pressure was -6.0 mmHg for orlistat-treated subjects and -2.6 mmHg for placebo-treated subjects.

7.12.2 Diastolic Blood Pressure

Pooled Phase III studies

The mean change in diastolic blood pressure showed a favorable trend for the orlistat 60 mg and 120 mg treatment groups. At 6 months (Week 24), the orlistat 60 mg group showed a mean change of -0.3 mmHg, the orlistat 120 mg group had a mean change of -0.6 mmHg, and the placebo group showed a mean change of 0.4 mmHg. This trend was seen as early as Week 12 (-0.6 mmHg for orlistat 60 mg, -0.3 mmHg for orlistat 120 mg, and 0.5 mmHg for placebo).

Phase III Study NM17247 (4 month study)

The mean change from baseline to the end of treatment at 4 months for diastolic blood pressure was -3.7 mmHg for the orlistat-treated subjects and -0.7 mmHg for the placebo-treated subjects.

7.12.3 Pulse Rate

Overall, there were no clinically meaningful changes in the pulse rate measurements related to orlistat treatment.

7.13 Other Clinical Safety Data

7.13.1 Electrocardiograms

Twelve-lead electrocardiograms (ECGs) were performed at screening, baseline, and after each year of treatment in all Phase III studies. No obvious differences in ECG values could be discerned between the placebo and the orlistat treatment groups.

7.13.2 Renal Ultrasound

There is a theoretical concern that unesterified fatty acids would compete with oxalates for calcium binding in the colon. This could increase the amount of absorbed and excreted oxalates, and increased urinary oxalates could potentially facilitate renal stone formation. Renal ultrasound assessments were performed prior to

randomization and at the end of one year double-blind treatment in 1854 subjects in five Phase III studies conducted by Roche. These assessments were also performed in 1,550 subjects in year 2 of double-blind treatment. There was no consistent evidence of increased risk of renal stone formation in these trials. In addition, urinary oxalate levels were not significantly different between placebo and orlistat 60 mg and 120 mg over 2 years of treatment.

7.13.3 Gallbladder Ultrasound

Gallbladder ultrasound assessments were performed prior to randomization and at the end of one year double-blind treatment in 2539 subjects in seven Phase III studies conducted by Roche. These assessments were also performed in 1,417 subjects in year 2 of double-blind treatment. The gallbladder ultrasound performed prior to randomization was used to identify abnormalities of and around the gallbladder, specifically the presence or absence of cholelithiasis. The gallbladder ultrasound performed at study end was used to identify changes to the gallbladder over the course of the study. There was no meaningful increase in gallbladder ultrasound abnormalities produced by two years of treatment with orlistat.

7.14 Potential Drug Interactions

As previously described in Section 4 (Pharmacology), drug interaction studies have been conducted as part of the original and ongoing Rx clinical development program. The results of these drug interaction studies, as well as those originating in published literature, are described in the current approved Rx package insert, which contains a comprehensive listing of drugs that have been shown to not interact with orlistat (see Appendix 1). The present discussion focuses on potential interactions as they relate to the proposed OTC label.

- Drug interaction studies have demonstrated a reduction in cyclosporine levels (by approximately 30%) with co-administration of orlistat. To reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 2 hours before or after taking orlistat, as stated in the Rx Xenical prescribing information. However, for ease of understanding, the OTC label instructs individuals taking cyclosporine not to use orlistat

- Co-administration of warfarin and orlistat did not result in any change in the pharmacokinetics or pharmacodynamics of warfarin.[24] However, vitamin K levels may decline in subjects taking orlistat. Therefore, the OTC label instructs individuals taking warfarin to ask their doctor or pharmacist prior to taking orlistat.

- Orlistat has not been shown to have any drug interactions with medications used for diabetes. However, dosage reductions for diabetic medications may be required when taken concomitantly with orlistat since modest weight loss improves glycemic control. In clinical studies involving diabetes patients, orlistat was associated with implementing significant reductions in doses of oral sulfonylureas and insulin compared to placebo.[25, 26, 27] The OTC label instructs individuals taking medications for diabetes to ask their doctor or pharmacist prior to taking orlistat.

- No clinically relevant drug interactions were seen when orlistat was taken in combination with weight loss drugs phentermine or sibutramine. Since no other published studies were found evaluating the concomitant use of orlistat with other weight loss drugs, the OTC label instructs individuals taking other weight loss drugs to ask their doctor or pharmacist prior to taking orlistat.

Of the orlistat drug interactions described above, cyclosporine (direct interaction) and warfarin (indirect interaction) raise potential concern in an OTC setting because of the possible clinical consequences. To understand the potential risk posed to these two populations, a comprehensive review of post-marketing surveillance data and published literature was conducted. The results of the safety review are summarized in the following section.

7.15 Review of Cyclosporine and Warfarin Safety Data

The available post-marketing surveillance data and published literature evaluating concomitant use of orlistat and either cyclosporine or warfarin is reviewed in detail below.

7.15.1 Cyclosporine

A review of the literature and Roche worldwide safety database has revealed few reports of low cyclosporine levels in association with orlistat use. Of a total of 29,333 reports in the Roche worldwide safety database through November 2005, there have been 38 reports of low cyclosporine levels. This includes 9 publications involving 17 patients.

The majority of these reports had no clinical consequence for the patient. There have been two reports of acute graft rejection. Of these, one was classified as a non-significant rejection episode requiring no treatment. The other was a significant rejection episode that was effectively treated. The rejection recurred, however, once

orlistat had been discontinued and despite therapeutic levels of cyclosporine, suggesting orlistat was unlikely to have played a role.

Actions to Manage Risk in an OTC Setting

Although cyclosporine use is not contraindicated in the Rx setting, GSK has taken steps in the proposed OTC label to manage risks in the population of transplant patients by including the warning, "**Do not use** if you are taking cyclosporine (a drug taken after organ transplant)."

GSK has also taken steps to understand how cyclosporine users may react to the proposed OTC label by conducting a targeted labeling/self-selection study in cyclosporine users. The results of this research, including potential labeling enhancements, are summarized in Section 8.

GSK is proposing additional measures such as educational programs to further minimize any risks to this population. These are described in greater detail in Section 9 of this briefing document.

7.15.2 Warfarin

Warfarin is a vitamin K antagonist. It is well known that many factors can significantly affect the coagulation profile of patients on warfarin such as diet and medication use (including over-the-counter drugs and dietary supplements). In fact, many current OTC drugs contain warning statements relating to warfarin use.*

Given that the orlistat/warfarin interaction is indirect via Vitamin K, it is reassuring to note that Vitamin K levels (assessed indirectly by measurement of prothrombin time), have shown no clinically relevant changes after up to 2 years of treatment with orlistat. Further in the four year XENDOS study that examined the effects of 120 mg tid orlistat in over 3000 adults, vitamin K levels were measured directly and no subjects had plasma vitamin K levels below the reference range throughout the study.[12]

However, there have been reports of decreased prothrombin, increased International Normalized Ratio (INR) and unbalanced anticoagulant treatment resulting in change of hemostatic parameters in patients treated concomitantly with anticoagulants.

* Examples of current OTC drugs and dietary supplements that interact with warfarin include:
OTC Drugs - acetaminophen, miconazole, cimetidine, omeprazole, salicylates, corticosteroids, ranitidine, and NSAIDS such as ibuprofen, naproxen and aspirin;
Dietary Supplements- Vitamin C, vitamin E, garlic, ginkgo balboa, dashen, Coenzyme Q10, St. John's Wort, alfalfa, capsicum, ginger, licorice, black cohosh, chamomile, cassia

Review of the literature revealed 1 case report of a 66 year old man reported to have a prolongation of coagulation time (INR of 4.7) eighteen days after starting orlistat having previously been stable on warfarin. Satisfactory control was achieved on a lower dose of warfarin and there were no clinical sequelae.

The Roche Worldwide database through November 2005 includes 184 cases with warfarin as a co-suspect or concomitant. Of these 45 report an increased INR. Eight of these 45 cases were associated with any kind of bleeding episode of which 4 were considered to be significant. These were: a 62 year old male made a full recovery following hospitalization for a splenic hematoma and intra-abdominal bleed, a 69 year old female was hospitalized for urinating blood and recovered with treatment, a 72 year old was hospitalized for an unspecified hematoma; treatment and outcome were not known and finally, a 33 year old female who experienced bruising and bleeding into her joints was hospitalized with an INR>10. Orlistat was discontinued and events improved. Her other medications included ibuprofen, oxycodone and an acetaminophen/codeine preparation.

There were a further 12 case reports of a bleeding episode where the INR or prothrombin time were not provided or the PT/INR was low. Of these, only one case was considered significant. A 52 year old female with insulin dependent diabetes with diabetic retinopathy and a history of bilateral retinal hemorrhage experienced a recurrence of retinal hemorrhage.

Actions to Manage Risk in an OTC Setting

Since orlistat may indirectly impact warfarin effects on blood clotting based on the absorption of vitamin K, warfarin users should consult with their doctor before using orlistat. Therefore, the OTC label instructs individuals to," **Ask a doctor or pharmacist before use if you are** taking warfarin (blood thinning medicine)".

This warning statement is consistent with the standard OTC drug facts warning regarding all drug-drug or food-drug interactions. Further, it is identical to the warning statement currently in place for other OTC drugs that interact with warfarin.

As with cyclosporine users, GSK has conducted targeted labeling/self-selection research with warfarin users to understand their response to OTC orlistat and evaluate opportunities to increase consumer awareness. This information is presented in Section 8 of this briefing document.

7.15.3`Conclusions Related to Cyclosporine and Warfarin

GSK believes the risks posed by these interactions can be appropriately managed in an OTC setting through the labeling statements described above and educational programs aimed at increasing awareness among potential users and healthcare practitioners. Additional discussion regarding GSK's continued evaluation of labeling options to optimize consumer compliance can be found in Section 8.4. Additionally, GSK's commitments in terms of post-marketing surveillance and educational support are described in Section 9.3.

7.16 Overall Post marketing Surveillance

7.16.1 Safety Profile of Orlistat 120 mg (Rx Xenical®)

Xenical® (orlistat) 120 mg capsules was approved in the United States in 1999 and is currently marketed in over 145 countries worldwide. Review of worldwide pharmacovigilance data for Xenical® 120 mg capsules and published literature have showed no evidence of any newly emerging safety signals nor revealed any new areas of concern. Results are consistent with the safety data from clinical trials. These data have been reported periodically to FDA in accordance with the requirements for the routine reporting of postapproval safety data.

7.16.2 Safety Profile of Orlistat 120 mg in Foreign OTC Markets

Background

Currently, Xenical® (orlistat) 120 mg capsules have been switched from prescription to OTC status ('pharmacy-only') in 6 countries (Thailand, Philippines, Malaysia, Australia, New Zealand and Singapore) for the indication of weight loss and obesity management. Information for two major markets, Australia and New Zealand, was included in the Safety Update to the OTC NDA. In these countries, the classification of a drug as a 'pharmacy-only medicine' indicates that the medication is available without a doctor's prescription, but cannot be obtained via general sale on 'open' shelves. The product can be obtained directly from a pharmacist following consultation. Although this status affords a level of intervention by pharmacists beyond that required for US OTC products, the experience gained in these markets provides useful information as to how the product is likely to be used by consumers.

Safety Data

The adverse event profile in Australia and New Zealand was comparable to the overall pattern of worldwide adverse events. Evaluation of these safety data suggest that the well-established safety profile of the drug has not been affected by the

reclassification of Xenical® (orlistat 120 mg capsules) from 'prescription-only' to a 'pharmacy only' drug, supporting the appropriateness of orlistat 60 mg capsules as an OTC weight loss aid.

7.17 Overall Safety Conclusions

The safety profile of orlistat 60 mg (1 to 2 capsules) is appropriate for OTC use based on the following evidence:

- Orlistat at a dose of 60 mg tid was generally well-tolerated in subjects with a broad range of BMI scores of 25.0 - 45.8 kg/m^2.
- Most of the adverse events reported were gastrointestinal in nature and not unexpected due to the drug's mechanism of action. These were generally mild in intensity, transient and less frequent with the 60 mg dose.
- In response, the proposed OTC label suggests 60 mg as the ideal starting dose to most appropriately manage gastrointestinal effects as the consumer gains experience with the product. Further, the label and in-pack materials emphasize the need to maintain a reduced calorie, low fat diet to limit these effects.
- There were no significant differences between active and placebo groups in standard laboratory parameters, ECGs, gallbladder ultrasound, or renal ultrasound. Nonetheless, the OTC label will contain precautionary statements for people with gallbladder problems, problems absorbing food and kidney stones.
- There were beneficial changes seen for total cholesterol and LDL-cholesterol.
- In subjects not receiving vitamin supplementation, orlistat has been observed to reduce absorption of some fat soluble vitamins. As a precaution, the OTC label will instruct consumers to take a multivitamin.
- With respect to drug-drug interactions, we believe the risks posed with cyclosporine and warfarin can be effectively managed via the proposed warnings that appear in OTC label and in-pack educational materials and programs.
- Extensive postmarketing data have not revealed any new safety findings or areas of concern, even in countries where the product has been reclassified as an over-the-counter medicine.

8. Consumer Understanding and Use in an OTC Setting

8.1 Introduction and Overview of Label Development Program

This section of the briefing document examines the consumers' understanding of the proposed OTC label for orlistat 60 mg capsules and potential usage behavior in an OTC setting.

The proposed Drug Facts labeling for orlistat 60 mg capsules is contained in Section 3.2.1. As with all OTC drug products, the Drug Facts section contains the key information for the safe and effective use of the product in an OTC environment. The proposed Drug Facts label is consistent with the content and format requirements in place for over-the-counter drug products (21 CFR 201.66) and has been extensively tested and reviewed by experts in nutrition as well as potential consumers.

This process of label development was iterative and multifaceted. It comprised several different types of labelling studies intended to provide insight into consumer understanding and label performance in a real-world setting. These studies were conducted over the span of several years as identified inTable 8-1.

Table 8-1
Summary of Key Label Development Activities

Study Description	Sponsor*	Timing
Label Comprehension (LC) 1	HLR	August 2002
Label Comprehension (LC) 2	HLR	October 2002
End of Phase II meeting with FDA	HLR	July 2002
Actual Use Trial	HLR	April 2003
Label Comprehension (LC) 3	HLR	May 2004
Pre-NDA meeting with FDA	GSK	December 2004
Label Comprehension (LC) 4	GSK	January 2005
OTC NDA Submission	GSK	June 2005
Teen Self Selection Study	GSK	October 2005
Cyclosporine User Self Selection Study	GSK	October 2005
Warfarin Self Selection Study	GSK	October 2005

*GSK (GlaxoSmithKline Consumer Healthcare) acquired the rights to develop orlistat 60 mg as an OTC weight loss aid in July 2004

HLR (Hoffmann-La Roche)

It is important to note that the label has undergone substantial revision during its evolution. For example, early in development the label attempted to differentiate between an overweight and obese population of users through messages related to weight status (i.e. BMI, lbs to lose) and the presence of comorbid conditions likely to be associated with obesity. However, it became clear that consumers do not define themselves in this manner or make these distinctions. Moreover, the product has been demonstrated safe and effective with individuals defined as obese or overweight in the presence of risk factors. Since these consumers are likely to benefit from weight loss, the OTC indication was thought to be appropriate to the wide range of overweight adults. Therefore, in subsequent discussions with the FDA, the decision was made to modify the label to reflect an inclusive population of 'overweight' adults.

These and other label changes have been logical and intentional; the proposed OTC label is the culmination of this label development process designed to:

- improve label comprehension (based on previous Label Comprehension study results)
- align with OTC labelling guidelines as defined in 21 CFR 201.66
- reflect appropriate levels of safety concern associated with certain label warnings and exclusions
- incorporate learnings from consumer use studies
- address feedback received from FDA

The current briefing document focuses on the following critical data as these provide the most comprehensive information relating to consumer understanding and use of the proposed OTC label:

- data from Actual Use Trial NM17285 (self-selection, product usage, safety and perceived effectiveness)
- results of final label comprehension study (LC 4)
- results of 3 focused self-selection studies designed to measure appropriate heeding of the label warnings in special populations

For reviewer reference, key differences between the labels used in the Actual Use Trial and the subsequent Label Comprehension and self-selection studies are identified on the following page in Table 8-2.

Table 8-2
Comparison of Label Warnings from Actual Use Trial and Label Comprehension Study LC 4

Actual Use Trial Label (April 2003)	Final Label Comprehension Study Label (LC4, January 2005)	Rationale for Current Label Statements
Allergy Alert: Do not use if you are allergic to orlistat or any of the ingredients in this product.	Allergy warning relocated to Do not use section	Individuals with known hypersensitivity to orlistat or to any of the inactive ingredients should not take this product; moved to Do not use section.
Do not use	*Per 21CFR201.66(c)(5)(iii) - Drug Facts label **absolute contraindications** for which a consumer should not use the product or requires prior physician diagnosis prior to use:*	
• if you are taking cyclosporine (a drug given after transplant surgery), warfarin (blood thinning medicine), or prescription medicines for diabetes	• if you are taking cyclosporine (a drug given after organ transplant) * • if you have been diagnosed with problems absorbing food • if you are allergic to orlistat or any of the ingredients. • *Note: the following additional bullet was added after Jan 2005 to the final proposed OTC label: "Do not use if you are not overweight*	• Precaution on Rx label; elevated to Do not use in the OTC label due to the potential serious consequences of non-heeding. • Contraindication on Rx label; more consumer friendly language used to describe 'chronic malabsorption syndrome' • Warfarin and diabetes medicines warnings relocated to Ask a doctor (see below) • Based on FDA feedback
Ask a doctor before use if you have	*Per 21CFR201.66(c)(5)(iv) - Drug Facts label **conditional exclusions** (preexisting conditions or symptoms) for a doctor should be consulted prior to use:*	
• problems absorbing food (malabsorption) • gallbladder problems • more than 30 pounds to lose • been given a diet recommended by a doctor • diabetes, high blood pressure, or high cholesterol/triglyceride levels	• gall bladder problems or kidney stones	Individuals with a history of gallbladder or kidney problems should check with their doctor before use since: • Orlistat may be contraindicated in patients with cholestasis. • Some patients may develop increased levels of urinary oxalate following treatment with orlistat.

Actual Use Trial Label (April 2003)	Final Label Comprehension Study Label (LC4, January 2005)	Rationale for Current Label Statements
		The other labeled conditions were initially included as a means to differentiate the OTC and Rx populations by weight status/obesity related conditions. However, use of orlistat in these persons poses minimal safety risk, and they will likely benefit from weight loss. Thus, these statements were removed.
Ask a doctor or pharmacist before use if you are	*Per 21CFR201.66(c)(5)(v) - Drug Facts label **conditional exclusions** (all drug-drug or food-drug interactions)*	
• taking medicines for diabetes, high blood pressure, or high cholesterol/triglyceride levels. These prescription doses may need to be changed during weight loss. • taking any other weight loss medications or supplements	• taking medicine for diabetes. Your medication dose may need to be adjusted during weight loss. • taking warfarin (blood thinning medicine) * • taking other weight loss drugs	• Since orlistat does not directly or indirectly (via weight loss) interact with medications for high cholesterol, triglycerides or blood pressure, these exclusions were removed from the label. • Weight loss may result in improved metabolic control in diabetes, and may require a reduction in oral hypoglycemic medication (e.g., sulfonylureas, or insulin). • Although not a true drug to drug interaction, vitamin K levels may decline in individuals taking orlistat. Thus, individuals on stable doses of warfarin should consult their doctor before and during orlistat use. • There is no evidence of orlistat interaction with other weight loss drugs. As a precaution, it is prudent for consumers to check with their doctor before use based on the wide range of weight loss "medications" and supplements currently available.

* Additional research has been conducted to understand these populations and potentially optimize heeding of these label warnings; see Section 8.4 for details.

8.2 Label Comprehension Studies

8.2.1 Description of Label Comprehension Studies

Four separate label comprehension studies were conducted, involving more than 2200 individuals. The four label comprehension studies are described in Table 8-3 in terms of size, target population and method of recruitment, primary endpoint, and key demographic information. Study participants reflect representation from the general population, low literacy population and the target population of overweight adults. The gender and age distribution was generally similar to that observed in clinical trials.

Table 8-3
Summary of Label Comprehension Studies

Study	Size	Design Features	Key Endpoints	Demographics
LC 1	390	General population 16 years or older mall intercept	Comprehension	55.4% female 16.4% Low literacy majority= 18 - 34 yrs
LC 2	551	Target population pharmacy based 18 years or older	Comprehension/ Self-selection	80% female 10.4% Low literacy majority= 18 - 54 yrs
LC 3	920	Target population pharmacy based 18 years or older	Comprehension/ Self-selection	72% female 13.9% Low literacy majority= 18 - 54 yrs
LC 4	410	Target population mall intercept with pre-recruitment of low literacy from site databases 18 years or older	Comprehension	65% female 39% Low literacy* majority= 18 - 59 yrs

*18% from the general cohort; remainder were specifically recruited as low literacy

Key findings from earlier label comprehension studies (LC 1, 2 and 3) were carried forward to the final label tested in consumer label comprehension study LC 4, considered the pivotal label comprehension study. The label used in this study reflects the iterative learning's from all previous studies and FDA interactions and, therefore, represents our best assessment of how consumers understand our proposed OTC label for Orlistat 60 mg capsules.

As the data presented in this report focuses on the results of pivotal study LC 4, the specific study objectives, design and methodology are presented for this study.

8.2.2 Study Objectives, Designs and Methodology(ies)

The objective of LC4 was to ensure that consumers could understand the following key communication objectives on the label:

1. what the product is used for
2. warnings (Do not use and Ask a doctor/pharmacist before use)
3. directions for use (dose, duration of use, multivitamin use)
4. what to expect during product usage (When using this product….)
5. where to find additional information (in-package materials)

Label Comprehension Study 4 (LC 4) Design

This was a multi-site (13) study conducted in two cohorts of the target population who expressed an interest in weight loss: 1) adults representative of the general population and 2) low-literate adults. Participants took the Rapid Estimate of Adult Literacy in Medicine (REALM) test to assess literacy in medicine and determine cohort placement. Low literacy was defined as at or below a 7^{th} grade reading level.

Label Comprehension Study 4 (LC 4) Methodology

Subjects were given realistic mock-ups of the proposed OTC Drug Facts label and asked to read the labelling, including tables of contents for in-package materials (User's Guide, At Home Guide, Away from Home Guide). Participants were given as much time as they needed and then asked a series of open-ended, scenario-based questions or questions related to where information is located in labelling. In many cases the questions asked if it was "okay or not okay" to use the product in that situation. Other question structures were also used to minimize subjects' ability to detect response patterns.

Responses were prospectively defined as Correct / Acceptable / Incorrect as follows:

Correct	Either (1) a response that is initially answered correctly or (2) one that was not initially correct (i.e. incomplete) but a follow-up probe indicated correct action.
Acceptable	Response is not what the label directs, but would not be incorrect in terms of product usage.
Incorrect	Response indicates the subject did not understand the label.

The primary analysis evaluated the proportion of subjects successfully meeting each communication objective.

8.2.3 Label Comprehension Results

Results are presented in the order of key communication objectives.

Table 8-4 Label Comprehension (LC 4) Results

Communication Objective	Gen Population n=304	Low Literacy n = 160
Target Population	**% Correct/Acceptable**	
Orlistat is used to lose weight	100	100
Not Okay to use Orlistat if not overweight	79	78
Product Warnings		
Not Okay to use Orlistat while taking warfarin.	94	93
Okay to use Orlistat if experiencing problems sleeping. [1]	93	91
Not Okay to use Orlistat if diagnosed with problems absorbing food.	92	89
Not Okay to use Orlistat while breastfeeding.	96	93
Not Okay to use Orlistat if had kidney stones in the past.	97	97
Okay to use Orlistat if experiencing a headache. [1]	90	77
Okay to use Orlistat if experiencing loose stools and bowel changes.	93	85
Not Okay to use Orlistat while taking cyclosporine.	96	90
Not Okay to use Orlistat if allergic.	99	97
Not Okay to use Orlistat if currently taking medicine for diabetes.	97	96
Okay to use Orlistat if not currently taking any other medication for weight loss.	98	98
Not Okay to use Orlistat if having gallbladder problems.	99	97
Not Okay to use Orlistat if under 18 years old	98	98
Label Directions		
Maximum capsules of Orlistat in one day	86	67
Recommended dosage of Orlistat	95	91
Concern about vitamin absorption	93	88
Recommended timing or taking a multivitamin	79	66
Weight loss goal not met after 6 months	78	74
When to increase dosage	89	80
What to Expect During Product Usage		
How to decrease the likelihood of loose stool and bowel changes	86	69
How Orlistat works to promote weight loss	84	64
Changing eating patterns before starting Orlistat	96	93
Timeframe of when to expect results when taking Orlistat	82	69
Why weight loss will vary per person	83	64
Where to find information on using Orlistat	96	95

[1] These conditions do not pertain to orlistat and were included as control questions.

8.2.4 Summary of Label Comprehension

Target Population and Indication

Label comprehension results in Table 8-4 show that people clearly understood that the product was indicated for weight loss. Comprehension was somewhat lower as to whether it was acceptable for people who were not overweight to use orlistat.

When interviewed, respondents noted that the label did not specifically say the product should not be used by people who were not overweight.

As a result, GSK has added additional statements to the current label within the ***Use*** (overweight adults) and ***Warnings*** section of the label ("**Do not use** if you are not overweight") to address this point.

Warnings

Both conditional ("ask a doctor" or "ask a doctor or pharmacist") and unconditional ("do not use") exclusions were extremely well understood, in both the general and low literacy populations. The lowest comprehension score was 77% (Low Literacy group) and related to use of orlistat while experiencing a headache. Although not contraindicated on the label, and thus, technically incorrect, the response that orlistat was 'not okay to use if you had a headache' was a safe approach.

Directions for Use

Consumers generally understood the directions for use and where to find information related to how to use the product (Reference guide). Comprehension was somewhat lower for 2 concepts in particular:

- ***what to do after six months*** - some consumers indicated they could continue to use the product until they reached their weight loss goal
- ***timing of multivitamin use*** - consumers understood very well that vitamins should be taken daily when using orlistat; however, they were less clear as to when the vitamin should be taken in relation to orlistat dosing (2 hours before or after orlistat). The fact that many vitamins may contain direction to 'take with meals' may contribute to this confusion since orlistat is directed to be taken along with meals containing fat.

What to Expect During Product Usage

The primary focus of this section of the label (When using this product….) is to describe potential gastrointestinal effects associated with orlistat use, why they occur and how to minimize them. Specifically it describes:

- the need to follow a diet that is reduced in calories and low in fat (≤30%)
- how the products works by preventing the absorption of about 25 - 30% of the fat you eat
- how the mechanism of action may result in bowel changes and how to manage them by reducing dietary fat
- when to expect results

The results show that most consumers generally understand that use of orlistat may be associated with some gastrointestinal effects due to the way the product works. Very importantly, most participants in both the general and low literacy populations understood the need to change their eating patterns.

Since this section of the label is somewhat more complex in relation to other sections of the label and contains numerical concepts, it is not surprising that comprehension in the low literacy population was reduced. It is reassuring that both subgroups scored high in response to the question of where to find information on using orlistat, as the in-package materials provide additional guidance in terms of how the product works, the connection between eating fat and GI side-effects and the consequent need for following a reduced calorie diet and low fat diet.

Overall Summary of Label Comprehension

The findings from pivotal final label comprehension study LC 4 were very positive. They demonstrate that subjects (both General Population and Low Literacy Cohorts) understand what the product is used for and who should use this product. Additionally, they show that subjects have positive comprehension for the key communication points on the Drug Facts label – Product Usage and Warnings, Label Directions and Product Information. Together, these results demonstrate that the current label is appropriate for the OTC setting.

8.3 Actual Use Trial (Study NM17285)

8.3.1 Study Objectives, Design and Methodology

An actual use study was conducted:

- to understand if consumers can do the following:
    1. identify their condition
    2. correctly select orlistat for their own use (self-selection) based on label information
    3. follow the label directions for use, heed warnings
    4. use the product safely
    5. use the product effectively as a weight loss aid
- to identify areas of the label that should be strengthened or clarified for optimal consumer use

Study design

The actual use trial was a multi-center, pharmacy-based, open-label, 3-month trial. The 3-month duration was chosen to provide information related to consumer selection and actual use. A total of 18 pharmacies participated in this study. This study was designed to simulate a "real world" OTC setting where subjects could walk into a pharmacy and purchase an OTC medicine. No restrictions were placed on subjects screened for the study with the exception of age (≥18yrs). Consumers were able to purchase up to three product packages of 90 count bottles of 60 mg capsules at any one time and were not limited to how often they could return to the pharmacy for additional drug. Subjects were recruited via in-store posters and advertisements in local newspapers near selected pharmacies, targeting mild to moderately overweight individuals, consistent with the label tested in the AUT.

Study Methodology—Pharmacy Enrollment, Selection and Purchase

The subject was first given a package of orlistat (realistic OTC package with Drug Facts labeling) and told to imagine that they were in a store seeing a new over-the-counter medicine. Subjects were asked "Do you think this medicine is appropriate for you to use?"

The pharmacist or other study personnel recorded some basic demographic information, administered the REALM test, and then gave the subjects a health

survey to complete on their own. Selection decisions were evaluated based on the information reported in the health survey.

All subjects were then asked, "The cost of this medication is $45 for a bottle of 90 capsules. Would you like to purchase the medication today?" If subjects answered yes, they were allowed to enter the usage phase of the study unless they did not meet any of the following exclusion criteria (largely based on labeled exclusions):

- Allergic to orlistat or one of its ingredients
- Currently treated with medication for diabetes
- Currently treated with warfarin
- Currently treated with cyclosporine
- Pregnant or breast-feeding
- Previously on orlistat 120 mg (Xenical)
- Participated in previously conducted orlistat label comprehension studies

A weight and height measure was collected on all subjects including those who were excluded from purchasing or did not wish to purchase.

Study Methodology--Usage Phase

During the usage phase, participants used the product, unsupervised, as they would in a normal OTC environment, with no face to face counseling and only the following in-package materials for guidance: Orlistat User Guide, a Personal Food Diary, a Pocket Fat Gram Counter, a Fat Gram Wheel; a portion size information card; and a Orlistat Diet Success Planner which provided lifestyle information designed to help consumers in their weight loss efforts. Importantly, these in-package materials were consistent with those used in Study NM17247, the 4-month clinical study in overweight (BMI 25-28 kg/m^2) individuals.

During the usage phase data were collected via nurse conducted telephone interviews (14, 30, 60, and 90 days after enrollment) to assess:

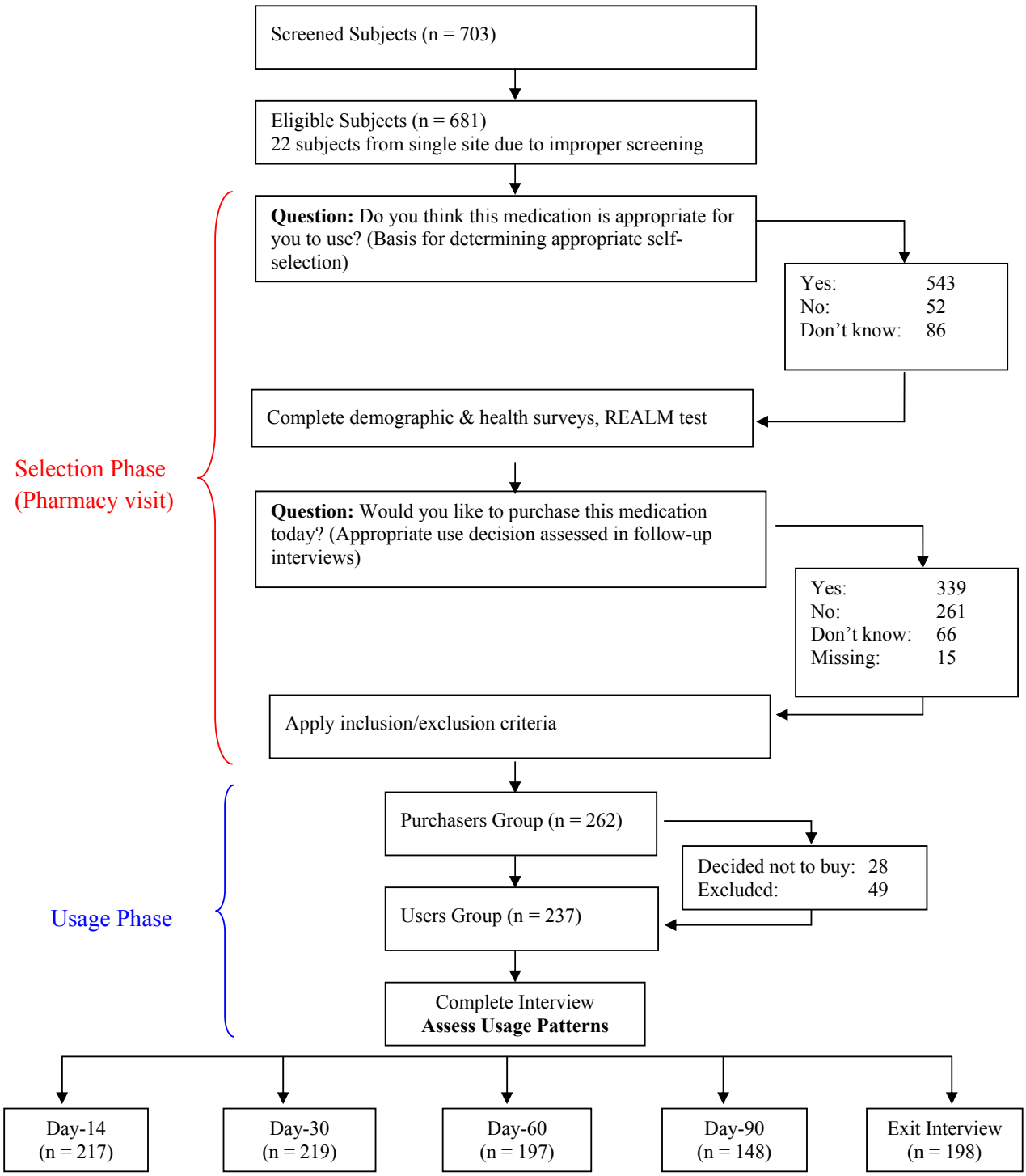
- **Appropriate Use Decision**: Did those with conditional labeled exclusions speak to a doctor or pharmacist about the study medicine before first use.
- **Appropriate Product Usage** based on compliance with the directions for use
- **Safety** based on adverse events (spontaneous reports and interview data)
- **Effectiveness** based on subject-reported weight loss and satisfaction.

Subjects were also weighed at the pharmacy site upon their return to re-purchase or at the end of their participation in the study.

8.3.2 Disposition of Subjects

The study population is outlined in Figure 8-1. A total of 703 subjects were screened, 543 said the product was appropriate, 49 were excluded, 262 subjects purchased the product and 237 actually used the product.

Figure 8-1: Flow of Subjects in Study NM17285



Target Population and Indication

As discussed earlier, the target population and indication for orlistat OTC 60 mg capsules is "to promote weight loss in overweight adults when used along with a reduced calorie and low fat diet".

This indication is founded on the premise that the condition of overweight is self-recognizable in the absence of more specific criteria such a BMI restriction and that obesity is a subset of the greater population of overweight consumers.

In terms of actual behavior, Table 8- 5 shows that the overwhelming majority of people who responded to the recruitment ads and used the product in the actual use trial conform to the FDA-agreed target population of overweight individuals with BMIs ranging from slightly overweight to obese.

Table 8- 5
Weight Status of Subjects in Actual Use Trial NM17285

BMI (kg/m^2)	Eligible Subjects (N=681) n	(%)	Users (N=237) n	(%)
<20	0		0	
20 - 20.9	1	(0.2)	1	(0.4)
21 - 21.9	4	(0.6)	2	(0.8)
22 - 22.9	12	(1.8)	5	(2.1)
23 - 23.9	11	(1.6)	1	(0.4)
24 - 24.9	21	(3.1)	9	(3.8)
Total <25	49	(7.2)	18	(7.6)
25 - <30	181	(26.6)	76	(32.1)
≥30	444	(65.2)	143	(60.3)
Missing	7	(1.0)	0	
Mean ± SD	33.1 ± 6.68		32.0 ± 5.84	
Median	32.1		31.6	
Range	20.9 - 62.6		20.9 - 53.3	
N	674		237	

Very importantly, the data in Table 8- 5 also show that few normal weight subjects (7.6% of users had a BMI in the range of 18.5 - 24.9) and no underweight (BMI< 18.5 kg/m^2) individuals used the product in this unrestricted environment.

8.3.3 Consumer Self-Selection Decisions

The actual use study (NM17285) provides insight into the decisions that consumers are likely to make in an OTC environment with respect to orlistat 60 mg capsules.

Initial Decision to Use Orlistat

As shown in Figure 8-1, most eligible subjects felt orlistat was appropriate for them to use (approximately 80%). The main reason given by almost 50% of these subjects was they were able to identify that they were overweight and needed to lose weight. Other reasons given by subjects who felt orlistat was appropriate to use were: fit label specifications, wanted an aid to lose weight, and willing to try something new since other methods didn't work.

Fewer thought that it was inappropriate (8%) or were unsure (12%).The main reasons given by the 62% of subjects who felt orlistat was inappropriate to use were unconditional and conditional exclusions (see Table 8-6 for listing of exclusions). A considerably smaller percent (13.5%) mentioned possible side effects; they didn't need the product (7.7%), didn't want to use an unknown product (7.7%) or needed to talk to a health care professional (5.8%).

Decision to Purchase

Figure 8-1 also shows that about 50% of subjects actually wanted to purchase the medication, for reasons similar to why they felt it was appropriate for them, the need to lose weight. Approximately 40% did not want to purchase the medication and 10% of subjects did not know. The main reason provided by about 60% of subjects who did not want to purchase the product was cost.

Appropriateness of Self-Selection

One of the main objectives of this trial was to see whether subjects would make appropriate decisions to use or not use orlistat based on their reading of the product label and their understanding of their own health conditions. These results are presented in Table 8-6.

Table 8-6
Appropriate Initial Self-Selection Decision
All Eligible Subjects

Labeled Exclusion	Number of Subjects[1] N= 681	Appropriate Initial Selection Decision N[2] (%)[3]
Subjects with Any Labeled Condition	**465 (68.3)**	
Subjects with Unconditional Labeled Exclusions (Do not use)		
Allergic to Ingredients	0	N/A
Taking Cyclosporine	2	1 (50.0)
Taking Warfarin	14	7 (50.0)
Taking Medicine for Diabetes[4]	46	16 (34.8)
Subjects with Conditional Labeled Exclusions (Ask a doctor…)		
Problems Absorbing Food	12	2 (16.7)
Gall Bladder Problems	25	10 (40.0)
Have High Blood Pressure	166	73 (44.0)
Have High Cholesterol / Triglyceride Levels	147	68 (46.3)
More than 30 Pounds to Lose	346	73 (21.1)
On a Diet Recommended by a Doctor	48	26 (54.2)
Taking Another Weight Loss Medication	33	4 (12.1)
Subjects with No Labeled Conditions	**216 (31.7)**	

1 Total number of eligible subjects
2 Number of subjects who mentioned any labelled condition or need to talk to MD in Q1 and Q32 open ended responses
3 This percentage is based on total number of subjects who reported the specific condition
4 This group includes 44 subjects with diabetes taking medicine for diabetes and 2 untreated diabetics

For those subjects who were not excluded by label criteria (Do not use) and entered the usage phase, the appropriate use decision is presented in Table 8-7. These data represent the proportion of subjects with labelled conditions who strictly followed the label directions to ask a doctor or pharmacist before their initial use of orlistat 60 mg capsules as determined in follow-up interviews.

Table 8-7
Appropriate Use Decision
Subjects with Conditional Labeled Exclusions

Conditional Labeled Exclusion	N[1]	Purchaser n (%)[2]	Appropriate Use Decision n (%)[3]
Problems Absorbing Food	12	1 (8.3)	0
Gallbladder Problems	25	7 (28.0)	2 (28.6)
Have High Blood Pressure	166	54 (32.5)	21 (38.9)
Have High Cholesterol / Triglyceride Levels	147	49 (33.3)	21 (42.9)
More than 30 Pounds to Lose	346	114 (32.9)	27 (23.7)
On a Diet Recommended by a Doctor	48	10 (20.8)	5 (50.0)
Taking Another Weight Loss Medication	33	12 (36.4)	3 (25.0)

1 Total number of subjects who reported the specific condition
2 This percentage is based on total number of subjects who reported the specific condition
3. This percentage is based on total number of subjects who purchased orlistat and who talked to a healthcare professional about orlistat or the labelled exclusions prior to use.

Discussion of Self-Selection and Use Decision Results

Results from actual use study NM17285 suggest that certain individuals with labelled exclusions may elect to use the product despite label warnings.

As previously described in Section 8.0, several of the conditions that appeared on the actual use label such as 'needing to lose more than 30 pounds'; 'having diabetes, high blood pressure, "on a diet recommended by a doctor" or high cholesterol/triglyceride levels' have been removed since they pose minimal risk to the consumer or were originally intended to help differentiate obese and overweight populations. Further, inclusion of conditions for which a doctor would likely recommend the need to lose weight creates confusion.

Removal of these unnecessary exclusions also allows for greater emphasis on the remaining safety messages, such as those directed to users of cyclosporine or warfarin.

Because of changes in the warning section and limited selection data in certain special populations, GSK has undertaken consumer research to better understand the factors that influenced the consumer's decision-making process. These data are presented in Section 8.4 of this briefing document.

The usage patterns and the product's safety and effectiveness observed in the actual use trial NM17285 are presented in the following sections.

8.3.4 Consumers Follow Label Directions for Use

The actual use trial label directed consumers to take 1 to 2 capsules (60 mg) per day with meals containing fat, up to three times a day. Consumers were also instructed to be on a reduced calorie, low fat diet. Further, they were recommended to take a daily multivitamin 2 hours before or 2 hours after taking the product.

Number of Capsules per Day

The results show that the overwhelming majority of subjects took 2 - 3 capsules per day (Table 8-8). Consistent with label instructions to take the products with "meals containing fat", subjects who took only two capsules per day may have avoided taking a dose during breakfast since this meal may not consist of any significant amount of fat. It is important to also note that only one subject exceeded the maximum dose of 6 capsules per day (at the Day 90 interview only).

Table 8-8
Number of Capsules Used per Day (NM17285 Users Group N=237)

Capsules used per day	Day 14 Interview (N=217) n (%)	Day 30 Interview (N=219) n (%)	Day 60 Interview (N=197) n (%)	Day 90 Interview (N=148) n (%)
0	1 (0.5)	1 (0.5)	1 (0.5)	0
1	15 (6.9)	15 (6.8)	28 (14.2)	15 (10.1)
2	42 (19.4)	51 (23.3)	48 (24.4)	24 (16.2)
3	105 (48.4)	87 (39.7)	61 (31.0)	61 (41.2)
4	16 (7.4)	29 (13.2)	28 (14.2)	20 (13.5)
5	18 (8.3)	14 (6.4)	6 (3.0)	10 (6.8)
6	19 (8.8)	18 (8.2)	21 (10.7)	13 (8.8)
7 or more	0	0	0	1 (0.7)
No answer	0	2 (0.9)	4 (2.0)	1 (0.7)
Missing	1 (0.5)	2 (0.9)	0	3 (2.0)

Number of Doses per Day

The majority of subjects took 2-3 doses per day over the course of the study. Again, it is important to note that only 4 people took more than 3 doses per day, reiterating

that most subjects followed the labeled instructions for dosing. Moreover, 95% of subjects stated they took their dose with their meals.

Number of Capsules per Dose

The number of capsules taken per dose is shown in Table 8-9. Approximately 70% of subjects used one capsule per dose at the start of the study and 28% of subjects used two capsules per dose. By the end of study, this proportion had shifted to 59.5% taking 1 capsule and 37.2% using two. This suggests that while most subjects continued to take the same number of capsules, some subjects gradually adjusted their diets and dosing patterns as they gained experience with the product.

Table 8-9
Number of Capsules per Dose (NM17285 Users Group N=237)

Capsules per dose	Day 14 Interview (N=217) n (%)	Day 30 Interview (N=219) n (%)	Day 60 Interview (N=197) n (%)	Day 90 Interview (N=148) n (%)
0	1 (0.5)	1 (0.5)	1 (0.5)	0
1	153 (70.5)	148 (67.6)	129 (65.5)	88 (59.5)
2	61 (28.1)	64 (29.2)	64 (32.5)	55 (37.2)
3 or more	0	1 (0.5)	0	1 (0.7)
No answer	1 (0.5)	3 (1.4)	3 (1.5)	1 (0.7)
Missing	1 (0.5)	2 (0.9)	0	3 (2.0)

Diet Compliance

Approximately 60% of subjects were following a diet throughout the duration of the trial and 87% of subjects reported being on a diet at some point during the trial. A large portion (74%) of product users followed what they considered to be a low fat diet as instructed in the product labelling. Of those subjects participating in the Day 90 interview, over 90% considered themselves "successful" in following a diet.

Multivitamin Use

Based on the first subject interviews, the majority of subjects (74.3%) used a multivitamin while taking orlistat. Approximately 55% of subjects were regularly using a multivitamin and 50% of the subjects who were originally not using a multivitamin started to do so during the study. Nearly 75% of subjects took one

vitamin daily and approximately 15% of subjects indicated taking a multivitamin occasionally. Approximately 50% of the entire sample took a multivitamin > 2 hours before or after orlistat.

Table 8-10
Use of Multivitamin (NM17285 Users Group N=237)

	Vitamin use during study							
Vitamin use before study	**Yes**		**No**		**Missing**		**Total**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Yes	118	(49.8)	12	(5.1)	0		130	(54.9)
No	56	(23.6)	48	(20.3)	1	(0.4)	105	(44.3)
Missing	2	(0.8)	0		0		2	(0.8)
Total	176	(74.3)	60	(25.3)	1	(0.4)	237	(100.0)

8.3.5 Safety Data

Demographics & Subject Characteristics

The 237 subjects with dosing information for this trial were primarily female (85%) and Caucasian (82%), with a mean age of 44.9 years (range 18 to 75 years). Mean baseline body weight was 195.3 lb (range 118 to 353 lb) [88.6 kg (range 53.5 to 160.1 kg)]. Mean baseline BMI was 32.0 kg/m^2 (range 20.9 to 53.3 kg/m^2), and 60% of the population had a BMI ≥30 kg/m^2 at the start of the study.

Disposition of the Study Population

The safety population for this study includes 284 subjects who purchased orlistat. This includes 22 purchasers from one site that was later disqualified due to protocol violations.

Of the 262 eligible subjects who purchased the product, 237 provided information on medication use. These 237 subjects reported ingesting at least one dose of orlistat and completed at least one follow-up interview. Eighty-seven percent (86.9%) of the 237 subjects were still taking orlistat at the Day 14 interview; 86.1% were still taking orlistat at the Day 30 interview; 63.3% were still taking orlistat at the Day 60 interview; and 46.4% were still taking orlistat at the Day 90 interview.

Adverse Events in 6 Months of Treatment

Incidence

Approximately seventy-two percent (71.8%) of 284 subjects in the safety population experienced a total of 703 AEs during treatment with orlistat. Consistent with the AEs seen in the Phase II and III studies, the AEs with an incidence of at least 5% included gastrointestinal AEs. More than 10% of subjects exposed to orlistat experienced the gastrointestinal AEs of abdominal pain not otherwise specified (NOS), oily spotting, fecal urgency, flatulence, liquid stools, and flatus with discharge. Subjects in this study also reported headache with an incidence of 5.6%. The incidence for headache was comparable to placebo in Phase III trials.

Intensity

The majority of AEs (93%, 655 of 703 AEs) were rated as mild to moderate in intensity. A total of 7% (48 AEs) were rated as severe. The majority of the severe AEs (26 of 48) were AEs of the gastrointestinal system.

GI Adverse Events

The overall incidence of gastrointestinal AEs seen for 60 mg orlistat (59.2%) was similar to that observed in controlled clinical trials and in some instances, lower.

Of the 493 gastrointestinal AEs, 66% were rated as mild, 29% were moderate, and 5% were severe in intensity.

Discontinuations Due to Adverse Events

There were 43 subjects (15.1%) who discontinued the study due to an AE. Consistent with the Phase III data, gastrointestinal AEs were the primary reason for discontinuation.

Interestingly, as shown in Table 8-11, in this naturalistic setting, a relatively small proportion of those subjects who experienced an orlistat-related GI AE actually discontinued treatment.

Table 8-11
Defecation Pattern Change Adverse Events and Actions Taken
3-Month Phase IV Study NM17285

	60 mg Orlistat tid (N=284)			Action Taken[a]					
				None		Interrupted		Discontinued	
	n	(%)	NAE	n	(%)	n	(%)	n	(%)
Any defecation pattern change AE	136	(47.9)	322	89	(65.4)	23	(16.9)	24	(17.6)
Oily spotting	38	(13.4)	52	31	(81.6)	4	(10.5)	3	(7.9)
Fecal urgency	36	(12.7)	51	26	(72.2)	5	(13.9)	5	(13.9)
Liquid stools	31	(10.9)	44	17	(54.8)	9	(29.0)	5	(16.1)
Flatus with discharge	30	(10.6)	39	22	(73.3)	5	(16.7)	3	(10.0)
Fecal incontinence	23	(8.1)	33	15	(65.2)	3	(13.0)	5	(21.7)
Fatty/oily stool	20	(7.0)	26	18	(90.0)	2	(10.0)	0	
Oily evacuation	20	(7.0)	27	14	(70.0)	3	(15.0)	3	(15.0)
Increased defecation	15	(5.3)	19	10	(66.7)	3	(20.0)	2	(13.3)
Decreased defecation	14	(4.9)	17	10	(71.4)	1	(7.1)	3	(21.4)
Soft stools	12	(4.2)	14	9	(75.0)	0		3	(25.0)

n (%) are number (percent) of subjects, NAE is the number of adverse events
[a] the most extreme outcome is tabulated for each subject (discontinuation, interruption, no action, in that order)

8.3.6 Summary of Product's Effectiveness and Satisfaction

As the actual use trial is not a controlled clinical study, efficacy per se is not evaluated. However, it does provide useful information about effectiveness in an OTC environment as assessed by the following parameters: self reported weight loss, measured weight loss, satisfaction with the study drug, and perceived efficacy.

Measured weight loss

Weight loss was measured only in those subjects (45% of users) who returned to the pharmacy to repurchase drug. The mean weight loss observed was approximately five pounds within the first thirty days of using orlistat and about ten pounds after sixty days of using orlistat.

Self reported weight loss

These data reflect only those subjects who indicated they lost weight. The interview question was, "Since you started using the study medication have you lost any weight?" and only those who indicated they lost weight were asked the next question, "About how many pounds have you lost?". The median self reported weight loss was approximately five pounds within the first thirty days of using orlistat and about eight pounds after sixty days of using orlistat. A significant number of users lost weight at

each time measurement: 45.2%, 73.5%, 83.2% and 90.5% reported losing weight at the day 14, 30, 60 and 90 interviews, respectively. These results were very consistent with the measured weight loss results.

Satisfaction

Approximately, 80% of the subjects indicated they were satisfied or very satisfied with the product, and this percentage remained consistent across all four interviews for the duration of this study. The main reason provided by 63% of subjects for satisfaction was weight loss and 55% of subjects felt the drug was working. Other reasons provided for satisfaction were: the drug helped maintain their diet and provide fat content awareness and did not cause side effects.

An overwhelming majority of subjects (>90%), indicated that they were very successful or somewhat successful in maintaining their diet throughout the study. During the final interview, approximately 32% of subjects indicated that they exercised more than they did prior to study enrollment. Additionally, approximately 50% of subjects indicated more frequent exercise or longer exercise at some point during the study.

The five educational self-help tools provided with the OTC package of orlistat were used by nearly 80% of users and were rated as useful or very useful by 80% of them.

Perceived efficacy

Approximately 73% of subjects believed that the drug helped them lose weight mainly because they felt orlistat was an effective product and helped modify their eating habits and increased eating awareness

Overall, these results provide solid reinforcement that orlistat coupled with the educational self-help tools successfully encourage positive lifestyle changes.

8.4 Post-NDA Targeted Consumer Research

As previously discussed in Section 8.3, based on the self-selection data from the actual use trial, a certain percentage of consumers elected to use the product in an OTC setting based on the label tested.

In response, GSK has conducted targeted follow-up studies in certain populations of interest in order to determine the appropriate measures necessary to ensure the safe and effective use of orlistat 60 mg in an OTC setting. The specific groups evaluated are identified below and discussed in greater detail in the paragraphs that follow:

- cyclosporine users
- warfarin users
- teens

Follow-up activities related to cyclosporine users

Use of orlistat by cyclosporine patients is a labelled condition thought to potentially present risk to consumers if they chose to neglect the warning statement.

Only two cyclosporine users participated in the actual use study, one of whom indicated that orlistat was appropriate for them to use. Since results from 2 people cannot be generalized to a larger group, GSK has conducted a follow-up targeted study in cyclosporine users to understand how they react to the proposed OTC label.

In preparation for this study, GSK modified the wording of the cyclosporine warning to include an additional statement to augment the existing warning. The intention was to increase understanding and heeding by including a more descriptive statement related to the consequences of concomitant use with orlistat, as shown below:

Previous language	Revised wording
Do not use • if you are taking cyclosporine (a drug given after organ transplant)	**Do not use** • if you are taking cyclosporine (a drug given after organ transplant). Orlistat can lower levels of cyclosporine

Using a national consumer database that tracks the medical conditions of people in a general research panel, over 1,000 individuals were invited to participate in an internet-based survey designed to assess the likely selection behaviours of cyclosporine users. These consumers identified themselves as post transplant patients. Participants did not know they were contacted because of their potential cyclosporine

use and were asked if they were interested in losing weight. Those who responded affirmatively were shown the Orlistat OTC label on-screen (with enhanced warning) and asked if the product was appropriate for them to use.

A total of 381 post-transplant patients completed the survey, of which, 89 said they were taking cyclosporine. Of these, 46 users were interested in losing weight. The results demonstrate that 41 (89%) out of 46 cyclosporine users in this study made a correct selection decision by indicating the product was not appropriate for them to use.

Additionally, follow-up questions asked of all 89 participants to address frequency of communication with their doctor suggest that these patients are very cautious in adopting new medications and that they are in close contact with their physicians for monitoring and consultation. The majority of cyclosporine users indicated that they communicated with their physician and had blood work done at least every 2-3 months. All cyclosporine users indicated that they routinely discussed the medications they are taking with their doctor.

The results of the targeted self-selection survey and interview data are encouraging and provide evidence that the likelihood of cyclosporine users taking orlistat as an OTC weight loss aid would be quite low.

GSK is proposing additional measures to further minimize any risks to this population, including educational programs as described in Section 9 of this briefing document. Label graphics (highlighting the cyclosporine warning in yellow) can also be used to increase prominence on the label.

Follow-up activities related to warfarin use

Since orlistat may indirectly impact warfarin effects on blood clotting based on the absorption of vitamin K, warfarin users should consult with their doctor before using orlistat. In the actual use trial, 14 warfarin users participated and 7 inappropriately self-selected. To better understand this population's behavior, GSK conducted a follow-up study intended to augment this small sample size and target the population of interest.

A targeted self-selection study was conducted in warfarin users who were identified from patient medical databases. Users of warfarin (or Coumadin) were contacted via telephone and screened by asking about interest in a variety of personal care areas (including weight loss). If the subject expressed interest in losing weight, he/she was invited to participate in the study (participants did not know they were contacted

because of their use of warfarin). Participants were shown the actual Orlistat OTC label and asked if the product was appropriate for them to use.

A total of 54 warfarin users participated in the study. The results indicate that 39 of the 54 participants (72%) appropriately self-selected based on their condition (taking warfarin) by expressing an intent to contact a doctor before use. These results are numerically higher than those observed in the actual use trial, but suggest that a proportion of consumers using anticoagulants may inappropriately select the product without consulting a doctor prior to use. Encouragingly, more than 97% of warfarin users indicated that they discussed their concomitant medications with their physicians and 91% said they routinely had lab work done to monitor warfarin levels.

In consideration of potential measures to enhance compliance with this labeling statement, GSK proposes the following options for consideration to potentially draw increased attention to the proposed labelling statements to Ask a doctor before use. This enhanced labelling would be used in conjunction with educational activities as described in Section 9.

- move warfarin to appear as the first warning in the Ask a doctor section
- use label graphics to highlight the warning in yellow to increase prominence

It is important to note that prescribing physicians and warfarin users are frequently reminded about potential interactions with warfarin and other OTC drugs, dietary supplements, herbal products and foods The labelling for warfarin lists over 80 products available OTC that are associated with direct and indirect interactions that can alter warfarin's effect on coagulation. A partial list is provided below.

> **OTC Drugs**: acetaminophen, miconazole, omeprazole, aspirin, naproxen, ranitidine, ibuprofen
>
> **Dietary Supplements**: Vitamin C, vitamin E, garlic, ginkgo balboa, dashen, Coenzyme Q10, St. John's Wort, alfalfa, capsicum, ginger, licorice, black cohosh, chamomile, cassia

Follow-up activities related to teens

Another population of potential concern to GSK is adolescents. The safety and efficacy of orlistat in ages 12-16 years has been demonstrated as part of the Rx clinical development program, however, this population has not been included in any of the OTC consumer research studies. GSK believes this population is currently best

managed in an Rx setting, however, it is important to anticipate how this population will likely react if orlistat 60 mg capsules are available as an OTC weight loss aid.

To assess the potential behaviour of teens when presented with an OTC weight loss aid, GSK conducted a targeted self-selection study in teens aged 14 - 17 years. The teens were recruited via flyers distributed or posted in areas likely to attract teenagers. The flyers indicated a need for people interested in losing weight. Those interested in participating were shown the proposed OTC label and asked if they thought the product was appropriate for them to use. There were a total of 1050 subjects who responded to the ad and were screened. Of that group, 147 (14%) were teenagers and went on to complete the study.

According to the label, this product is not appropriate for anyone under 18 years of age to use. When asked to read the label, forty-one percent (41%, N=60) of the teenagers in this study responded incorrectly by selecting the product. However, when all participants were then asked if they would be interested in purchasing such a product today for $55 if it were available as an OTC medication, only 19 of the 147 teenagers (13%) responded that they would purchase the product.

As with cyclosporine users, GSK is taking steps to minimize risk in this population as described in Section 9 of this briefing document.

8.5 Conclusions - Consumer Understanding and Usage

In conclusion, the cumulative data from all labelling studies support that consumers:

- can identify the condition of overweight and are looking for tools to help them lose weight
- understand the label and make self-select decisions based on their need to lose weight.
- use orlistat according to the labelled directions for use
- can use the product safely and effectively in the absence of physician intervention as demonstrated by the excellent safety profile and trends in reported weight loss and satisfaction.

There is no expectation of 100% compliance with labelled selection criteria or instructions for use. GSK is confident that the areas of concern identified in our research will be appropriately addressed by the programs outlined in this document.

GSK is also convinced that the high consumer satisfaction, excellent compliance with dosing instructions, positive change in dietary behaviour and exercise, and acceptable and consistent safety profile make orlistat an ideal weight loss therapy for the OTC environment.

9. Summary of Benefits and Potential Risks

9.1. Benefits

9.1.1 Increased Access and Utilization

Although one in three American adults is engaging in a weight loss attempt[9] at any particular time, most do not consult a health care professional. This lack of interaction limits the potential benefits of FDA-approved weight loss medications, which are currently available only by prescription.

OTC availability provides increased access, and theoretically, increased utilization. This model of OTC availability increasing medication access and utilization is well established. For example, smoking cessation, a prototypical behavioral medicine challenge, was not well managed or treated when pharmacotherapy was available only by prescription. The vast majority of smokers reported they were unlikely to see a physician for a medication to help them quit smoking.[28] In addition, physicians rarely initiated treatment with nicotine replacement therapy (NRT); instead, prescriptions were overwhelmingly patient-initiated.[29, 30] As a consequence, utilization of NRT was significantly limited by prescription-only status. The OTC availability of NRT significantly increased utilization and quit attempts and played a significant role in the national strategy to decrease the prevalence of smoking nationwide.[31] The behavioral support programs provided with OTC NRT products yielded an incremental benefit, over and above the impact of NRT itself.[32] We should also not underestimate the impact of OTC advertising and promotion of smoking cessation products in increasing awareness of the problems of tobacco dependence and therefore helping to initiate cessation attempts.

Given the parallels between smoking and excess weight (e.g., both chronic relapsing conditions, physician time restraints to engage, pharmacotherapy not a "magic bullet," critical need for behavior change, etc.) it is likely that similar public health benefits can be realized from OTC availability of orlistat. OTC orlistat, in conjunction with a behavioral support program, will encourage and support national efforts to educate the public about the health risks of being overweight and provide information and encouragement about how to achieve and maintain a healthy weight.

Increased availability of orlistat will increase the overall number of Americans actively trying to lose weight by introducing them to a weight loss strategy they have not tried or to which they have not previously had access. This is important because, although weight loss attempts are common in the U.S., not all people who would

benefit from weight loss are making an attempt. Notably, attempted weight loss has been found to be associated with lower all-cause mortality, independent of actual weight change.[33]

Use of Orlistat 60 mg capsules at a dose of 60 - 120 mg (1 to 2 capsules tid) has been shown to produce significant weight loss in overweight and obese individuals in an OTC-like setting without dietary counseling. OTC availability of orlistat can increase the success rate for those contemplating a weight loss attempt or already actively trying to lose weight by allowing them to incorporate pharmacotherapy into their weight loss efforts.

In summary, OTC availability of orlistat will increase access to and utilization of a safe and effective FDA-approved weight loss treatment.

9.1.2 Weight Loss

Orlistat 60 mg capsules at a dose of 60-120 mg tid provide significant weight loss in overweight and obese individuals compared to placebo. The safety and efficacy of orlistat 120 mg dose was demonstrated and approved in NDA 20-766 in April 1999. The three clinical studies evaluating the efficacy of orlistat 60 mg in controlled clinical trials were described in detail in Section 6 of this briefing document. The two long-term trials showed the mean percent reduction from baseline weight at the end of 6 months was approximately 5% and significantly different from placebo. The proportion of subjects achieving a 5% weight loss was significantly greater in the 60 mg and 120 mg treatment groups. Consistent weight loss was observed in the 4-month trial in overweight subjects. The actual use trial demonstrated that people can effectively use orlistat 60 mg capsules in an OTC-like setting to lose weight.

Overall, orlistat 60-120 mg consistently provides significant weight loss compared to diet alone in overweight and obese individuals with minimal dietary intervention, regardless of the degree of overweight.

9.1.3 Quality of Life (QOL)

Controlled clinical studies (NM14161, BM14149, and NM17247) have shown an improvement in most parameters of quality of life (e.g. physical appearance, self-regard and overweight distress) with orlistat 60 mg and 120 mg. A significant difference in favor of orlistat 60 mg and 120 mg was seen compared to placebo for "satisfaction with orlistat for weight loss" in overweight and obese subjects.

The Nurse's Health Study[34] funded by the NIH evaluated the association between weight change and quality of life in greater than 40,000 women. Weight loss in overweight women was associated with improved physical function, vitality and decrease in bodily pain.

In another study[35], quality of life was evaluated in overweight individuals after a 13 week lifestyle modification treatment program. This study found that weight loss in the short-term was associated with significantly higher quality of life scores compared to baseline for physical functioning, general health, vitality, and mental health domains. A one year follow-up[36] showed that the improvements seen after 13 weeks of treatment for general health and vitality were maintained regardless of whether the weight loss was maintained.

The most compelling data are from a recent 27 week study which used a validated QOL questionnaire.[37] The results for 120 mg (Rx Xenical®) demonstrated:

- at the end of the study, 92% of the patients treated with orlistat had implemented 87 ± 7% of the established program of physical activity, as compared to 67% of the patients treated with placebo, who only implemented 51 ± 9% of the program ($p < 0.01$).

- 25% of the patients treated with orlistat reported a significant ($p<0.01$) improvement in their opinion of themselves, as opposed to 3% of the patients treated with placebo

9.1.4 Prevention of Obesity and Reduction of Comorbidities

Overweight and obese adults are considered at risk for developing associated morbidities or diseases such as hypertension, high blood cholesterol, type 2 diabetes, and CHD. Orlistat treatment for obesity management has a beneficial effect on lipids, blood pressure, glucose, insulin, and glycosolated hemoglobin. The Sponsor believes that a long term treatment plan focused on these indications are more appropriate for Rx orlistat use, but are highlighted in this section for informational purposes and to emphasize that these comorbidities can be controlled or reduced in conjunction with a broad public health initiative to better manage overweight and obesity.

Beneficial effect on lipids

Orlistat at 60-120 mg has been shown to have beneficial effects on lipids in obese and overweight individuals. In controlled clinical studies at 6 months, orlistat 60 mg provided a reduction of total cholesterol by at least 3.1% and a reduction of LDL cholesterol by at least 5.2% in overweight and obese individuals. Orlistat 120 mg

provided a reduction of total cholesterol by about 5% and a reduction of LDL cholesterol by approximately 6.5%. Data from large clinical trials have shown that every 1% decrease in plasma cholesterol concentration results in a 2% decrease in incidence of coronary heart disease in the first two years.[38]

A recent comprehensive review of controlled clinical studies[39] evaluated the efficacy of orlistat 120 mg on lipid lowering. This review included more than 10,000 patients and found that overall, orlistat provided statistically significant improvement in the lipid profile.

Effect on blood pressure

Unlike centrally-acting weight loss drugs, orlistat at 60-120 mg does not have an adverse impact on blood pressure. In controlled studies at 6 months in obese subjects, a change of -0.7 mmHg was seen in systolic pressure for both 60 and 120 mg and a decline of -0.3 and -0.6 mm Hg was seen in diastolic pressure for 60 and 120 mg respectively. In overweight subjects (BMI 25-28 kg/m^2) orlistat 60 mg provided a reduction in systolic blood pressure of -4.51 mmHg and a reduction of -2.77 mmHg for diastolic blood pressure.

The Framingham Heart study[40] suggested that about 78% of hypertension in men and 65% in women can be directly attributed to excess body weight. Data from multiple population studies suggest that excess weight gain is a consistent predictor for subsequent development of essential hypertension.

Beneficial effect on glycemic parameters

Orlistat 120 mg has beneficial effects on glycemic parameters and has been shown to reduce the risk of developing diabetes by approximately 37.3% in the recent XENDOS Study.[12] These benefits are outlined in the current Rx approved labeling (see Appendix 1).

9.1.5 Reinforcement of Healthy Lifestyle Behaviors

Orlistat is intended to be used in conjunction with healthy lifestyle change and dietary modifications. The OTC package will include in-pack dietary and lifestyle information to help facilitate and reinforce dietary compliance. All orlistat users will also have access to a state-of-the-art web-based behavioral support program.

The actual use trial (NM17285) showed that approximately 60% of subjects were following a diet throughout the duration of the trial and 87% of subjects reported being on a diet at some point during the trial. A large portion (74%) of product users

followed what they considered to be a low fat diet as instructed in the product labelling. Of those subjects participating in the Day 90 interview, over 90% considered themselves "successful" in following a diet. In addition, approximately 32% of subjects indicated they exercised more after taking orlistat in conjunction with the behavioral support tools than they did prior to study enrollment. Further, 50% of subjects reported more frequent exercise or longer exercise at some point during the study. These results further re-enforce the added benefit of providing consumers with behavioral support and educational tools for use in conjunction with orlistat OTC.

9.2. Potential Risks

9.2.1 Gastrointestinal Adverse Events

The pharmacological action of orlistat results in increases in fecal fat excretion; therefore, gastrointestinal adverse events (AEs) would be expected to occur in orlistat-treated subjects at a higher rate than in the placebo treated subjects. These effects may represent an inconvenience to the user but are not generally considered as safety concerns. The incidence of the gastrointestinal AEs related to orlistat treatment was generally lower for the 60 mg dose than for the 120 mg dose, especially for the first week of treatment. This provides a strong rationale for the dosing directions which recommend starting at a dose of 60 mg during which time consumers can become accustomed to the recommended dietary changes.

The orlistat-related AEs were most frequently considered mild to moderate in intensity. There is considerable evidence that orlistat-related GI events can be limited by controlling dietary fat intake to ≤30% of calories. However, significant GI effects, when they occur, will resolve almost immediately upon discontinuation of treatment.

9.2.2 Fat Soluble Vitamin Absorption

Treatment with orlistat will produce a slight decrease in the absorption of some fat-soluble vitamins as expected from its mode of action. The effect of orlistat 60-120 mg on the absorption of vitamins A, D, E, K, and beta carotene is minimal with mean plasma levels consistently remaining well within the reference range at 6 months, 1 year and up to 4 years (described below). The maximum recommended continuous treatment duration will be 6 months at 60-120 mg for OTC use.

In a 4 year clinical trial conducted as part of the Rx clinical development program (XENDOS Study) subjects were not taking multivitamins. In this study, after 4 years of continuous use of orlistat 120 mg tid, a significant decrease in fat soluble vitamins was seen compared to levels observed in the placebo group. However, the mean level

of each fat soluble vitamin remained well within the reference range at all times during the 4 year study in the orlistat treatment group.

In the actual use trial (NM17285), the majority of individuals (74.3%) reported taking a multivitamin when using orlistat. Based on previous clinical experience, we do not anticipate adverse clinical consequences associated with 6 months of orlistat use without multivitamin supplementation. Nonetheless, as a precaution, the OTC label will instruct consumers to take a multivitamin; this advice is beneficial to all consumers undertaking a weight loss program.

9.2.3 Drug Interactions

Drug interaction studies have demonstrated a reduction in cyclosporine levels (by approximately 30%) with co-administration of orlistat. Therefore orlistat should not be ingested at the same time as cyclosporine. While the Rx Xenical® PI states that cyclosporine should be taken at least 2 hours before or after taking orlistat to minimize this effect, the OTC label instructs individuals taking cyclosporine not to use orlistat.

Co-administration of warfarin and orlistat did not result in any change in the pharmacokinetics or pharmacodynamics of warfarin. However, vitamin K levels may decline in subjects taking orlistat. Therefore, subjects on warfarin who are using orlistat should be monitored for changes in coagulation parameters. The OTC label instructs individuals taking warfarin to ask their doctor or pharmacist prior to taking orlistat.

Orlistat has not been shown to have any drug interactions with medications used for diabetes. However, dosage reductions for diabetic medications may be required when taken concomitantly with orlistat since even modest weight loss can improve glycemic control. The OTC label instructs individuals taking medications for diabetes to ask their doctor or pharmacist prior to taking orlistat.

No clinically relevant drug interactions were seen when orlistat was taken in combination with weight loss drugs phentermine or sibutramine. No other published studies were found evaluating the concomitant use of orlistat with other weight loss drugs. The OTC label instructs individuals taking other weight loss drugs to ask their doctor or pharmacist prior to taking orlistat.

9.2.4 Abuse/Misuse

In the clinical pharmacology program and the clinical studies program, there was no evidence of central nervous system effects indicative of abuse potential. Systemic exposure to orlistat is minimal and plasma levels of orlistat even after two years of continual treatment were extremely low and near the lowest levels of detection. However, as with any weight loss agent, there is the potential for misuse or inappropriate use. Of potential concern are individuals with eating disorders who are not overweight but might consider using the drug.

Common behaviors observed in these individuals suggest that misuse potential is low:

- Anorexics are unlikely to take orlistat or to be ingesting a diet sufficiently high in fat for orlistat to have any effect.[41] Phase I studies in subjects given orlistat in conjunction with a very low fat diet showed virtually no effect on fecal fat levels.

- Bulimics most commonly seek fast acting purgative agents such as laxatives and diuretics. Orlistat would not provide bulimics with the purgative mechanism they desire, making orlistat an unfavorable choice for these individuals.

Nonetheless, potential safety concerns in these populations were assessed in terms of post-marketing data and clinical experience. There have been only four cases of orlistat misuse from post-marketing reports. These four cases come from three articles in the literature.[42,43,44] Prior to starting orlistat, all four patients had a long-history of eating disorders, including misuse of laxatives, diuretics and other weight control measures such as purging. There were no clinically significant safety concerns reported in these case reports.

Additionally, the absence of effects on other non-lipolytic digestive enzymes (amylase and trypsin) or electrolyte disturbances during the course of long-term treatment provide additional reassurance that intentional misuse would not produce clinically important safety issues in the OTC setting.

9.2.5 Use During Pregnancy and Breastfeeding

As specified in the current approved prescription label of orlistat 120 mg, orlistat is categorized as a Pregnancy Category B drug based on non-clinical data and information received from subjects who became pregnant during the clinical study

program. Periodic reviews of post marketing information from 1999 to date have not revealed any new information that would necessitate a revision in the labeling.

Since there are no adequate and well-controlled studies of orlistat in pregnant women and it is not known if orlistat is secreted in human milk, orlistat is not recommended for use during pregnancy or breast-feeding. Primarily out of concern for a woman's nutritional status, the proposed OTC label contains the statement, "Do not use if you are pregnant or breast-feeding."

9.2.6 Adolescent Use

The use of Rx Xenical® (orlistat) for the management of obesity in adolescents aged 12 to 16 yrs was approved by FDA in September 2003 based on the following:

- safety and efficacy of orlistat 120 mg in adults
- 54 week efficacy and safety study obese adolescent subjects aged 12 to 16 years
- 21 day mineral balance study in obese adolescent subjects aged 12 to 16 years.

Orlistat has not been studied in pediatric subjects below the age of 12 years.

However, at a meeting of the Pediatric Advisory Committee on February 14th, 2005, it was recommended that Xenical usage in ages 12 to 16 yrs should be monitored for an additional year and reported back to the committee. The limited time and relative absence of prescribing experience in this population were stated as reasons for extending this oversight period in this population.

Note: GSK believes that the adolescent use of orlistat should be restricted to the Rx setting.

9.2.7 Diversion from Care

As noted in Section 2.2 of this document, the number of patients receiving treatment advice for overweight and obesity is low when compared to the increasing prevalence of these conditions in the US population. The availability of OTC orlistat is unlikely to impact the frequency of patients seeking physician care, since most individuals are not seeking advice for weight loss from their physician.

OTC orlistat fulfils an unmet medical need in providing individuals access to pharmacotherapy and behavioral support that is unavailable in the current

environment. Increased utilization of orlistat as a weight loss aid can increase the number of overweight individuals who are actively trying to lose weight. The OTC label will also encourage consumers to speak with a physician after six months of orlistat use if their weight loss goal is not achieved.

9.3 GSK Launch Commitments

9.3.1 Post-Marketing Surveillance

An active surveillance program can give the sponsor continuous data on how their product is perceived and used, and by what types of consumers. GSK will reinstitute a program developed in smoking control that will **monitor** nationwide print, radio and television for any mention of OTC orlistat. Any and all media coverage of positive or negative mentions of OTC orlistat will be collected and analyzed by GSK for information about how the product is being used and by what subgroups. The company will be looking for any signals of abuse and/or misuse by individuals or groups. Of particular interest is potential use under the age of 18 years and by individuals with eating disorders. GSK will also establish contacts with institutions (Eating Disorder Clinics) and individuals (eg., Safe and Drug Free School Coordinators) that interact directly with special populations of interest to survey and report. GSK will work with experts to develop educational programs to help prevent and/or correct any observed risk.

9.3.2 Age Verification at Retail Purchase

Inappropriate use in an underage population can best be managed by restricting access to the product at the point of purchase. Age verification at retail purchase is extensively used in several retail categories including alcohol, tobacco and smoking cessation products. GSK will utilize this technology to restrict access to OTC orlistat for all purchasers under the age of 18 years. This system identifies products requiring age verification based on the price scanning code and incorporates a prompt for the cashier to verify the age of the purchaser before proceeding to the next item.

9.3.3 Pediatric Development Plan (>12 Yrs)

GSK has been granted a pediatric assessment deferral by FDA for the assessment of the OTC product in the age group 12 to 17 years.

9.3.4 Education Programs

The only significant drug interactions of potential clinical concern are with cyclosporine (direct) and warfarin (indirect). However, GSK believes the risks posed by these interactions can be appropriately managed in an OTC setting through

labeling and implementation of comprehensive awareness/educational programs aimed at potential users as well as health care practitioners.

9.3.4.1. Professional Educational Programs

GSK has an extensive network of medical marketing professionals who will call upon physicians, pharmacists, nurses, and other health care professionals to educate them about OTC orlistat.

9.3.4.2. Consumer Directed Education Programs

Advertising and promotion of an FDA approved weight loss aid can improve awareness and education about the health problems of overweight and obesity. In addition to television, radio, and print, GSK will make extensive use of internet site(s) that will provide consumers with information on diet and healthy food choices. Educational information will also assist consumers with food and lifestyle choices after completing OTC orlistat treatment.

9.4 Summary of Risk/Benefit Profile

According to the National Institutes of Health and Centers for Disease Control, the number of overweight and obese individuals in the U.S. has been increasing dramatically over the past decade. Currently, there are no FDA approved OTC products on the market for weight loss. OTC products provide additional options for consumers. This is particularly important in weight control where treatment is primarily self-driven. In those cases where consumers seek the advice of healthcare professionals, consumers are typically provided with little or no instruction in diet and exercise modification.[45]

Individual success rates to specific therapies vary greatly so availability of treatment choices may increase the overall success rates. Although there is a wide array of unapproved herbal products that are available to consumers, many have unproven claims of safety and efficacy. Orlistat in conjunction with behavioral support tools and a reduced calorie, low fat diet is an ideal scientifically-supported alternative for consumers to use for weight loss.

By increasing consumer access to a safe and effective FDA-approved weight loss medication, non-prescription availability of orlistat has the potential to:

- increase the number of Americans actively trying to lose weight
- increase the success rates of those making a weight loss attempt

- increase the proportion of adults at a healthy weight

Even modest amounts of weight loss, if achieved on a widespread basis, could have important public health benefits. Increased access to pharmacotherapy through non-prescription availability of orlistat is responsive to the "call to action" issued by the federal government to prevent and decrease overweight and obesity in the U.S. OTC availability of orlistat holds considerable promise for improving the public health in the U.S. by potentially lowering the escalating rates of overweight and obesity.

We believe that OTC orlistat will be perceived as being more than a pharmacologic weight loss aid. OTC orlistat in conjunction with the behavioral support program and in-pack materials will serve as a weight loss program including a system of support tools and compliance aids. In conclusion, the OTC availability of orlistat will fill an unmet need for overweight and obese consumers and provide a safe and effective treatment option with benefits far exceeding the risks.

10. Overall Summary and Conclusions

This briefing document demonstrates that orlistat 60 mg capsules (at a dose of 1 to 2 capsules tid) can be used safely and effectively in an OTC environment to help overweight adults lose weight when used as directed in conjunction with a reduced fat and low calorie diet. The evidence includes:

- The efficacy of orlistat at a dose of 60 mg tid for up to 6 months continuous use has been demonstrated in two placebo-controlled weight loss trials (BM14149 & NM14161) in patients with a BMI range of 28 to 43. The efficacy data from these trials at the proposed dose and duration meets the approvability criterion proposed in the 1996 draft guidance for *prescription weight loss drugs at 1 year*. A 4-month study (NM17247) in patients with a BMI range of 25 to 28 supports and confirms results from studies carried out in a more obese population.

- The established safety profile of orlistat 60 - 120 mg for 6 months is suitable for the OTC setting since orlistat is minimally absorbed and has no medically significant systemic effects beyond its pharmacologic effect. Orlistat is well tolerated based on Phase 3 clinical trials and post marketing experience.

- With respect to drug-drug interactions, cyclosporine is the only direct drug-drug interaction of potential clinical consequence. We believe the risks posed by this interaction, as well as those posed by the indirect interaction with warfarin, can be effectively managed in an OTC setting via the warnings that appear in the proposed OTC label, in-pack materials, and proposed programs for both consumers and healthcare professionals.

- Dietary instructions for use of orlistat for weight loss and its unique mechanism of action encourage healthy dietary choices. The product is designed and will be promoted to work in conjunction with a reduced fat and low calorie diet.

- Weight loss as an OTC indication is both well-established and clearly understood by consumers. The consumer labelling and usage studies demonstrate that consumers can understand the proposed OTC label and use the product in the correct manner that allows them to achieve weight loss in a real-world setting.

- Lastly, GSK recognizes that the efficacy of any weight loss therapy is inherently tied to lifestyle changes and therefore, commits to providing educational in-package materials and behavioral support tools tailored to meet this challenge.

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Appendix 1

Rx Package Insert for

Xenical® (orlistat) 120 mg Capsules

Roche

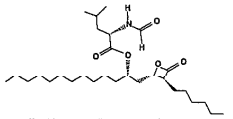
XENICAL®
(orlistat)
CAPSULES

℞ only

DESCRIPTION

XENICAL (orlistat) is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats.

Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[((2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight is 495.7. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 589 nm. The structure is:



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

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

CLINICAL PHARMACOLOGY

Mechanism of Action

Orlistat is a reversible inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control. Systemic absorption of the drug is therefore not needed for activity. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by approximately 30%.

Pharmacokinetics

Absorption

Systemic exposure to orlistat is minimal. Following oral dosing with 360 mg ^{14}C-orlistat, plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact orlistat were near the limits of detection (<5 ng/mL). In therapeutic studies involving monitoring of plasma samples, detection of intact orlistat in plasma was sporadic and concentrations were low (<10 ng/mL or 0.02 µM), without evidence of accumulation, and consistent with minimal absorption.

The average absolute bioavailability of intact orlistat was assessed in studies with male rats at oral doses of 150 and 1000 mg/kg/day and in male dogs at oral doses of 100 and 1000 mg/kg/day and found to be 0.12%, 0.59% in rats and 0.7%, 1.9% in dogs, respectively.

Distribution

In vitro orlistat was >99% bound to plasma proteins (lipoproteins and albumin were major binding proteins). Orlistat minimally partitioned into erythrocytes.

Metabolism

Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on an oral ^{14}C-orlistat mass balance study in obese patients, two metabolites, M1 (4-member lactone ring hydrolyzed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of total radioactivity in plasma. M1 and M3 have an open β-lactone ring and extremely weak lipase inhibitory activity (1000- and 2500-fold less than orlistat, respectively). In view of this low inhibitory activity and the low plasma levels at the therapeutic dose (average of 26 ng/mL and 108 ng/mL for M1 and M3, respectively, 2 to 4 hours after a dose), these metabolites are considered pharmacologically inconsequential. The primary metabolite M1 had a short half-life (approximately 3 hours) whereas the secondary metabolite M3 disappeared at a slower rate (half-life approximately 10.5 hours). In obese patients, steady-state plasma levels of M1, but not M3, increased in proportion to orlistat doses.

Elimination

Following a single oral dose of 360 mg ^{14}C-orlistat in both normal weight and obese subjects, fecal excretion of the unabsorbed drug was found to be the major route of elimination. Orlistat and its M1 and M3 metabolites were also subject to biliary excretion. Approximately 97% of the administered radioactivity was excreted in feces; 83% of that was found to be unchanged orlistat. The cumulative renal excretion of total radioactivity was <2% of the given dose of 360 mg ^{14}C-orlistat. The time to reach complete excretion (fecal plus urinary) was 3 to 5 days. The disposition of orlistat appeared to be similar between normal weight and obese subjects. Based on limited data, the half-life of the absorbed orlistat is in the range of 1 to 2 hours.

Special Populations

Because the drug is minimally absorbed, studies in special populations (geriatric, different races, patients with renal and hepatic insufficiency) were not conducted.

Pediatrics

Plasma concentrations of orlistat and its metabolites M1 and M3 were similar to those found in adults at the same dose level. Daily fecal fat excretions were 27% and 7% of dietary intake in orlistat and placebo treatment groups, respectively.

Drug-Drug Interactions

Drug-drug interaction studies indicate that XENICAL had no effect on pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release tablets), oral contraceptives, phenytoin, pravastatin, or warfarin. Alcohol did not affect the pharmacodynamics of orlistat.

Other Short-term Studies

Adults

In several studies of up to 6-weeks duration, the effects of therapeutic doses of XENICAL on gastrointestinal and systemic physiological processes were assessed in normal-weight and obese subjects. Postprandial cholecystokinin plasma concentrations were lowered after multiple doses of XENICAL in two studies but not significantly different from placebo in two other experiments. There were no clinically significant changes observed in gallbladder motility, bile composition or lithogenicity, or colonic cell proliferation rate, and no clinically significant reduction of gastric emptying time or gastric acidity. In addition, no effects on plasma triglyceride levels or systemic lipases were observed with the administration of XENICAL in these studies. In a 3-week study of 20 healthy male volunteers, XENICAL (120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, copper, and iron.

Pediatrics

In a 3-week study of 32 obese adolescents aged 12 to 16 years, XENICAL (120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, or copper. The iron balance was decreased by 64.7 µmole/24 hours and 40.4 µmole/24 hours in orlistat and placebo treatment groups, respectively.

Dose-response Relationship

A simple maximum effect (E_{max}) model was used to define the dose-response curve of the relationship between XENICAL daily dose and fecal fat excretion as representative of gastrointestinal lipase inhibition. The dose-response curve demonstrated a steep portion for doses up to approximately 400 mg daily, followed by a plateau for higher doses. At doses greater than 120 mg three times a day, the percentage increase in effect was minimal.

CLINICAL STUDIES

Observational epidemiologic studies have established a relationship between obesity and visceral fat and the risks for cardiovascular disease, type 2 diabetes, certain forms of cancer, gallstones, certain respiratory disorders, and an increase in overall mortality. These studies suggest that weight loss, if maintained, may produce health benefits for obese patients who have or are at risk of developing weight-related comorbidities. The long-term effects of orlistat on morbidity and mortality associated with obesity have not been established.

The effects of XENICAL on weight loss, weight maintenance, and weight regain and on a number of comorbidities (eg, type 2 diabetes, lipids, blood pressure) were assessed in the 4-year XENDOS study and in seven long-term (1- to 2-years duration) multicenter, double-blind, placebo-controlled clinical trials. During the first year of therapy, the studies of 2-year duration assessed weight loss and weight maintenance. During the second year of therapy, some studies assessed continued weight loss and weight maintenance and others assessed the effect of orlistat on weight regain. These studies included over 2800 patients treated with XENICAL and 1400 patients treated with placebo. The majority of these patients had obesity-related risk factors and comorbidities. In the XENDOS study, which included 3304 patients, the time to onset of type 2 diabetes was assessed in addition to weight management. In all these studies, treatment with XENICAL and placebo designates treatment with XENICAL plus diet and placebo plus diet, respectively.

During the weight loss and weight maintenance period, a well-balanced, reduced-calorie diet that was intended to result in an approximate 20% decrease in caloric intake and provide 30% of calories from fat was recommended to all patients. In addition, all patients were offered nutritional counseling.

One-year Results: Weight Loss, Weight Maintenance, and Risk Factors

Weight loss was observed within 2 weeks of initiation of therapy and continued for 6 to 12 months.

Pooled data from five clinical trials indicated that the overall mean weight loss from randomization to the end of 6 months and 1 year of treatment in the intent-to-treat population were 12.4 lbs and 13.4 lbs in the patients treated with XENICAL and 6.2 lbs and 5.8 lbs in the placebo treated patients, respectively. During the 4 week placebo lead in period of the studies, an additional 5 to 6 lb weight loss was also observed in the same patients. Of the patients who completed 1 year of treatment, 57% of the patients treated with XENICAL (120 mg three times a day) and 31% of the placebo-treated patients lost at least 5% of their baseline body weight.

The percentages of patients achieving ≥5% and ≥10% weight loss after 1 year in five large multicenter studies for the intent-to-treat populations are presented in Table 1.

Table 1 Percentage of Patients Losing ≥5% and ≥10% of Body Weight From Randomization After 1-Year Treatment*

	Intent-to-Treat Population†					
	≥5% Weight Loss			≥10% Weight Loss		
Study No.	XENICAL n	Placebo n	p-value	XENICAL n	Placebo n	p-value
14119B	35.5% 110	21.3% 108	0.021	16.4% 110	6.5% 108	0.022
14119C	54.8% 343	27.4% 340	<0.001	24.8% 343	8.2% 340	<0.001
14149	50.6% 241	26.3% 236	<0.001	22.8% 241	11.9% 236	0.02
14161‡	37.1% 210	16.0% 212	<0.001	19.5% 210	3.8% 212	<0.001
14185	42.6% 657	22.4% 223	<0.001	17.7% 657	9.9% 223	0.006

The diet utilized during year 1 was a reduced-calorie diet.

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
† Last observation carried forward
‡ All studies, with the exception of 14161, were conducted at centers specialized in treating obesity and complications of obesity. Study 14161 was conducted with primary care physicians.

The relative changes in risk factors associated with obesity following 1 year of therapy with XENICAL and placebo are presented for the population as a whole and for the population with abnormal values at randomization.

Population as a Whole

The changes in metabolic, cardiovascular and anthropometric risk factors associated with obesity based on pooled data for five clinical studies, regardless of the patient's risk factor status at randomization, are presented in Table 2. One year of therapy with XENICAL resulted in relative improvement in several risk factors.

Table 2 Mean Change in Risk Factors From Randomization Following 1-Year Treatment* Population as a Whole

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic:		
Total Cholesterol	-2.0%	+5.0%
LDL-Cholesterol	-4.0%	+5.0%
HDL-Cholesterol	+9.3%	+12.8%
LDL/HDL	-0.37	-0.20
Triglycerides	+1.34%	+2.9%
Fasting Glucose, mmol/L	-0.04	+0.0
Fasting Insulin, pmol/L	-6.7	+5.2
Cardiovascular:		
Systolic Blood Pressure, mm Hg	-1.01	+0.58
Diastolic Blood Pressure, mm Hg	-1.19	+0.46
Anthropometric:		
Waist Circumference, cm	-6.45	-4.04
Hip Circumference, cm	-5.31	-2.96

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
† Intent-to-treat population at week 52, observed data based on pooled data from 5 studies

Population With Abnormal Risk Factors at Randomization

The changes from randomization following 1-year treatment in the population with abnormal lipid levels (LDL ≥130 mg/dL, LDL/HDL ≥3.5, HDL <35 mg/dL) were greater for XENICAL compared to placebo with respect to LDL-cholesterol (-7.83% vs +1.14%) and the LDL/HDL ratio (-0.64 vs -0.46). HDL increased in the placebo group by 20.1% and in the XENICAL group by 18.8%. In the population with abnormal blood pressure at baseline (systolic BP ≥140 mm Hg), the change in SBP from randomization to 1 year was greater for XENICAL (-10.89 mm Hg) than placebo (-5.07 mm Hg). For patients with a diastolic blood pressure ≥90 mm Hg, XENICAL patients decreased by -7.9 mm Hg while the placebo patients decreased by -5.5 mm Hg. Fasting insulin decreased more for XENICAL than placebo (-39 vs -16 pmol/L) from randomization to 1 year in the population with abnormal baseline values (≥120 pmol/L). A greater reduction in waist circumference for XENICAL vs placebo (-7.29 vs -4.53 cm) was observed in the population with abnormal baseline values (≥100 cm).

Effect on Weight Regain

Three studies were designed to evaluate the effects of XENICAL compared to placebo in reducing weight regain after a previous weight loss achieved following either diet alone (one study, 14302) or prior treatment with XENICAL (two studies, 14119C and 14185). The diet utilized during the 1-year weight regain portion of the studies was a weight-maintenance diet, rather than a weight-loss diet, and patients received less nutritional counseling than patients in weight-loss studies. For studies 14119C and 14185, patients' previous weight loss was due to 1 year of treatment with XENICAL in conjunction with a mildly

hypocaloric diet. Study 14302 was conducted to evaluate the effects of 1 year of treatment with XENICAL on weight regain in patients who had lost 8% or more of their body weight in the previous 6 months on diet alone.

In study 14119C, patients treated with placebo regained 52% of the weight they had previously lost while the patients treated with XENICAL regained 26% of the weight they had previously lost (p<0.001). In study 14185, patients treated with placebo regained 63% of the weight they had previously lost while the patients treated with XENICAL regained 35% of the weight they had lost (p<0.001). In study 14302, patients treated with placebo regained 69% of the weight they had previously lost while the patients treated with XENICAL regained 32% of the weight that they had lost (p<0.001).

Two-year Results: Long-term Weight Control and Risk Factors

The treatment effects of XENICAL were examined for 2 years in four of the five 1-year weight management clinical studies previously discussed (see Table 1). At the end of year 1, the patients' diets were reviewed and changed where necessary. The diet prescribed in the second year was designed to maintain patient's current weight. XENICAL was shown to be more effective than placebo in long term weight control in four large, multicenter, 2-year double-blind, placebo-controlled studies.

Pooled data from four clinical studies indicate that 40% of all patients treated with 120 mg three times a day of XENICAL and 24% of patients treated with placebo who completed 2 years of the same therapy had ≥5% loss of body weight from randomization. Pooled data from four clinical studies indicate that the relative weight loss advantage between XENICAL 120 mg three times a day and placebo treatment groups was the same after 2 years as for 1 year, indicating that the pharmacologic advantage of XENICAL was maintained over 2 years. In the same studies cited in the **One-year Results** (see Table 1), the percentages of patients achieving a ≥5% and ≥10% weight loss after 2 years are shown in Table 3.

Table 3 Percentage of Patients Losing ≥5% and ≥10% of Body Weight From Randomization After 2-Year Treatment*

	Intent-to-Treat Population†					
	≥5% Weight Loss			≥10% Weight Loss		
Study No.	XENICAL n	Placebo n	p-value	XENICAL n	Placebo n	p-value
14119C	45.1% 133	23.6% 123	<0.001	24.8% 133	6.5% 123	<0.001
14149	43.3% 178	27.2% 158	0.002	18.0% 178	9.5% 158	0.025
14161‡	25.0% 148	15.0% 113	0.049	16.9% 148	3.5% 113	0.001
14185	34.0% 147	27.9% 122	0.279	17.7% 147	11.5% 122	0.154

The diet utilized during year 2 was designed for weight maintenance and not weight loss.
* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
† Last observation carried forward
‡ All studies, with the exception of 14161 were conducted at centers specializing in treating obesity or complications of obesity. Study 14161 was conducted with primary care physicians.

The relative changes in risk factors associated with obesity following 2 years of therapy were also assessed in the population as a whole and the population with abnormal risk factors at randomization.

Population as a Whole

The relative differences in risk factors between treatment with XENICAL and placebo were similar to the results following 1 year of therapy for total cholesterol, LDL-cholesterol, LDL/HDL ratio, triglycerides, fasting glucose, fasting insulin, diastolic blood pressure, waist circumference, and hip circumference. The relative differences between treatment groups for LDL cholesterol and systolic blood pressure were less than that observed in the year one results.

Population With Abnormal Risk Factors at Randomization

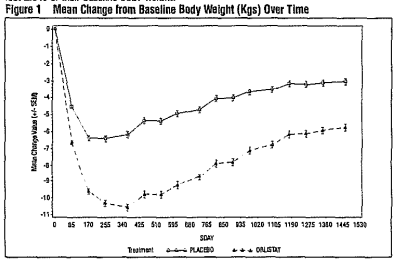
The relative differences in risk factors between treatment with XENICAL and placebo were similar to the results following 1 year of therapy for LDL- and HDL-cholesterol, triglycerides, fasting insulin, diastolic blood pressure, and waist circumference. The relative differences between treatment groups for LDL/HDL ratio and isolated systolic blood pressure were less than that observed in the year one results.

Four-Year Results: Long-term Weight Control and Risk Factors

In the 4-year double-blind, placebo-controlled XENDOS study, the effects of orlistat in delaying the onset of type 2 diabetes and on body weight were compared to placebo in 3304 obese patients who had either normal or impaired glucose tolerance at baseline. Thirty-four percent of the 1655 patients who were randomized to the placebo group and 52% of the 1649 patients who were randomized to the orlistat group completed the 4-year study.

At the end of the study, the mean percent weight loss in the placebo group was -2.79% compared with -5.17% in the orlistat group (p<0.001) (see Figure 1). Forty-five percent of the placebo patients and 73% of the orlistat patients lost ≥5% of their baseline body weight, and 21% of the placebo patients and 41% of the orlistat patients lost ≥10% of their baseline body weight following the first year of treatment. Following 4 years of treatment, 28% of the placebo patients and 45% of the orlistat patients lost ≥5% of their baseline body weight and 10% of the placebo patients and 21% of the orlistat patients lost ≥10% of their baseline body weight.

Figure 1 Mean Change from Baseline Body Weight (Kgs) Over Time



The relative changes from baseline in risk factors associated with obesity following 4 years of therapy were assessed in the XENDOS study population (see Table 4).

Table 4 Mean Change in Risk Factors From Randomization Following 4-Years Treatment*

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic:		
Total Cholesterol	-7.02%	-2.03%
LDL-Cholesterol	-11.66%	-3.85%
HDL-Cholesterol	+5.92%	+7.01%
LDL/HDL	-0.53	-0.33
Triglycerides	+3.64%	+1.30
Fasting Glucose, mmol/L	+0.12	+0.23
Fasting Insulin, pmol/L	-24.93	-15.71
Cardiovascular:		
Systolic Blood Pressure, mm Hg	-4.12	-2.60
Diastolic Blood Pressure, mm Hg	-1.93	-0.87
Anthropometric:		
Waist Circumference, cm	-5.78	-3.99

*Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
†Intent-to-treat population

Study of Patients With Type 2 Diabetes

A 1-year double-blind, placebo-controlled study in type 2 diabetics (N=321) stabilized on sulfonylureas was conducted. Thirty percent of patients treated with XENICAL achieved at least a 5% or greater reduction in body weight from randomization compared to 13% of the placebo-treated patients (p<0.001). Table 5 describes the changes over 1 year of treatment with XENICAL compared to placebo, in sulfonylurea usage and dose reduction as well as in hemoglobin HbA1c, fasting glucose, and insulin.

Table 5 Mean Changes in Body Weight and Glycemic Control From Randomization Following 1-Year Treatment in Patients With Type 2 Diabetes

	XENICAL 120 mg* (n=162)	Placebo* (n=159)	Statistical Significance
% patients who discontinued dose of oral sulfonylurea	11.7%	7.5%	†
% patients who decreased dose of oral sulfonylurea	31.5%	21.4%	
Average reduction in sulfonylurea medication dose	-22.8%	-9.1%	†
Body weight change (lbs)	-8.9	-4.2	†
HbA1c	-0.18%	+0.28%	†
Fasting glucose, mmol/L	-0.02	+0.54	†
Fasting insulin, pmol/L	-19.68	-18.02	ns

Statistical significance based on intent-to-treat population, last observation carried forward.
* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
† Statistically significant (p ≤ 0.05) based on intent-to-treat, last observation carried forward
ns nonsignificant, p>0.05

In addition, XENICAL (n=162) compared to placebo (n=159) was associated with significant lowering for total cholesterol (-1.0% vs +9.0%, p≤0.05), LDL-cholesterol (-3.0% vs +10.0%, p≤0.05), LDL/HDL ratio (-0.26 vs -0.02, p≤0.05) and triglycerides (+2.54% vs +16.2%, p≤0.05), respectively. For HDL cholesterol, there was a +6.49% increase on XENICAL and +8.6% increase on placebo, p>0.05. Systolic blood pressure increased by +0.61 mm Hg on XENICAL and increased by +4.33 mm Hg on placebo, p>0.05. Diastolic blood pressure decreased by -0.47 mm Hg for XENICAL and by -0.5 mm Hg for placebo, p>0.05.

Glucose Tolerance in Obese Patients

Two-year studies that included oral glucose tolerance tests were conducted in obese patients not previously diagnosed or treated for type 2 diabetes and whose baseline oral glucose tolerance test (OGTT) status at randomization was either normal, impaired, or diabetic.

The progression from a normal OGTT at randomization to a diabetic or impaired OGTT following 2 years of treatment with XENICAL (n=251) or placebo (n=207) were compared. Following treatment with XENICAL, 0.0% and 7.2% of the patients progressed from normal to diabetic and normal to impaired, respectively, compared to 1.9% and 12.6% of the placebo treatment group, respectively.

In patients found to have an impaired OGTT at randomization, the percent of patients improving to normal or deteriorating to diabetic status following 1 and 2 years of treatment with XENICAL compared to placebo are presented. After 1 year of treatment, 45.8% of the placebo patients and 73% of the XENICAL patients had a normal oral glucose tolerance test while 10.4% of the placebo patients and 2.6% of the XENICAL patients became diabetic. After 2 years of treatment, 50% of the placebo patients and 71.7% of the XENICAL patients had a normal oral glucose tolerance test while 26% of placebo patients were found to be diabetic and 1.7% of XENICAL patients were found to be diabetic after treatment.

Onset of Type 2 Diabetes in Obese Patients

In the XENDOS trial, in the overall population, orlistat delayed the onset of type 2 diabetes such that at the end of four years of treatment the cumulative incidence rate of diabetes was 8.3% for the placebo group compared to 5.5% for the orlistat group, p=0.01 (see Table 6). This finding was driven by a statistically-significant reduction in the incidence of developing type 2 diabetes in those patients who had impaired glucose tolerance at baseline (Table 6 and Figure 2). Orlistat did not reduce the risk for the development of diabetes in patients with normal glucose tolerance at baseline.

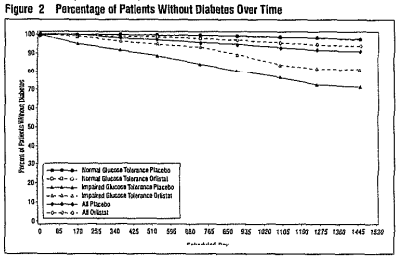
The effect of XENICAL to delay the onset of type 2 diabetes in obese patients with IGT is presumably due to weight loss, and not to any independent effects of the drug on glucose or insulin metabolism. The effect of orlistat on weight loss is adjunctive to diet and exercise.

Table 6 Incidence Rate of Diabetes at Year 4 by OGTT Status at Baseline*

OGTT at baseline	Normal		Impaired		All	
Treatment	Placebo	Orlistat	Placebo	Orlistat	Placebo	Orlistat
Number of patients*	1148	1235	324	337	1472	1572
# pts developing diabetes	16	21	62	48	78	69
Life table rate†	2.1%	1.7%	27.2%	18.7%	8.3%	5.5%
Observed percent	1.4%	1.7%	19.1%	14.2%	5.3%	4.4%
Absolute risk reduction						
Life table	0.4%		8.5%		2.8%	
Observed	-0.3%		4.9%		0.9%	
Relative risk reduction††	8%		42%		34%	
p-value	0.79		<0.01		0.01	

*Based on patients with a baseline and at least one follow-up OGTT measurement
†Rate adjusted for dropouts
††Computed as (1- hazard ratio)

Figure 2 Percentage of Patients Without Diabetes Over Time



Pediatric Clinical Studies

The effects of XENICAL on body mass index (BMI) and weight loss were assessed in a 54-week multicenter, double-blind, placebo-controlled study in 539 obese adolescents (357 receiving XENICAL 120 mg three times a day, 182 receiving placebo), aged 12 to 16 years. All study participants had a baseline BMI that was 2 units greater than the US weighted mean for the 95th percentile based on age and gender. Body mass index was the primary efficacy parameter because it takes into account changes in height and body weight, which occur in growing children.

During the study, all patients were instructed to take a multivitamin containing fat-soluble vitamins at least 2 hours before or after ingestion of XENICAL. Patients were also maintained on a well-balanced, reduced-calorie diet that was intended to provide 30% of calories from fat. In addition, all patients were placed on a behavior modification program and offered exercise counseling.

Approximately 65% of patients in each treatment group completed the study.

Following one year of treatment, BMI decreased by an average of 0.55 kg/m² in the XENICAL-treated patients and increased by an average of 0.31 kg/m² in the placebo-treated patients (p=0.001).

The percentages of patients achieving ≥5% and ≥10% reduction in BMI and body weight after 52 weeks of treatment for the intent-to-treat population are presented in Table 7.

Table 7 Percentages of Patients with ≥5% and ≥10% Decrease in Body Mass Index and Body Weight After 1-Year Treatment* (Protocol NM16189)

	Intent-to-Treat Population†			
	≥5% Decrease		≥10% Decrease	
	XENICAL n	Placebo n	XENICAL n	Placebo n
BMI	26.5% 347	15.7% 178	13.3% 347	4.5% 178
Body Weight	19.0% 348	11.7% 180	9.5% 348	3.3% 180

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
† Last observation carried forward

INDICATIONS AND USAGE

XENICAL is indicated 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/m² or ≥27 kg/m² in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia).

Table 8 illustrates body mass index (BMI) according to a variety of weights and heights. The BMI is calculated by dividing weight in kilograms by height in meters squared. For example, a person who weighs 180 lbs and is 5'5" would have a BMI of 30.

Table 8 Body Mass Index (BMI), kg/m²*

Height (in) \ Weight (lb)	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320
4'10"	25	27	29	31	34	36	38	40	42	44	46	48	50	52	54	57	59	61	63	65	67
4'11"	24	26	28	30	32	34	36	38	40	43	45	47	49	51	53	55	57	59	61	63	65
5'0"	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59	61	63
5'1"	23	25	27	28	30	32	34	36	38	40	42	44	45	47	49	51	53	55	57	59	61
5'2"	22	24	26	27	29	31	33	35	37	38	40	42	44	46	48	49	51	53	55	57	59
5'3"	21	23	25	27	28	30	32	34	36	37	39	41	43	44	46	48	50	51	53	55	57
5'4"	21	22	24	26	28	29	31	33	34	36	38	40	41	43	45	46	48	50	52	53	55
5'5"	20	22	23	25	27	28	30	32	33	35	37	38	40	42	43	45	47	48	50	52	53
5'6"	19	21	23	24	26	27	29	31	32	34	36	37	39	40	42	44	45	47	49	50	52
5'7"	19	20	22	24	25	27	28	30	31	33	35	36	38	39	41	42	44	46	47	49	50
5'8"	18	20	21	23	24	26	27	29	30	32	34	35	37	39	40	41	43	44	46	47	49
5'9"	18	19	21	22	24	25	27	28	30	31	33	34	36	37	39	40	41	43	44	46	47
5'10"	17	19	20	22	23	24	26	27	29	30	32	33	35	36	37	39	40	42	43	45	46
5'11"	17	18	20	21	22	24	25	27	28	29	31	32	34	35	36	38	39	41	42	43	45
6'0"	16	18	19	20	22	23	24	26	27	29	30	31	33	34	35	37	38	39	41	42	43
6'1"	16	17	19	20	21	22	24	25	26	28	29	30	32	33	34	36	37	38	40	41	42
6'2"	15	17	18	19	21	22	23	24	26	27	28	30	31	32	33	35	36	37	39	40	41

*Conversion Factors:
Weight in lbs ÷ 2.2 = weight in kilograms (kg)
Height in inches x 0.0254 = height in meters (m)
1 foot = 12 inches

CONTRAINDICATIONS

XENICAL is contraindicated in patients with chronic malabsorption syndrome or cholestasis, and in patients with known hypersensitivity to XENICAL or to any component of this product.

WARNINGS

Miscellaneous

Organic causes of obesity (eg, hypothyroidism) should be excluded before prescribing XENICAL.

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine. Therefore, XENICAL and cyclosporine should not be coadministered. To reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 2 hours before or after XENICAL in patients taking both drugs. In addition, in those patients whose cyclosporine levels are being measured, more frequent monitoring should be considered.

PRECAUTIONS

General

Patients should be advised to adhere to dietary guidelines (see DOSAGE AND ADMINISTRATION). Gastrointestinal events (see ADVERSE REACTIONS) may increase when XENICAL is taken with a diet high in fat (>30% total daily calories from fat). The daily intake of fat should be distributed over three main meals. If XENICAL is taken with any one meal very high in fat, the possibility of gastrointestinal effects increases.

Patients should be strongly encouraged to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene (see DOSAGE AND ADMINISTRATION). In addition, the levels of vitamin D and beta-carotene may be low in obese patients compared with non-obese subjects. The supplement should be taken once a day at least 2 hours before or after the administration of XENICAL, such as at bedtime.

Table 9 illustrates the percentage of adult patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during 1 and 2 years of therapy in studies in which patients were not previously receiving vitamin supplementation.

Table 9 Incidence of Low Vitamin Values on Two or More Consecutive Visits (Nonsupplemented Adult Patients With Normal Baseline Values — First and Second Year)

	Placebo*	XENICAL*
Vitamin A	1.0%	2.2%
Vitamin D	6.6%	12.0%
Vitamin E	1.0%	5.8%
Beta-carotene	1.7%	6.1%

*Treatment designates placebo plus diet or XENICAL plus diet

Table 10 illustrates the percentage of adolescent patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during the 1-year study.

Table 10 Incidence of Low Vitamin Values on Two or More Consecutive Visits (Pediatric Patients With Normal Baseline Values*)

	Placebo†	XENICAL†
Vitamin A	0.0%	0.0%
Vitamin D	0.7%	1.4%
Vitamin E	0.0%	0.0%
Beta-carotene	0.8%	1.5%

*All patients were treated with vitamin supplementation throughout the course of the study
†Treatment designates placebo plus diet or XENICAL plus diet

Some patients may develop increased levels of urinary oxalate following treatment with XENICAL. Caution should be exercised when prescribing XENICAL to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.

Weight-loss induction by XENICAL may be accompanied by improved metabolic control in diabetics, which might require a reduction in dose of oral hypoglycemic medication (eg, sulfonylureas, metformin) or insulin (see CLINICAL STUDIES).

Misuse Potential

As with any weight-loss agent, the potential exists for misuse of XENICAL in inappropriate patient populations (eg, patients with anorexia nervosa or bulimia). See INDICATIONS AND USAGE for recommended prescribing guidelines.

Information for Patients

Patients should read the Patient Information before starting treatment with XENICAL and each time their prescription is renewed.

Drug Interactions

Alcohol

In a multiple-dose study in 30 normal-weight subjects, coadministration of XENICAL and 40 grams of alcohol (eg, approximately 3 glasses of wine) did not result in alteration of alcohol pharmacokinetics, orlistat pharmacodynamics (fecal fat excretion), or systemic exposure to orlistat.

Cyclosporine

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine (see WARNINGS).

Digoxin

In 12 normal-weight subjects receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not alter the pharmacokinetics of a single dose of digoxin.

Fat-soluble Vitamin Supplements and Analogues

A pharmacokinetic interaction study showed a 30% reduction in beta-carotene supplement absorption when concomitantly administered with XENICAL. XENICAL inhibited absorption of a vitamin E acetate supplement by approximately 60%. The effect of orlistat on the absorption of supplemental vitamin D, vitamin A, and nutritionally-derived vitamin K is not known at this time.

Glyburide

In 12 normal-weight subjects receiving orlistat 80 mg three times a day for 5 days, orlistat did not alter the pharmacokinetics or pharmacodynamics (blood glucose-lowering) of glyburide.

Nifedipine (extended-release tablets)

In 17 normal-weight subjects receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not alter the bioavailability of nifedipine (extended-release tablets).

Oral Contraceptives

In 20 normal-weight female subjects, the treatment of XENICAL 120 mg three times a day for 23 days resulted in no changes in the ovulation-suppressing action of oral contraceptives.

Phenytoin

In 12 normal-weight subjects receiving XENICAL 120 mg three times a day for 7 days, XENICAL did not alter the pharmacokinetics of a single 300-mg dose of phenytoin.

Pravastatin

In a 2-way crossover study of 24 normal-weight, mildly hypercholesterolemic patients receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not affect the pharmacokinetics of pravastatin.

Warfarin

In 12 normal-weight subjects, administration of XENICAL 120 mg three times a day for 16 days did not result in any change in either warfarin pharmacokinetics (both R- and S-enantiomers) or pharmacodynamics (prothrombin time and serum Factor VII). Although undercarboxylated osteocalcin, a marker of vitamin K nutritional status, was unaltered with XENICAL administration, vitamin K levels tended to decline in subjects taking XENICAL. Therefore, as vitamin K absorption may be decreased with XENICAL, patients on chronic stable doses of warfarin who are prescribed XENICAL should be monitored closely for changes in coagulation parameters.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in rats and mice did not show a carcinogenic potential for orlistat at doses up to 1000 mg/kg/day and 1500 mg/kg/day, respectively. For mice and rats, these doses are 38 and 46 times the daily human dose calculated on an area under concentration vs time curve basis of total drug-related material.

Orlistat had no detectable mutagenic or genotoxic activity as determined by the Ames test, a mammalian forward mutation assay (V79/HPRT), an in vitro clastogenesis assay in peripheral human lymphocytes, an unscheduled DNA synthesis assay (UDS) in rat hepatocytes in culture, and an in vivo mouse micronucleus test.

When given to rats at a dose of 400 mg/kg/day in a fertility and reproduction study, orlistat had no observable adverse effects. This dose is 12 times the daily human dose calculated on a body surface area (mg/m²) basis.

Pregnancy

Teratogenic Effects: Pregnancy Category B.

Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryotoxicity or teratogenicity. This dose is 23 and 47 times the daily human dose calculated on a body surface area (mg/m²) basis for rats and rabbits, respectively.

The incidence of dilated cerebral ventricles was increased in the mid- and high-dose groups of the rat teratology study. These doses were 6 and 23 times the daily human dose calculated on a body surface area (mg/m²) basis for the mid- and high-dose levels, respectively. This finding was not reproduced in two additional rat teratology studies at similar doses.

There are no adequate and well-controlled studies of XENICAL in pregnant women. Because animal reproductive studies are not always predictive of human response, XENICAL is not recommended for use during pregnancy.

Nursing Mothers

It is not known if orlistat is secreted in human milk. Therefore, XENICAL should not be taken by nursing women.

Pediatric Use

The safety and efficacy of XENICAL have been evaluated in obese adolescent patients aged 12 to 16 years. Use of XENICAL in this age group is supported by evidence from adequate and well-controlled studies of XENICAL in adults with additional data from a 54-week efficacy and safety study and a 21-day mineral balance study in obese adolescent patients aged 12 to 16 years. Patients treated with XENICAL had a mean reduction in BMI of 0.55 kg/m² compared with an average increase of 0.31 kg/m² in placebo-treated patients (p=0.001). In both adolescent studies, adverse effects were generally similar to those described in adults and included fatty/oily stool, oily spotting, and oily evacuation. In a subgroup of 152 orlistat and 77 placebo patients from the 54-week study, changes in body composition measured by DEXA were similar in both treatment groups with the exception of fat mass, which was significantly reduced in patients treated with XENICAL compared to patients treated with placebo (-2.5 kg vs -0.6 kg, p=0.033). Because XENICAL can interfere with the absorption of fat-soluble vitamins, all patients should take a daily multivitamin that contains vitamins A, D, E, K, and beta-carotene. The supplement should be taken at least 2 hours before or after XENICAL (see CLINICAL PHARMACOLOGY: Other Short-term Studies; CLINICAL STUDIES: Pediatric Clinical Studies; ADVERSE REACTIONS: Pediatric Patients). XENICAL has not been studied in pediatric patients below the age of 12 years.

Geriatric Use

Clinical studies of XENICAL did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

ADVERSE REACTIONS

Commonly Observed (based on first year and second year data – XENICAL 120 mg three times a day versus placebo):

Gastrointestinal (GI) symptoms were the most commonly observed treatment-emergent adverse events associated with the use of XENICAL in the seven double-blind, placebo-controlled clinical trials and are primarily a manifestation of the mechanism of action. (Commonly observed is defined as an incidence of ≥5% and an incidence in the XENICAL 120 mg group that is at least twice that of placebo.)

Table 11 Commonly Observed Adverse Events

Adverse Event	Year 1 XENICAL* % Patients (N=1913)	Year 1 Placebo* % Patients (N=1466)	Year 2 XENICAL* % Patients (N=613)	Year 2 Placebo* % Patients (N=524)
Oily Spotting	26.6	1.3	4.4	0.2
Flatus with Discharge	23.9	1.4	2.1	0.2
Fecal Urgency	22.1	6.7	2.8	1.7
Fatty/Oily Stool	20.0	2.9	5.5	0.6
Oily Evacuation	11.9	0.8	2.3	0.2
Increased Defecation	10.8	4.1	2.6	0.8
Fecal Incontinence	7.7	0.9	1.8	0.2

*Treatment designates XENICAL three times a day plus diet or placebo plus diet

These and other commonly observed adverse reactions were generally mild and transient, and they decreased during the second year of treatment. In general, the first occurrence of these events was within 3 months of starting therapy. Overall, approximately 50% of all episodes of GI adverse events associated with orlistat treatment lasted for less than 1 week, and a majority lasted for no more than 4 weeks. However, GI adverse events may occur in some individuals over a period of 6 months or longer.

Discontinuation of Treatment

In controlled clinical trials, 8.8% of patients treated with XENICAL discontinued treatment due to adverse events, compared with 5.0% of placebo-treated patients. For XENICAL, the most common adverse events resulting in discontinuation of treatment were gastrointestinal.

Incidence in Controlled Clinical Trials

The following table lists other treatment-emergent adverse events from seven multicenter, double-blind, placebo-controlled clinical trials that occurred at a frequency of ≥2% among patients treated with XENICAL 120 mg three times a day and with an incidence that was greater than placebo during year 1 and year 2, regardless of relationship to study medication.

Table 12 Other Treatment-Emergent Adverse Events From Seven Placebo-Controlled Clinical Trials

Body System/ Adverse Event	Year 1 XENICAL* % Patients (N=1913)	Year 1 Placebo* % Patients (N=1466)	Year 2 XENICAL* % Patients (N=613)	Year 2 Placebo* % Patients (N=524)
Gastrointestinal System				
Abdominal Pain/ Discomfort	25.5	21.4	–	–
Nausea	9.1	7.9	2.8	2.7
Infectious Diarrhea	5.3	4.4	–	–
Rectal Pain/Discomfort	5.2	4.0	3.3	1.9
Tooth Disorder	4.3	3.1	2.9	2.3
Gingival Disorder	4.1	2.9	2.0	1.5
Vomiting	3.8	3.5	–	–
Respiratory System				
Influenza	39.7	36.2	–	–
Upper Respiratory Infection	38.1	32.8	26.1	25.8
Lower Respiratory Infection	7.8	6.6	–	–
Ear, Nose & Throat Symptoms	2.0	1.6	–	–
Musculoskeletal System				
Back Pain	13.9	12.1	–	–
Pain Lower Extremities	–	–	10.8	10.3
Arthritis	5.4	4.8	–	–
Myalgia	4.2	3.3	–	–
Joint Disorder	2.3	2.2	–	–
Tendonitis	–	–	2.0	1.9
Central Nervous System				
Headache	30.6	27.6	–	–
Dizziness	5.2	5.0	–	–
Body as a Whole				
Fatigue	7.2	6.4	3.1	1.7
Sleep Disorder	3.9	3.3	–	–
Skin & Appendages				
Rash	4.3	4.0	–	–
Dry Skin	2.1	1.4	–	–
Reproductive, Female				
Menstrual Irregularity	9.8	7.5	–	–
Vaginitis	3.8	3.6	2.6	1.9
Urinary System				
Urinary Tract Infection	7.5	7.3	5.9	4.8
Psychiatric Disorder				
Psychiatric Anxiety	4.7	2.9	2.8	2.1
Depression	–	–	3.4	2.5
Hearing & Vestibular Disorders				
Otitis	4.3	3.4	2.9	2.5
Cardiovascular Disorders				
Pedal Edema	–	–	2.8	1.9

*Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
– None reported at a frequency ≥2% and greater than placebo

In the 4-year XENDOS study, the general pattern of adverse events was similar to that reported for the 1- and 2-year studies with the total incidence of gastrointestinal-related adverse events occurring in year 1 decreasing each year over the 4-year period.

Other Clinical Studies or Postmarketing Surveillance

Rare cases of hypersensitivity have been reported with the use of XENICAL. Signs and symptoms have included pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis. Very rare cases of bullous eruption, increase in transaminases and in alkaline phosphatase, and exceptional cases of hepatitis that may be serious have been reported. No causal relationship or physiopathological mechanism between *hepatitis and orlistat* therapy has been established. Reports of decreased prothrombin, increased INR and unbalanced anticoagulant treatment resulting in change of hemostatic parameters have been reported in patients treated concomitantly with orlistat and anticoagulants.

In clinical trials in obese diabetic patients, hypoglycemia and abdominal distension were also observed.

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine (see WARNINGS).

Pediatric Patients

In clinical trials with XENICAL in adolescent patients ages 12 to 16 years, the profile of adverse reactions was generally similar to that observed in adults.

OVERDOSAGE

Single doses of 800 mg XENICAL and multiple doses of up to 400 mg three times a day for 15 days have been studied in normal weight and obese subjects without significant adverse findings.

Should a significant overdose of XENICAL occur, it is recommended that the patient be observed for 24 hours. Based on human and animal studies, systemic effects attributable to the lipase-inhibiting properties of orlistat should be rapidly reversible.

DOSAGE AND ADMINISTRATION

The recommended dose of XENICAL is one 120-mg capsule three times a day with each main meal containing fat (during or up to 1 hour after the meal).

The patient should be on a nutritionally balanced, reduced-calorie diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed over three main meals. If a meal is occasionally missed or contains no fat, the dose of XENICAL can be omitted.

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 (see PRECAUTIONS: General). The supplement should be taken at least 2 hours before or after the administration of XENICAL, such as at bedtime.

Doses above 120 mg three times a day have not been shown to provide additional benefit.

Based on fecal fat measurements, the effect of XENICAL is seen as soon as 24 to 48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to *pretreatment levels within 48 to 72 hours.*

The safety and effectiveness of XENICAL beyond 4 years have not been determined at this time.

HOW SUPPLIED

XENICAL is a dark-blue, hard-gelatin capsule containing pellets of powder.

XENICAL 120 mg Capsules: Dark-blue, two-piece, No. 1 opaque hard-gelatin capsule imprinted with Roche and XENICAL 120 in light-blue ink — bottle of 90 (NDC 0004-0256-52).

Storage Conditions

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed.

XENICAL should not be used after the given expiration date.

Distributed by:

Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

27898887

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