Orlistat Nonprescription Briefing Document
Joint Nonprescription Drugs Advisory Committee and
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NDA 21-887
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Table of Contents

SUMMARY

The National Institutes of Health's 2000 *Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*[1] defines normal weight as a body mass index (BMI) of 18.5 – 24.9 kg/m^2, overweight as a BMI of 25 – 29.9 kg/m^2, and obese as a BMI $\geq$ 30 kg/m^2.

The *Guide* recommends weight loss through a combination of diet modification, increased physical activity, and behavior therapy for obese patients, and for patients who are overweight or have a high-risk waist circumference, when accompanied by two or more risk factors. In the event that lifestyle changes do not promote weight loss after 6 months, drugs should be considered as adjunctive therapy for select patients who have a BMI $\geq$ 30 kg/m^2, or a BMI $\geq$ 27 kg/m^2 if concomitant obesity-related risk factors or disease exist. This mirrors FDA's current approach to the evaluation and approval of prescription weight-loss drugs.

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

FDA's *Guidance for the Clinical Evaluation of Weight-Control Drugs* provides two criteria to judge the efficacy of prescription weight-loss drugs: 1) The mean drug-associated weight loss exceeds the mean placebo-associated weight loss by at least 5% or 2) The proportion of subjects who reach and maintain a loss of at least 5% of their initial body weight is greater in subjects on drug than in those on placebo.

The efficacy benchmark of 5% is based on evidence that, in obese individuals, clinically meaningful improvements in blood pressure, cholesterol, glycemic control, and other metabolic and cardiovascular risk factors can be achieved with as little as a 5% reduction in body weight[2].

Obesity and overweight tend to be chronic conditions[3]. Successful drug treatment is therefore expected to be chronic. To assess the long-term efficacy and safety of prescription weight-loss drugs, FDA currently recommends that pre-approval trials be at least one year in duration.

Orlistat 120 mg three times a day (tid) was approved in 1999 as a prescription agent for long-term weight loss in adults with a BMI $\geq$ 30 kg/m^2 or a BMI $\geq$ 27 kg/m^2 with co-morbidities. The drug is only indicated for use in conjunction with a reduced-calorie diet

1 NIH Publication Number 00-4084: The Practical Guide: Identification, Evaluation and Treatment of Overweight and Obesity in Adults, U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, October 2000.
2 Goldstein DJ, et al. Am J Clin Nutr. 1994 Nov;60(5):647-57.
3 Yanovski SZ, et al. N Engl J Med. 2002 Feb 21;346(8):591-602.

containing approximately 30% fat. Orlistat induces weight loss by blocking hydrolysis of triglyceride in the stomach and small intestine, thereby inhibiting absorption of approximately 30% of dietary fat.

GlaxoSmithKline (GSK), the sponsor of the nonprescription orlistat NDA, seeks to market over-the-counter orlistat 60 to 120 mg tid to promote short-term weight loss (i.e., $\leq$ 6 months) in "overweight" adults. Overweight has been defined by the sponsor to encompass a broad range of BMIs, from overweight to obese. The orlistat 120 mg dose will continue to be marketed as a prescription product for weight loss in adults with a BMI $\geq$ 30 kg/m^2 or a BMI $\geq$ 27 kg/m^2 with co-morbidities.

Efficacy

The weight-loss efficacy of the 60 mg tid dose of orlistat was studied in the first year of two 2-year trials from the original prescription NDA in subjects with BMIs ranging from 30 - 43 kg/m^2 in one study and 28 - 43 kg/m^2 in the other as part of the prescription NDA, and in a 4-month trial designed specifically for the nonprescription NDA in subjects with BMIs of 25 - 28 kg/m^2.

Given the sponsor's proposal to market nonprescription orlistat for short-term use, the 6-month time point was chosen as the efficacy endpoint of interest from the two prescription NDA clinical studies. In these studies, which were pooled due to similar study designs and patient populations, 42% of subjects treated with orlistat 60 mg, 45% of subjects treated with orlistat 120 mg, and 23% of those treated with placebo achieved a weight loss of $\geq$ 5% at six months ($p < 0.001$, orlistat vs. placebo).

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

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

These findings raise the possibility that orlistat may be less effective in mildly overweight individuals (i.e., BMIs 25 - 28 kg/m^2) than in obese subjects. However, since the sponsor has not studied the effects of 6 months of orlistat therapy in mildly overweight subjects, this is pure speculation.

Table. Summary of Weight Loss (Kg) From Two 6-Month Studies and One 4-Month Study ITT Population

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

LOCF data, ITT Population, all sites

Orlistat-induced weight loss was associated with small favorable changes in lipids, fasting glucose, and blood pressure.

It is well known that once treatment with any weight-loss drug is stopped, lost weight tends to be regained and improvement in co-morbidities reversed. This pattern of weight change has been observed in long-term trials with orlistat[4].

Safety

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

Safety concerns with orlistat include the potential for reduced absorption of fat-soluble vitamins and drugs. In studies conducted under the original prescription NDA, mean plasma concentrations of vitamins D and E and beta-carotene were shown to be statistically significantly lower after one and two years of treatment with either orlistat 60 or 120 mg compared to placebo. Orlistat may also reduce serum concentrations of vitamin K and inhibit the absorption of lipid-soluble drugs such as cyclosporine and amiodarone.

The labeling for prescription orlistat recommends that all patients take a multivitamin supplement that contains fat-soluble vitamins and beta-carotene once a day at least two hours before or after administration of orlistat. Prompted by reports of transplant patients developing subtherapeutic levels of cyclosporine following treatment with orlistat, labeled recommendations include avoiding the contemporaneous administration of cyclosporine with orlistat, taking cyclosporine at least two hours before or after orlistat, and checking serum cyclosporine levels. Due to the potential for reductions in vitamin K,

4 Davidson M, et al. JAMA. 1999. Jan 20;281(3):235-242.

the prescription orlistat labeling further advises that patients on warfarin be monitored closely for changes in coagulation parameters.

Given the lack of a learned intermediary in the nonprescription setting, it is vital that labeling of nonprescription orlistat adequately communicate risk information. However, preliminary evidence suggests that nonprescription labeling may not adequately direct the safe use of orlistat. In a pilot Actual Use study, after reading the Drug Facts sheet for nonprescription orlistat, only 35% of subjects taking medication for diabetes mellitus correctly stated the drug was not appropriate for their use. Moreover, 50% of patients on cyclosporine or warfarin failed to realize that they should not take orlistat while on these medications.

Other potential safety issues with orlistat include nephrolithiasis, cholelithiasis, hepatitis, and possibly pancreatitis, although the causative role of orlistat in these conditions remains inconclusive, and in the case of pancreatitis, currently under investigation.

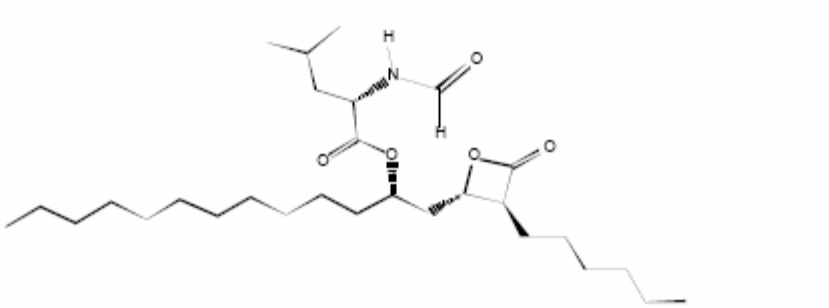
Several published case reports document the use of orlistat as a purgative in women with bulimia nervosa. The off-label use or misuse of orlistat would obviously take on greater significance in the nonprescription marketplace due to ease of access to the drug.

The sponsor's proposal to market nonprescription orlistat to overweight and obese adults raises a number of questions, the most fundamental being: Has GlaxoSmithKline provided sufficient evidence that the potential benefits of short-term orlistat therapy outweigh the potential risks when targeted to overweight and obese individuals without principal involvement of a learned intermediary?

1 INTRODUCTION AND BACKGROUND

1.1 Product Information

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



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

1.2 Currently Available Drug Treatments for Weight Loss

1.2.1 Prescription drugs

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

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

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

1.2.2 Nonprescription drugs

Benzocaine is currently category III for weight control efficacy under the draft weight loss monograph. Category III means that the drug has not been determined to be GRAS/GRAE (Generally Recognized as Safe/Effective). Benzocaine is not currently marketed in the US for a weight loss indication.

Phenylpropanolamine (PPA)-containing nonprescription drugs such as Dexatrim were removed from the market in 2000 due to concern that PPA increased the risk for hemorrhagic stroke.

1.3 Availability of Proposed Active Ingredient in the United States

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

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

Important labeling distinctions between orlistat and other approved weight-loss medications include: 1) its approval for use in children, aged 12-16 years, and 2) the inclusion of results of the XENDOS trial, which suggest that orlistat-related weight loss delays the onset of type 2 diabetes in subjects with impaired oral glucose tolerance at baseline.

1.4 Clinical Pharmacology

The pharmacology and pharmacokinetics of orlistat and its metabolites were thoroughly reviewed for the approval of the prescription orlistat NDA. This section will briefly discuss the pharmacodynamic effect of orlistat, namely, fecal fat excretion, for the 60 mg dose. Fecal fat was measured in the dose-ranging study BM14150 (see Section 2 for study description). After 24 weeks of tid treatment, the subjects receiving 60 mg had a mean increase in fecal fat content of 15.4 g/day and those receiving 120 mg had a mean increase of fecal fat content of 18.5 g/day (Table 1.4.A). There was no appreciable change in the amount of fecal fat excreted by the placebo-treated groups after 24 weeks (-0.1 g/day). Therefore, approximately 25% of dietary fat absorption was inhibited by orlistat 60 mg and approximately 30% by orlistat 120 mg. This suggests the pharmacodynamic effect is less than dose-proportional at doses greater than 60 mg.

Table 1.4.A. Summary Statistics of Daily Fecal Fat Excretion (grams/24 hours) Over Time (Observed Data; 72 hour Fecal Fat Collection) Intent-to-Treat Population; Study BM14150

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

GSK Doc ID: 0900233c8032b59e
NDA Document Page: 83 of 589

These findings are corroborated by fecal fat results obtained in the phase 3 study NM14161 (see Section 2 for study description), in which mean fecal fat excretion was increased from the start of double-blind treatment by approximately 16 g/day in the orlistat 60 mg group and by 21 g/day in the orlistat 120 mg group after 52 and 104 weeks. There was little change in the amount of fecal fat excreted by placebo-treated patients at these time points. These results indicate that the pharmacologic effect of orlistat is maintained over 2 years.

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

2 STUDY DESCRIPTIONS

Seven studies were submitted in support of the orlistat nonprescription NDA. Studies BM14149, NM14161, BM14150, and NM14302 were performed under the original prescription orlistat NDA. As Table 2.A illustrates, BMI ranged in these studies from 28 - 43 kg/m^2, doses ranged from 30 - 240 mg, and duration ranged from six months to two years.

Study NM17247 was the pivotal study conducted under the nonprescription orlistat IND, and is the only placebo-controlled trial that studied individuals with a BMI of 25 - 28 kg/m^2. The only orlistat dose used in this trial was 60 mg. The study was four months in duration. The data from this study in addition to that of studies BM14149 and NM14161 were combined to present the efficacy of the orlistat 60 mg dose.

Studies NM17285 and RCH-ORL-002 were also conducted under the nonprescription orlistat IND and were the Actual Use and Consumer Use studies, respectively. The Actual Use study has been reviewed in detail by Dr. Karen Feibus, medical officer in the Office of Nonprescription Products. The results of studies NM17285 and RCH-ORL-002 will be presented in this document as they relate to the efficacy and safety evaluation.

Table 2.A. Listing of Studies to be Included in Nonprescription NDA for Orlistat

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

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

Adapted from GSK Doc ID: 0900233c8032b59e
NDA Document Page: 2 of 5

2.1 Efficacy Studies

2.1.1 Screening

All efficacy studies included screening assessments performed within 21 or 28 days prior to entry into the study. Screening included the subjects' medical history, physical examination (including body weight), electrocardiogram, measurement of laboratory and safety parameters (vital signs), and a pregnancy test (when appropriate). Tables 2.1.1.A and 2.1.1.B outline the inclusion and exclusion criteria for the efficacy studies (BM14149, NM14161, and NM17247).

Table 2.1.1.A. Inclusion Criteria for 60 mg Phase III Studies			
	NM14161	**BM14149**	**NM17247**
Age: ≥ 18 years	X	X	X
Gender: men and non-pregnant women	X	X	X
BMI (kg/m^2):			
28-43		X	
30-43	X		
25-28			X

Table 2.1.1.B. Exclusion Criteria for 60 mg Phase III Studies			
	NM14161	**BM14149**	**NM17247**
Weight loss > 4 kg 3 months prior to screening	X	X	
Weight loss ≥ 3 kg 3 months prior to screening			X
GI surgery for weight reduction	X	X	X
Myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty within 6 months prior to screening	X	X	X
Uncontrolled hypertension	X	X	
Chronically treated psychiatric/neurologic disorders	X	X	X
Lactating females	X	X	X
Excessive alcohol intake; use of substances of abuse	X	X	X
Change in smoking habit / cessation 6 months prior	X	X	X
Drug treated diabetes	X	X	X
Clinically significant abnormal lab results	X	X	X
Inability to comply with protocol requirements	X	X	X
Recent clinical trial participation, any orlistat trial	X	X	X
History/presence of significant:			
GI disorders	X	X	X
Cardiac, renal, hepatic, endocrine disorders	X	X	
Recurrent nephrolithiasis	X	X	
Symptomatic cholelithiasis	X	X	X
Post surgical adhesions	X	X	
Active peptic ulcer disease or malabsorption syndromes	X	X	X
Pancreatic enzyme deficiency or pancreatitis	X	X	X
Cancer except resected basal cell carcinoma of skin	X	X	
Bulimia or laxative abuse	X	X	X
Hypo/Hyperthyroidism unless euthyroid and controlled on stable dose of medication for at least 6 months			X
Drugs administered for the first time or withdrawn during the past 6 months which have significant impact on body weight			X
Use of certain medications, including appetite suppressants and lipid lowering drugs			X
Use of certain medications during 8 weeks before the screening period, including appetite suppressants and lipid soluble vitamin supplements	X	X	

2.1.2 Randomization

In studies BM14149 and NM14161, subjects were stratified by amount of weight lost during the lead-in phase in order to balance the placebo and drug-treated groups in terms of probable success in weight loss with diet alone. Subjects who lost 2 kg or less were

assigned randomization codes sequentially within stratum 1; subjects who lost greater than 2 kg were assigned randomization codes sequentially within stratum 2. In these studies, regardless of stratification, subjects were randomized to treatment groups through the sequential assignment of randomization codes.

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

2.1.3 Study design

The original objectives of study BM14149 were to determine the long-term weight control effect of 60 mg orlistat, 120 mg orlistat, or placebo, all administered tid in combination with dietary counseling for two years, and to determine the long-term tolerability of orlistat. Subjects (BMI 28 - 43 kg/m^2) were placed on a hypocaloric diet [(basal metabolic rate x 1.3) - 600 kcal/d] with 30% calories as fat during a 4-week placebo lead-in period. Subjects were not provided with a multivitamin. On day 1, subjects were randomized to placebo or orlistat in a 1:1:1 ratio. The minimum allowable prescribed caloric level was 1200 kcal/d. If at any time during the study a subject achieved a BMI $\leq$ 22 kg/m^2 on two consecutive visits, the caloric intake was increased to achieve weight stability by recalculating the diet based on the formula 1.3 x BMR minus 10% kcal/d. Dietary adjustments were made at the end of 24 weeks (i.e., -300 additional kcal/day or 1000 kcal/d for those prescribed 1200 kcal/d at screening). At the end of 52 weeks, subjects were placed on a eucaloric diet and maintained on the same drug treatment regimen for the next 52 weeks of the study. If during therapy a subject's BMI was $\leq$ 20 on two sequential visits, the visit at which the second BMI was determined would be considered the final visit.

The original objectives of study NM14161 were to determine the long-term weight control effect of 60 mg orlistat, 120 mg orlistat, or placebo, all administered tid for two years, and to determine the long-term tolerability of orlistat. Obese subjects (BMI 30 - 43 kg/m^2) were placed on a hypocaloric diet (1200 kcal/d if screening weight was < 90 kg, 1500 kcal/d if screening weight was $\geq$ 90 kg) with 30% calories as fat during a 4-week placebo lead-in period. Subjects were not provided with a multivitamin. On day 1, subjects were randomized to placebo or orlistat in a 1:1:1 ratio. At the end of 52 weeks, the daily prescribed caloric intake was increased by 300 kcal/d for those subjects who lost more than 3 kg between weeks 48 and 52. Subjects who lost < 3 kg during this period were considered relatively weight stable and had no dietary adjustment. If any subject lost sufficient weight that his/her BMI became $\leq$ 18 kg/m^2, the visit at which that BMI was determined was considered the final visit, and the study would be considered complete for that subject.

Study NM17247 was a multi-center, double-blind, randomized, placebo-controlled trial conducted under the nonprescription orlistat IND. The objectives were to determine the weight loss effect of orlistat 60 mg or placebo administered tid in combination with a hypocaloric diet over a 4-month duration and to determine the safety and tolerability of orlistat 60 mg tid over four months. This study consisted of two periods:

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

The caloric intake assignment was as follows:

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

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

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

2.1.4 Lifestyle Intervention

In all studies, a hypocaloric diet containing approximately 30% of calories from fat was prescribed for the weight loss portions of the studies. However, lifestyle intervention differed somewhat between studies BM14149, NM14161, and NM17247 (Table 2.1.4.A), such that studies NM14161 and NM17247 were considered by GSK to have 'minimal' intervention. Nevertheless, the amount of intervention described below involves some degree of contact with health professionals, as well as varying degrees of requirements for completing food records.

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

completion of the diet diaries. Subjects then met regularly throughout the study with the study dietitian for continued dietary counseling and diary review. Subjects were counseled on attaining their dietary goals and adherence to the prescribed diet. Diaries were completed 15 times during the one-year treatment period.

In study NM14161, a 3-day comprehensive diary of food and beverage intake was completed to help subjects monitor food intake. At week -4, subjects received brief instructions on how to complete the food intake records accurately, and they subsequently viewed a video on food records to reinforce the skills learned. Subjects recorded all food and beverages consumed for a period of three consecutive days (which included two weekdays and one weekend day). The diaries were completed at seven time points in the first year (as compared with 15 in study BM14149). Food intake records were analyzed by food analysis software. No feedback based on these dietary records were given to the subjects, nor were the results of the food record analyses communicated to the physicians or staff until the subjects had completed the study. Although no group meetings or counseling sessions were held, at four points during the first year, subjects viewed on their own one of four videos, which were based on a behavioral support program *Wise Weighs* (developed by the University of Minnesota) and covered topics such as goal-setting, exercise, identifying 'food cues' and characteristics of successful weight maintainers.

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

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

However, the original sponsor of this study, Hoffman-La Roche, states in the NM17247 study report that dietary instruction was provided at each treatment visit and dietary compliance was checked with the use of food diaries. They also note, however, that this study was conducted in a primary care setting without the use of dieticians or behavior modification specialists in order to mimic how the compound might be used in a real-world setting.

At the beginning of study NM17247, each subject received a Dietary/Lifestyle Information Binder. These materials were initially developed for use with orlistat as part of the XeniCare® Program, the behavioral support program used in conjunction with the prescription drug. The original XeniCare® materials were revised for the study to reflect the 60 mg dosage. These revisions were described as providing a more consumer-

friendly, self-instructional approach. The purpose of these materials was to reinforce dietary compliance while the subject was participating in the study. They were incorporated into the Dietary/Lifestyle Information Binder with the following tabbed sections and topics:

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

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

Table 2.1.4.A. Diet, Behavior Modification, and Exercise across all Controlled Double-Blind Studies

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

PLA=placebo

2.1.5 Compliance

During specified clinic visits, the subject returned his/her entire drug supply (including empty, full, and partially full blister cards/plates/bottles) to the clinic and a staff member counted the number of capsules returned by the subject and calculated the number of capsules consumed. A comment indicating the reason why all blister cards or bottles were not returned was added to the case report form. Compliance in all studies was assessed on the basis of number of capsules taken per day.

In studies BM14149 and NM14161, subjects were counseled about remaining diligent to the treatment if compliance to drug treatment fell below 75% at any visit. The consumption of less than 70% of capsules was considered 'noncompliant'. Cumulative compliance was used to determine whether subjects were considered eligible for evaluation at the various study time points, and overall compliance was considered to determine whether subjects were evaluable for standard efficacy analysis at critical time points. As is discussed in Section 3.4.1, the intent-to-treat (ITT) population comprised all randomized subjects who received at least one dose of study medication and had body weight measurements before and after randomization, and therefore, did not appear to take medication compliance into account. Given that this drug will be used in a

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

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

2.1.6 Pooling

To support the efficacy of the orlistat 60 mg dose, data from the first year (weight loss phase) of the prescription orlistat NDA phase 3 two-year studies BM14149 and NM14161 were analyzed pooled together (hereafter referred to as 'pooled studies' in the efficacy portion of this document) as well as individually, with an emphasis on the 6-month time point. The efficacy data from study NM17247 were presented separately.

2.2 Safety and Supporting Studies

Study NM14302 included a 60 mg treatment arm but was not included in the evaluation of efficacy because the main objective of this study was to assess the efficacy of orlistat in preventing weight regain after six months of diet-induced weight loss. This study is pooled with studies BM14149 and NM14161 in the analysis of safety. The original objectives of study NM14302 were to determine the weight loss maintenance and prevention of weight gain effects of orlistat (30 mg, 60 mg, or 120 mg) or placebo tid for 52 weeks after losing weight by conventional diet therapy. During the 24-week lead-in period, subjects (BMI 28 - 38 kg/m^2) were placed on a hypocaloric diet [(BMR x 1.3) - 1000 kcal/d] with 30% calories as fat. On day 1, subjects who lost at least 8% of their initial body weight were randomly assigned to receive orlistat or placebo in a 1:1:1:1 randomization to be administered for 52 weeks. On day 1, subjects were placed on a eucaloric diet.

The phase 2 study BM14150 was a 24-week dose-ranging study conducted under the original prescription NDA. This study evaluated orlistat at doses of 30, 60, 120, and 240 mg compared to placebo in subjects with BMIs 28 - 43 kg/m^2. It is a supportive study in this nonprescription NDA, and its results are presented separately. The original objectives were to determine the weight loss effect and tolerability of orlistat 30 mg, 60 mg, 120 mg, and 240 mg versus placebo, in combination with a hypocaloric diet [(BMR x 1.3) - 600 kcal/d] and 30% of calories as fat for 24 weeks.

Study NM14185 from the original prescription NDA also contained a 60 mg treatment arm but was not included in the current NDA since treatment with orlistat 60 mg tid occurred only after one year of treatment with orlistat 120 mg tid. The safety database is limited to some extent because study NM14185, as well as two other studies from the original NDA that included only the 120 mg dose (i.e., those without a separate 60 mg dose arm), were excluded. This reviewer will refer, when appropriate, to the prescription NDA review for relevant safety data for the 120 mg dose.

Study NM17285 was the Actual Use trial, and as stated previously, has been reviewed in detail by Dr. Feibus. The primary objectives of this study were to evaluate the ability of consumers to correctly select orlistat for their own use based on labeled directions, to provide initial information regarding how consumers use orlistat in the absence of physician supervision, and to evaluate the adverse event profile in an actual use setting. The study was designed as a multi-center, pharmacy-based, open-label, 3-month trial. Subjects were self-selecting individuals 18 years of age or older, who were able to give written informed consent and able and available to participate in telephone follow-up interviews. Notable exclusion criteria included: allergy to orlistat; previously treated with Xenical; treated with medication for diabetes, warfarin, or cyclosporine; or pregnant or breast feeding. Subjects were instructed to take 1-2 capsules (60-120 mg) three times a day for up to six months. The following materials were included in an 'OTC package': one bottle of 90 orlistat 60 mg capsules, the Orlistat User Guide, a Personal Food Diary, a Pocket Fat Gram Counter, a Fat Gram Wheel and a portion size information card. In addition, the Orlistat Diet Success Planner was provided to each purchaser with the first purchase. The Orlistat Diet Success Planner provided lifestyle information designed to help consumers in their weight loss efforts. The package received in repeat purchases was identical to that of the first purchase. Subjects could purchase up to three product packages of 90 count bottles of 60 mg capsules at any one time and were not limited on how often they could return to the pharmacy for additional drug.

Study RCH-ORL-002 was a 4-week Consumer Use study administered in a naturalistic setting. The primary objective was to determine the feasibility and consumer satisfaction of 60 mg orlistat given three times a day plus diet over a 4-week in-home-use period. RCH-ORL-002 was designed as an open-label, multi-center, non-randomized, uncontrolled study in which subjects were recruited by mall intercept. Recruitment for this study took place at 16 shopping malls in the United States, where shoppers were intercepted and a concept interview was performed. The interview consisted of model questions, attributes, category usage, and demographics. Any subjects expressing "Top Three Box" purchase intent (i.e., definitely would buy, probably would buy, might or might not buy) were eligible for being a candidate subject to participate in the clinical portion of the study. Subjects were then asked to read and sign an informed consent form. A West Pharmaceutical Services (WPS) nurse reviewed the consent via telephone and addressed and responded to all study-related questions. Notable inclusion criteria included: having an interest in losing weight; being considered by the shopping mall research agency interviewer and the Central Medical Operations Group (CMOG), composed of a nurse and physician from WPS, to be motivated to participate in and complete the study as instructed; understanding and signing an informed consent form; being in good health as assessed by a medical history conducted by the CMOG of WPS; and being willing and able to use the study drug and complete the diary as instructed, participate in the follow-up telephone interview, and return the unused product, product packaging material, and diary at the end of the study. Notable exclusion criteria included: BMI < 27 kg/m^2 based on self-reporting, being pregnant or breastfeeding, chronic malabsorption, gallbladder problems, taking cyclosporine or warfarin, or having an eating disorder such as anorexia nervosa or bulimia. The enrolled subjects were instructed to use the study drug during the 4-week study period according to the label on

the drug bottle, the Product Information Sheet (adaptation of the approved package insert of Xenical), and the Product Brochure (modified from the patient brochure currently in use by patients taking Xenical). The subjects received the Project Information Sheet and the Product Brochure along with the study drug after enrollment. During the 4-week study period, subjects were told to take 60 mg of orlistat 3 times a day with diet. Subjects were also instructed to take daily multivitamins and to eat a nutritionally balanced, reduced-calorie diet containing no more than 30% fat. The enrolled subjects were instructed to record product usage, concomitant medications, initial and final body weight, and adverse events on a diary during the study period.

3 EFFICACY

3.1 Discussion of Endpoints

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

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

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

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

The efficacy benchmark of 5% used for prescription weight-loss drugs is based on evidence that, in obese individuals, clinically meaningful improvements in blood pressure, cholesterol, glycemic control, and other metabolic and cardiovascular risk factors can be achieved with as little as a 5% reduction in body weight[2].

Obesity is considered a chronic condition[3], and it is assumed that in order to reap clinical benefit from drug-induced weight loss, drug treatment must be maintained long-term or chronically. As such, it is difficult to define the clinical benefits of short-term treatment with orlistat.

This issue is further complicated by the fact that no data exist to support the clinical benefits of weight loss in subjects who are mildly overweight (i.e., BMI range of 25 - 27 kg/m^2). In fact, some evidence suggests that the overweight BMI range of 25 - < 30 kg/m^2 is not associated with increased mortality, and that those with a BMI of 25 kg/m^2 have a lower mortality risk than individuals with BMIs below or above this value[5]. Moreover, there is some suggestion that the positive relationship with BMI and risk of death decreases with age. In fact, weight loss is generally not recommended in the aging population without a concerted effort by the health practitioner to rule out concomitant disease; manage medications; address nutritional issues such as adequate protein, vitamin

5 Flegal KM, et al. JAMA. 2005 Apr 20;293(15):1861-7.

D, and calcium; and minimize loss of lean body mass and bone mass[6]. Issues related to orlistat in the aging population are further discussed in Section 5.2.

Ultimately, the benefits of weight loss are considered to be due to the reduction of risk for co-morbidities. However, in addressing the purported clinical benefits of weight loss the sponsor states in the NDA that, "serum lipid concentrations and blood pressure are not included in the integrated summary of efficacy [section in the nonprescription NDA]. This is mainly because the [nonprescription] indication is to promote weight loss and all other benefits achieved from orlistat would be most appropriately handled under the supervision of a physician."

GlaxoSmithKline appears to be saying that overweight individuals with weight-related co-morbidities such as type 2 diabetes, hypertension, or dyslipidemia are inappropriate candidates for nonprescription orlistat because weight loss in such patients will require management by a physician to ensure that such changes will favorably alter overall cardiovascular risks.

It is difficult to imagine the proposed dichotomization of the target population into mildly-to-moderately overweight adults with and without weight-related co-morbidities, with the former appropriate, and the latter inappropriate for nonprescription orlistat, succeeding in the real-world setting.

The data on lipids, blood pressure, and carbohydrate metabolism were provided by the sponsor in the Integrated Summary of Safety rather than the Efficacy section of their NDA. This reviewer is therefore including these findings in Section 4 of this document, the safety review.

3.2 Subject Enumeration

Table 3.2.A enumerates subjects in the various efficacy analysis populations by study and treatment group. The percentage of subjects completing the 6-month time point in the pooled studies was similar between orlistat 60 mg- and 120 mg-treated groups (~81%). The orlistat groups in the pooled studies had a slightly higher rate of completion than the placebo group (~75%).

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

6 Villareal DT, et al. Am J Clin Nutr. 2005 Nov;82(5):923-34.

Table 3.2.A. Overview of Analysis Populations: Weight Loss in Overweight and Obese Subjects during 4-6 Months of Treatment				
Population	**Pooled Studies (NM14161 and BM14149)**	**Study BM14149**	**Study NM14161**	**Study NM17247**
Enrolled	1579	783	796	498
Randomized	1371	729	642	391
Intent to Treat				
Placebo	448	236	212	184
60 mg tid	452	239	213	194
120 mg tid	451	241	210	N/A
Completers*				
Placebo	341 (74.6%)	185 (76.1%)	156 (72.9%)	140 (71.8%)
60 mg tid	367 (80.5%)	198 (81.8%)	169 (79.0%)	152 (77.6%)
120 mg tid	373 (81.4%)	202 (82.8%)	171 (79.9%)	N/A
*Completers were defined as all subjects who did not have any protocol violations thought to affect efficacy and completed at least 22 weeks of treatment and had efficacy measurements between 154 and 182 days in the pooled studies and as all subjects who were randomized and completed 113 days of treatment in study NM17247.				

Adapted from GSK Doc ID: 0900233c8035b481
NDA Document Page: 27 of 53

3.3 Demographics

The majority of subjects in the studies were female (Tables 3.3.A and 3.3.B). In the pooled studies as well as study NM17247, a slightly higher proportion of subjects in the 60 mg group than in the placebo or 120 mg groups were male. Most subjects were White and had a mean age of 43 years in the pooled studies and 46 years in study NM17247. Very few randomized subjects were ≥ 65 years old. The mean initial weight in the pooled studies (weight before the lead-in period), mean baseline weight in study NM17247, and mean baseline BMI were similar across all treatment groups in the pooled studies and in study NM17247, although not between studies.

This reviewer has bolded the BMI groups 25 - 28 and 28 - 30 kg/m^2 in Table 3.3.A in order to highlight the number of overweight subjects in the pooled studies [approximately 50-60 subjects (10-12%) per group]. Therefore, the pooled studies are considered to be made up of a primarily obese population (and may be referred to as such), as compared to study NM17247, which is made up of subjects in the 25 - 28 kg/m^2 BMI range, a low-overweight range.

Table 3.3.A. Demographics and Baseline Characteristics – Studies BM14149 and NM14161						
	Placebo (N=448)		Orlistat 60 mg tid (N=452)		Orlistat 120 mg tid (N=451)	
	N	(%)	n	(%)	N	(%)
Sex						
Male	78	(17.4)	103	(22.8)	84	(18.6)
Female	370	(82.6)	349	(77.2)	367	(81.4)
Age Group						
< 65 years	438	(97.8)	442	(97.8)	439	(97.3)
≥ 65 years	10	(2.2)	10	(2.2)	12	(2.7)
Race						
Caucasian	428	(95.5)	436	(96.5)	423	(93.8)
Black	16	(3.6)	11	(2.4)	20	(4.4)
Hispanic	4	(0.9)	2	(0.4)	6	(1.3)
Other Race	0	(0.0)	3	(0.7)	2	(0.4)
BMI at Baseline (kg/m^2)						
≥ 25 to 28	**8**	**(1.8)**	**6**	**(1.3)**	**4**	**(0.9)**
≥ 28 to 30	**49**	**(10.9)**	**41**	**(9.1)**	**51**	**(11.3)**
≥ 30 to 35	178	(39.7)	211	(46.7)	198	(43.9)
≥ 35	213	(47.5)	194	(42.9)	198	(43.9)
Age (years)						
Mean SD	43.1 +/- 10.33		43.7 +/- 10.87		43.4 +/- 10.80	
(Min, Max)	(18, 71)		(20, 72)		(18, 78)	
Initial Weight (kg)						
Mean +/- SD	99.64 +/- 14.750		99.69 +/- 14.475		98.51 +/- 14.126	
(Min, Max)	(67.4, 155.5)		(68.9, 152.0)		(68.4, 147.3)	
BMI at Baseline (kg/m^2)						
Mean +/- SD	34.82 +/- 4.010		34.59 +/- 3.788		34.42 +/- 3.611	
(Min, Max)	(26.7, 45.9)		(26.7, 42.7)		(27.1, 42.8)	
ITT Population						

GSK Doc ID: 0900233c8035b481
NDA Document Page: 29 of 53

Table 3.3.B. Demographics and Baseline Characteristics – Study NM17247				
	Placebo (N=184)		Orlistat 60 mg tid (N=194)	
	N	(%)	N	(%)
Sex				
Male	9	(4.9)	12	(6.2)
Female	175	(95.1)	182	(93.8)
Age Group				
< 65 years	176	(95.7)	182	(93.8)
≥ 65 years	8	(4.3)	12	(6.2)
Race				
Caucasian	165	(89.7)	172	(88.7)
Black	12	(6.5)	18	(9.3)
Hispanic	0	(0.0)	1	(0.5)
Other Race	7	(3.8)	3	(1.5)
BMI Group (kg/m^2)				
< 25	4	(2.2)	5	(2.6)
≥ 25 to 28	161	(87.5)	167	(86.1)
≥ 28 to 30	19	(10.3)	22	(11.3)
Age (years)				
Mean +/- SD	46.6 +/- 10.91		45.8 +/- 11.89	
Median	47.0		45.0	
(Min, Max)	(19, 72)		(20, 80)	
N	184		194	
Baseline Weight (kg)				
Mean +/- SD	72.76 +/- 6.61		72.76 +/- 6.97	
(Min, Max)	(56.2, 89.8)		(57.4, 102.5)	
BMI at Baseline (kg/m^2)				
Mean +/- SD	26.84 +/- 0.944		26.82 +/- 0.960	
(Min, Max)	(23.7, 28.6)		(24.5, 29.0)	
ITT Population				

Adapted from GSK Doc ID: 0900233c8035b481
NDA Document Page: 30 of 53

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

3.4 Statistical Considerations

3.4.1 Analysis populations

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

pooled studies, the observed ITT population analysis was similar to a completer analysis, except that it included all subjects who reached the 6-month time point, not just that of the 'completers' (those without important protocol violations).

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

This reviewer will be presenting efficacy analyses using the ITT LOCF population, with the exception of the presentation of body weight change over time (Section 3.5.1.2), which uses the ITT observed population. Although a LOCF analysis may provide more information than a completer or observed analysis, in a case where a greater number of subjects from the placebo group discontinued the study due to lack of efficacy and a greater number of subjects from the orlistat groups discontinued due to adverse events, a LOCF analysis could be favorably biased towards orlistat. This reviewer evaluated all of the population analyses that were provided. In general, it appears that the different population analyses provided similar results; therefore, the impact of such bias appears minimal.

3.4.2 Study windows

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

3.4.3 Hypothesis testing

In the pooled studies, the primary efficacy analysis was the comparison of weight change from baseline to 24 weeks in the 60 mg tid treatment group to placebo using the ITT population. The pooled studies were originally designed to study the weight loss effect of orlistat plus a hypocaloric diet for one year, with a second year of orlistat or placebo plus a eucaloric diet to assess weight maintenance. Because the intent of this application is to market orlistat as a nonprescription product for a 6-month treatment duration, the 6-month time point was used as the primary efficacy time point in the nonprescription NDA.

Analysis of covariance (ANCOVA) was used to compare change in weight from baseline to six months among treatment groups. The factors in the model were study, site nested

within study, category of lead-in period weight loss (≤ 2 kg, >2 kg), baseline weight, and, in some cases, site by baseline weight interaction. Least squares means were computed for the treatment groups and each of the orlistat treatment groups was compared to the placebo group. Comparisons of 5% responder rates between each orlistat group and the placebo group were conducted using the Fisher's exact test.

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

Because the responder analysis is considered the primary analysis of interest, it will be presented first in the efficacy section of this document (Section 3.5.1.1).

3.4.3.1 Body weight measurement

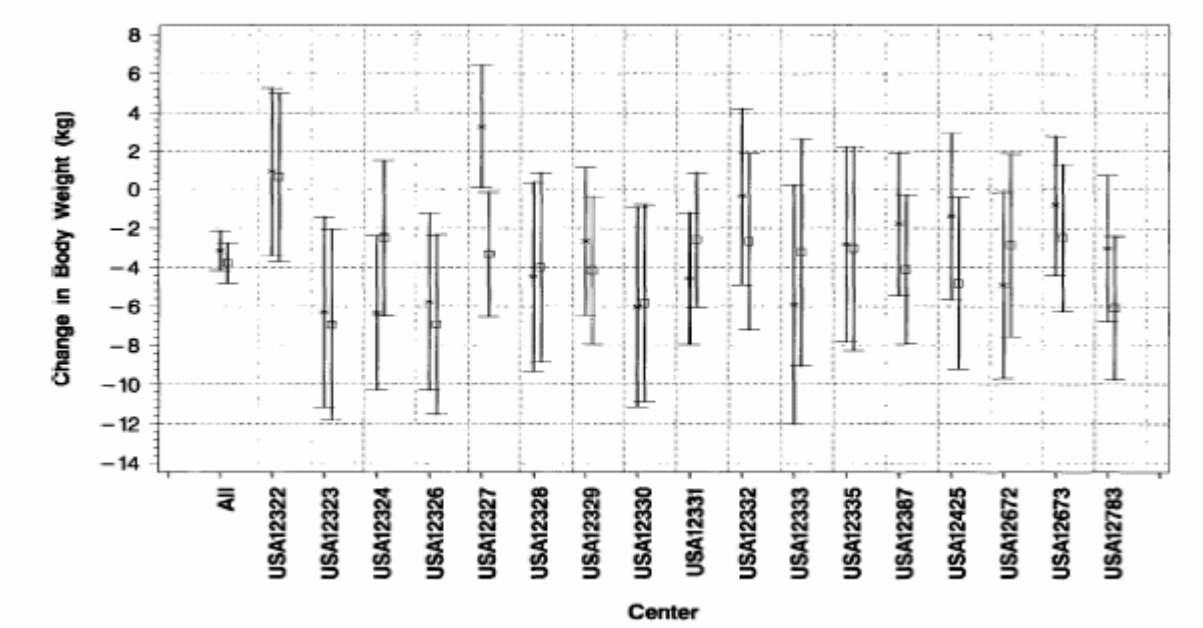
In all three studies, body weight was recorded at every visit with subjects wearing light indoor clothing, and no shoes, outerwear, or accessories. Body weight was measured in kilograms and recorded to one decimal place, using the same calibrated scale every time to ensure consistent weight measurements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

3.4.4 Site outlier

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

The orlistat 60 mg group at this site actually saw a mean weight gain, as presented in Figure 3.4.4.A below. (Although there is not a legend associated with this figure, it is presumed that the lines on the left represent orlistat 60 mg and lines on the right represent orlistat 120 mg.)

Figure 3.4.4.A. Study NM14161: 95% Confidence Intervals for Change in Body Weight at 52 Weeks; Difference from Placebo in LS Mean; Intent-to-Treat Population



The sponsor was requested to provide analyses that include this site, and therefore all sites are presented in the adjusted mean analyses for pooled studies in this document. In general, the conclusions are similar to those in which the site is excluded.

3.5 Efficacy Findings

3.5.1 Body Weight

3.5.1.1 Responder Analysis

Table 3.5.1.1.A describes the categorical weight loss in the pooled studies (obese population) using the ITT LOCF population. A statistical analysis was only performed on the ≥ 5% category. As seen below, a similar proportion of subjects randomized to the orlistat 60 and 120 mg doses reached the ≥ 5% benchmark after six months (42% and 45%, respectively). This was highly statistically significant for both groups versus placebo (23%). Results were similar in the ITT observed population (≥ 5% weight loss in 26%, 47%, and 49% of placebo, orlistat 60 mg, and orlistat 120 mg treatment groups, respectively; $p < 0.001$ orlistat vs. placebo) and the 6-month completers population (29%, 49%, and 52%, respectively; $p < 0.001$ orlistat vs. placebo).

In all analysis populations it appears that both orlistat 60 and 120 mg also had a higher rate of individuals losing at least 10% of body weight than placebo at six months, although statistical testing was not done.

Table 3.5.1.1.A. Percent Body Weight Change from Baseline to 6 Months – LOCF ITT Population						
Studies: BM14149, NM14161						
	Placebo (N=448)		**Orlistat 60 mg tid (N=452)**		**Orlistat 120 mg tid (N=451)**	
Weight Change from Baseline	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Gained ≥ 5%	13	(2.9)	6	(1.3)	6	(1.3)
Gained ≥ 0 - < 5%	138	(30.8)	76	(16.8)	59	(13.1)
Lost > 0 - < 5%	194	(43.3)	179	(39.6)	185	(41.0)
Lost ≥ 5 - <10%	78	(17.4)	125	(27.7)	124	(27.5)
Lost ≥ 10%	25	(5.6)	66	(14.6)	77	(17.1)
Total	448	(100.0)	452	(100.0)	451	(100.0)
Lost ≥ 5%	**103**	**(23.0)**	**191**	**(42.3)**	**201**	**(44.6)**
P-value vs. Placebo (Fisher's exact test)			**<0.001**		**<0.001**	

GSK Doc ID: 0900233c8035b481
NDA Document Page: 1 of 1

In study NM17247, the difference in the percent of subjects achieving a 5% weight loss in the orlistat versus placebo-treated subjects did not reach statistical significance (Table 3.5.1.1.B). The percent of subjects achieving a 3% weight loss was significantly greater for the orlistat- compared to the placebo-treated subjects, however (Table 3.5.1.1.C). Results were similar for the completers population (≥ 5%: 35% vs. 45%, placebo vs. orlistat, respectively, p = 0.142; ≥ 3%: 51% vs. 67%, p = 0.004). A 3% weight loss is not a recognized efficacy benchmark by the Division of Metabolism and Endocrinology Products.

Table 3.5.1.1.B. Subjects who Lost ≥ 5% of Baseline Body Weight by 4 months – Study NM17247					
	Placebo		**Orlistat 60 mg tid**		**P-value[a]**
Observed Data	36.2%	(50/138)	43.5%	(67/154)	0.206
LOCF	28.3%	(52/184)	36.1%	(70/194)	0.104
[a] from Fisher's exact test					

GSK Doc ID: 0900233c8035b481
NDA Document Page: 35 of 53

Table 3.5.1.1.C. Subjects who Lost ≥ 3% of Baseline Body Weight by 4 months – Study NM17247					
	Placebo		**Orlistat 60 mg tid**		**P-value[a]**
Observed Data	51.4%	(71/138)	66.9%	(103/154)	0.007
LOCF	41.8%	(77/184)	56.7%	(110/194)	0.004
[a] from Fisher's exact test					

Adapted from GSK Doc ID: 0900233c8032b59e
NDA Document Page: 51 of 744

It is of some interest to note that while the proportion of 5% responders at four months in the orlistat 60 mg group (36%) was slightly less than the 60 mg group in the 6-month pooled studies (42%), the proportion of responders in the placebo group from study NM17247 was somewhat higher than that of the placebo group in the pooled studies (28% vs. 23%, respectively). It is difficult to attribute all of this placebo effect to differences in dietary counseling between the studies; therefore, one consideration is whether subjects in this lower BMI group are more successful with dietary treatment than those in the higher BMI groups, resulting in a lesser drug effect. This will be addressed further in Section 3.5.1.3, in the discussion of the placebo-subtracted adjusted mean body weight change.

Finally, although one might not necessarily expect a significantly greater number of orlistat- versus placebo-treated subjects to achieve 5% weight loss as early as four months, it is notable that in the pooled studies BM14149 and NM14161, which included patients with higher baseline BMIs than those in study NM17247, a statistically significantly greater number of orlistat 60 mg-treated subjects compared with placebo-treated subjects reached this benchmark at four months (33.6% vs. 17.4%; $p < 0.001$). These findings further support the possibility that orlistat may be less effective in overweight compared with obese individuals.

3.5.1.2 Body Weight Change over Time

In the pooled studies, NM14161 and BM14149, all treatment groups lost similar amounts of weight during the 4-week placebo lead-in period. Weight loss was seen as early as 15 days after randomization. At 4 weeks, a separation of the weight loss effect was apparent from baseline values, with reduction of 1.01%, 1.69%, and 1.81% for placebo, 60 mg, and 120 mg respectively (Table 3.5.1.2.A).

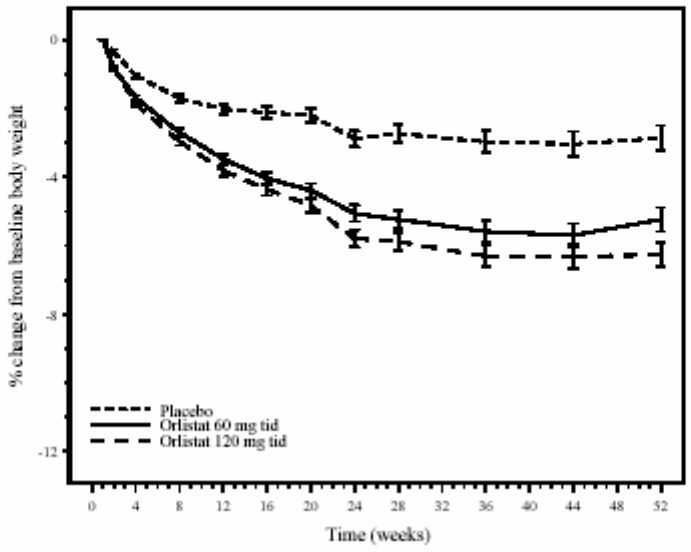
The mean percent reduction from baseline weight at the end of 24 weeks was 2.55%, 4.95%, and 5.65% for placebo, orlistat 60 mg, and orlistat 120 mg treatment groups, respectively; equivalent to an unadjusted placebo-subtracted percent weight loss at 24 weeks of 2.4% for orlistat 60 mg and 3.1% for orlistat 120 mg. Although not the time point of interest in the current application, the 52-week results are also relevant, since conceivably some individuals will continue to take the medication beyond the labeled 6 months in a nonprescription setting. Observed weight loss is graphically represented in Figure 3.5.1.2.A, and corroborates the claim that weight loss in the orlistat 60 and 120 mg groups is very similar early on in the studies (up to 24 weeks).

Table 3.5.1.2.A. Body Weight over Time; ITT Population, Pooled Studies										
Treatment Group	**Study Day**	**Value (kg) at Scheduled Visit**			**Change from Baseline Value**			**% Change from Baseline Value**		
		N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Placebo	Week -4	446	99.64	14.750	446	2.49	2.035	446	2.63	2.120
	Day 1	448	97.16	14.704	448	0.00	0.000	448	0.00	0.000
	Week 4	439	96.09	14.502	439	-0.96	1.450	439	-1.01	1.509
	Week 12	422	95.16	15.127	422	-1.94	3.420	422	-2.05	3.497
	Week 24	387	94.47	15.424	387	-2.41	4.561	387	-2.55	4.711
	Week 52	304	93.81	16.015	304	-2.40	5.963	304	-2.60	6.200
60 mg tid	Week -4	450	99.69	14.475	450	2.53	2.089	450	2.66	2.186
	Day 1	452	97.26	14.392	452	0.00	0.000	452	0.00	0.000
	Week 4	449	95.67	14.352	449	-1.62	1.556	449	-1.69	1.574
	Week 12	445	93.70	14.778	445	-3.59	3.521	445	-3.75	3.619
	Week 24	407	92.71	15.390	407	-4.73	5.014	407	-4.95	5.088
	Week 52	349	92.16	15.923	349	-5.00	6.217	349	-5.24	6.294
120 mg tid	Week -4	450	98.51	14.126	450	2.52	2.213	450	2.67	2.303
	Day 1	451	95.97	13.791	451	0.00	0.000	451	0.00	0.000
	Week 4	446	94.27	13.677	446	-1.73	1.430	446	-1.81	1.503
	Week 12	441	92.13	13.926	441	-3.89	3.600	441	-4.09	3.734
	Week 24	408	90.48	14.312	408	-5.36	4.920	408	-5.65	5.129
	Week 52	352	89.97	14.737	352	-5.68	6.122	352	-5.97	6.307

Adapted from GSK Doc ID: 0900233c8035b481
NDA Document Page: 1 of 2

Figure 3.5.1.2.A.

Mean percent change (±SEM) from baseline weight over time - BM14149 and NM14161

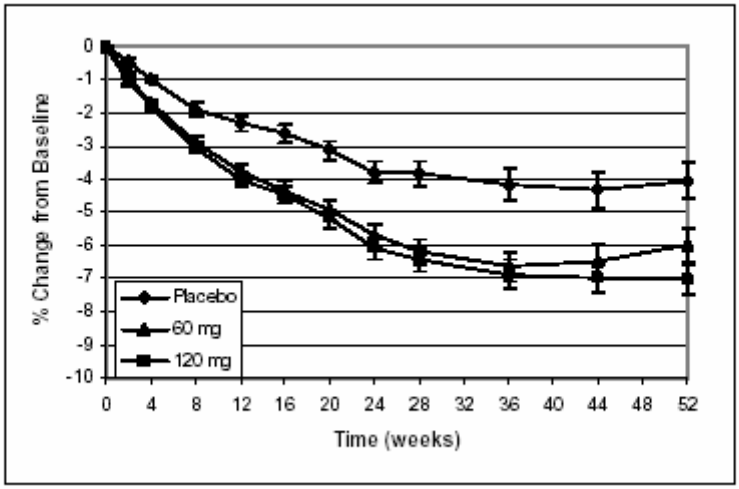


GSK Doc ID: 0900233c8035b481
NDA Document Page: 32 of 53

The graphical representation of percent weight loss over time is particularly interesting when comparing the two phase 3 studies (Figures 3.5.1.2.B and 3.5.1.2.C). BM14149, the study with intensive dietary intervention, demonstrates a robust placebo response, whereas study NM14161, the study with less dietary intervention, demonstrates a minimal placebo response and less weight loss in all groups over time.

Figure 3.5.1.2.B.

Mean percent change (±SEM) from baseline weight over time - study BM14149

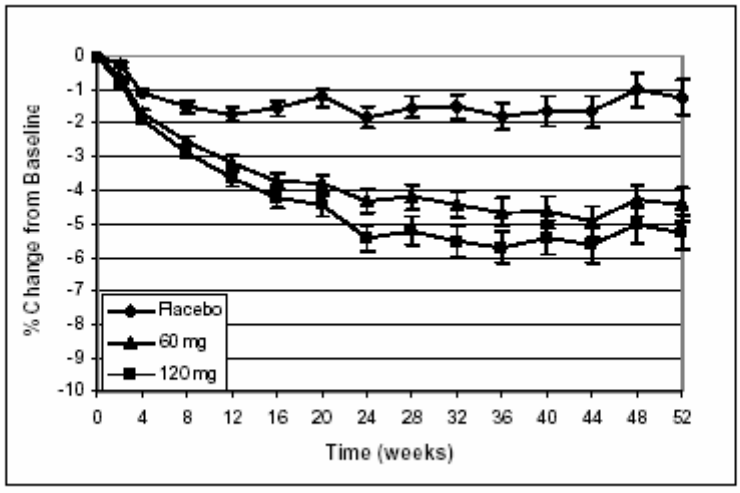


ITT population, observed data

GSK Doc ID: 0600233c8022fed6

Figure 3.5.1.2.C.

Mean percent change (±SEM) from baseline weight over time - study NM14161



ITT population, observed data

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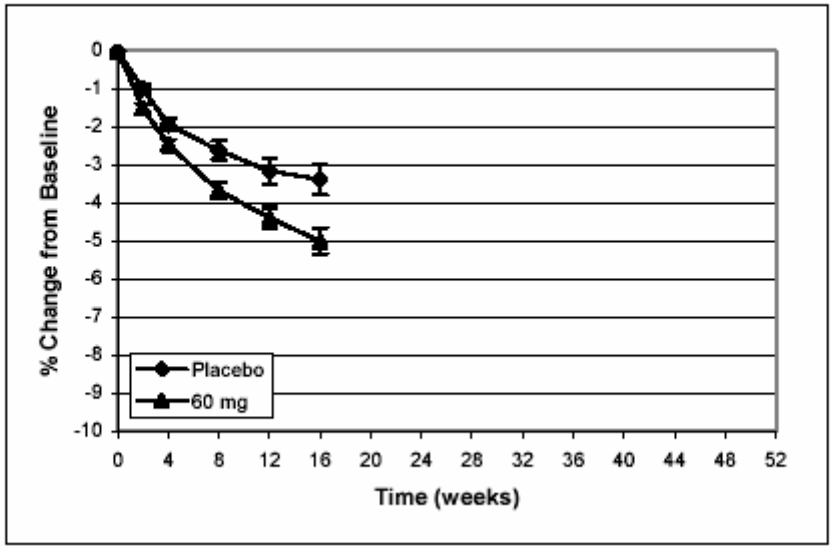
In study NM17247, after 15 days of treatment after randomization, weight loss from baseline was 0.73 kg (1.00%) and 1.10 kg (1.51%) for placebo and orlistat 60 mg, respectively. As illustrated in Figure 3.5.1.2.B, after 16 weeks of treatment the mean percent weight reduction from baseline was 2.45 kg (3.38%) and 3.65 kg (5.00%) for

subjects randomized to placebo and orlistat 60 mg, respectively; equivalent to a 1.6% placebo-subtracted weight loss (similar to the placebo-subtracted percent weight loss at week 12 in the pooled studies; see Table 3.5.1.2.A, above). Results were similar for the completers population and somewhat lower in each treatment group in the LOCF ITT population (2.70% versus 4.25%, respectively).

Figure 3.5.1.2.D.

Mean percent change (±SEM) from baseline weight over time - study NM17247



ITT population, observed data

3.5.1.3 Differences in Mean Weight Change (4-6 Months)

Table 3.5.1.3.A demonstrates that there was a statistically significant difference in weight loss between placebo and both the 60 mg and 120 mg orlistat treatment groups in all clinical studies at the time point of interest (six months, pooled studies; four months, NM17247). The least mean square analyses for the ITT observed and completers populations were similar.

Table 3.5.1.3.A. Least Squares Mean Differences from Placebo at 6 Months (Weight in kg); LOCF ITT, All Study Sites

			Difference from Placebo		
Study	**Treatment Group**	**Adjusted Mean Change from BL +/- SE**	**Adjusted Mean +/- SE**	**95% Confidence Interval**	**P-Value**
BM14149	Placebo	-2.88 ± 0.318			
	Orlistat 60 mg	-4.89 ± 0.311	-2.02 ± 0.433	(-2.87, -1.17)	<0.001
	Orlistat 120 mg	-5.19 ± 0.314	-2.32 ± 0.430	(-3.16, -1.47)	<0.001
NM14161	Placebo	-0.85 ± 0.310			
	Orlistat 60 mg	-3.37 ± 0.306	-2.52 ± 0.430	(-3.36, -1.67)	<0.001
	Orlistat 120 mg	-4.21 ± 0.307	-3.36 ± 0.434	(-4.21, -2.50)	<0.001
Pooled Studies	Placebo	-1.88 ± 0.223			
	Orlistat 60 mg	-4.14 ± 0.218	-2.29 ± 0.308	(-2.89, -1.68)	<0.001
	Orlistat 120 mg	-4.71 ± 0.221	-2.88 ± 0.309	(-3.49, -2.28)	<0.001
NM17247*	Placebo	-1.90			
	Orlistat 60 mg	-3.05	-1.15 ± 0.31	(-1.76, -0.54)	<0.001

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

The phase 3 study with intensive dietary intervention (NM14149) demonstrated greater weight loss in all groups, including placebo; however, the placebo-subtracted weight loss was numerically lower in this study than in the phase 3 study with less dietary intervention (NM14161). Adjusted mean weight loss in the placebo group in study NM14161 was much lower than that seen in other studies, including the study in subjects with a lower BMI (NM17247). The orlistat 60 mg adjusted mean difference from placebo is numerically less in study NM17247 than in the other studies, probably due to a combination of the lower baseline body weight and the shorter study duration.

It is important to highlight the absolute degree of placebo-corrected weight loss seen in the above studies. For example, in study NM17247 (a lower baseline BMI population to which the nonprescription product is being targeted), one might question the clinical relevance of a 1.2 kg weight loss. Furthermore, in this population, the amount of weight loss conceivably attributable to the diet (1.9 kg, weight loss in the placebo-treated group) is somewhat greater than that attributable to the drug (1.2 kg, placebo-subtracted weight loss).

Because of the mechanism of action of orlistat, weight loss is likely to be undermined by compensating for the decrease in fat intake/absorption by an increase in carbohydrate or protein intake, and by excessive snacking. Ostensibly, those who lose weight on orlistat without making the necessary lifestyle adjustments will regain weight as soon as the drug is withdrawn. Therefore, compliance with a hypocaloric diet, with fat intake distributed among three meals per day, is critical for successful use of the drug. However, given the degree of interaction with the health care provider, the above studies cannot address how well individuals will comply with the provided materials or benefit without the aid of a learned intermediary.

3.5.1.4 Differences in Mean Weight Change (One Year)

The following data, derived from the original study reports from studies BM14149 and NM14161, are provided to demonstrate that although weight loss remains durable over one year, the absolute amount of placebo-subtracted weight loss is still modest; particularly in study BM14149, the phase 3 study with intensive dietary intervention. It is also notable that there is loss of statistical significance in the orlistat 60 mg group at one year in the completers population in this study. This may be a reflection of the benefit that intensive dietary counseling provided the placebo group, particularly in those who completed the study. Of particular interest in study NM14161 under a setting of less dietary intervention, is the minimal weight loss seen in the placebo group after one year, and relatively greater drug effect.

Table 3.5.1.4.A. Least Square Mean (LSM) Change in Body Weight (kg) from the Start of Double-Blind Treatment to End of 52 Weeks of Treatment; Study BM14149

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

Adapted from GSK Doc ID: 0900233c8032b59e
NDA Document Page: 60 of 870

Table 3.5.1.4.B. Least Square Mean (LSM) Change in Body Weight (kg) from the Start of Double-Blind Treatment to End of 52 Weeks of Treatment; Study NM14161 (all sites)

				Difference from Placebo		
Analysis Population	Treatment Group	N	LSM Change from Randomization	LSM +/- SE	95% CI	p-value
ITT	Placebo	212	-0.33			
	Orlistat 60	237	-3.48	-3.15 +/- 0.52	-4.17, -2.12	0.000
	Orlistat 120	240	-4.12	-3.78 +/- 0.56	-4.81, -2.75	0.000
Completers	Placebo	120	-1.20			
	Orlistat 60	152	-4.42	-3.22 +/- 0.79	-4.77, -1.67	0.001
	Orlistat 120	149	-5.26	-4.05 +/- 0.79	-5.61, -2.50	0.000

GSK Doc ID: 0900233c8032b59e
NDA Document Page: 324 of 1014

3.5.1.5 Subgroup Analysis

In general, the weight loss results from subgroup analyses were similar to the overall results. Lack of statistical significance for certain subgroups (non-white, ≥ 65 years, BMI ≥ 28 - 30 kg/m^2 [bolded] in pooled studies; male, ≥ 65 years, BMI ≥ 28 - 30 kg/m^2 in study NM17247) was likely due to small sample sizes and reduced statistical power. It is of interest that a population of interest in this application, the BMI group 28 - 30 kg/m^2, has only a marginal placebo-subtracted effect in the pooled studies. Although this finding may reflect low sample size, it speaks to the fact that the database has a limited number of subjects in this BMI range.

It is noted that the subjects treated with orlistat 60 mg in the highest BMI group (≥ 35 kg/m^2) actually had less absolute and placebo-adjusted weight loss than those in the moderately obese group (BMI 30 - 35 kg/m^2). This pattern was not observed for the 120 mg dose.

Table 3.5.1.5.A. Body Weight Change at 6 Months by Subgroup – BM14149 and NM14161					
	Adjusted Mean Change from Baseline			**Adjusted Mean Difference**	
Subgroup	**Placebo**	**Orlistat 60 mg tid**	**Orlistat 120 mg tid**	**60 mg vs Placebo**	**120 mg vs Placebo**
	-1.85 ± 0.718	-4.24 ± 0.599	-4.93 ± 0.689	-2.40 ± 0.856	-3.08 ± 0.915
Male	n=67	n=96	n=75	(p=0.006)	(p<0.001)
	-2.02 ± 0.264	-4.32 ± 0.261	-5.02 ± 0.253	-2.30 ± 0.357	-3.00 ± 0.348
Female	N=320	n=311	n=333	(p<0.001)	(p<0.001)
	-2.19 ± 0.251	-4.49 ± 0.239	-5.10 ± 0.241	-2.30 ± 0.334	-2.91 ± 0.335
White	N=368	n=393	n=387	(p<0.001)	(p<0.001)
	-2.67 ± 1.717	-2.38 ± 1.590	-6.59 ± 1.781	0.29 ± 1.886	-3.92 ± 1.532
Non-white	n=19	n=14	n=21	(p=0.879)	(p=0.015)
	-2.16 ± 0.247	-4.41 ± 0.235	-5.12 ± 0.238	-2.25 ± 0.332	-2.96 ± 0.331
< 65 years	N=377	n=398	n=397	(p<0.001)	(p<0.001)
	-0.79 ± 1.295	-5.50 ± 1.304	-3.55 ± 1.247	-4.71 ± 2.019	-2.76 ± 1.807
≥ 65 years	n=10	n=9	n=11	(p=0.045)	(p=0.161)
	-2.13 ± 0.660	**-4.10 ± 0.777**	**-3.76 ± 0.705**	**-1.96 ± 0.958**	**-1.63 ± 0.895**
≥ 28-30 kg/m^2	**n=45**	**n=38**	**n=48**	**(p=0.043)**	**(p=0.072)**
	-2.08 ± 0.336	-4.65 ± 0.307	-4.95 ± 0.307	-2.57 ± 0.448	-2.87 ± 0.445
≥ 30-35 kg/m^2	N=153	n=186	n=180	(p<0.001)	(p<0.001)
	-2.14 ± 0.397	-4.18 ± 0.404	-5.33 ± 0.405	-2.03 ± 0.558	-3.18 ± 0.556
≥ 35 kg/m^2	N=182	n=178	n=177	(p<0.001)	(p<0.001)

Adjusted mean change from baseline was adjusted for study, site nested in study, baseline weight, and lead-in period weight loss category. An interaction term for site by baseline weight was also included for the female, white, and < 65 years subgroups.
There were too few observations to fit a model for the BMI <28 kg/m^2 subgroup.

Adapted from GSK Doc ID: 0900233c8035b481
NDA Document Page: 39 of 53

Table 3.5.1.5.B. Body Weight Change at 4 Months by Subgroup – Study NM17247			
	Adjusted Mean Change from Baseline		Adjusted Mean Difference
Subgroup	**Placebo**	**Orlistat 60 mg tid**	
Male	-6.62 +/- 1.228	-2.56 +/- 1.237	4.06 +/- 2.275
	n=8	n=9	(p=0.149)
Female	-2.31 +/- 0.292	-3.51 +/- 0.273	-1.20 +/- 0.384
	N=130	n=145	(p=0.002)
White	-2.34 +/- 0.305	-3.56 +/- 0.278	-1.23 +/- 0.399
	N=122	n=138	(p=0.002)
Non-white	-2.07 +/- 0.493	-3.70 +/- 0.548	-1.63 +/- 0.746
	n=16	n=16	(p=0.046)
<65 years	-2.29 +/- 0.291	-3.46 +/- 0.267	-1.17 +/- 0.380
	N=131	n=145	(p=0.002)
≥ 65 years	-3.31 +/- 2.165	-4.48 +/- 2.056	-1.17 +/- 3.468
	n=7	n=9	(p=0.759)
≥ 25-28 kg/m^2	-2.47 +/- 0.308	-3.51 +/- 0.291	-1.04 +/- 0.412
	N=119	n=129	(p=0.012)
≥ 28-30 kg/m^2	-2.31 +/- 0.803	-3.85 +/- 0.590	-1.54 +/- 0.954
	n=16	n=20	(p=0.122)
Adjusted mean change from baseline is adjusted for site and baseline weight. There were too few observations to fit a model for the BMI <25 kg/m^2 subgroup.			

GSK Doc ID: 0900233c8035b481
NDA Document Page: 40 of 53

3.5.2 Body Mass Index

The following tables demonstrate the change in BMI in both obese (Table 3.5.2.A) and overweight (Table 3.5.2.B) subjects. Differences in mean BMI change in the orlistat groups were statistically significant from placebo, and reflect mean weight changes.

Table 3.5.2.A. Pooled Studies: BMI Change at 6 Months – LOCF Data, ITT Population								
	Within Treatment			Difference from Placebo				
Treatment	N	Mean Baseline Value	LS Mean Change From Baseline	LS Mean	SE	95% CI Lower	95% CI Upper	P-value
Placebo	448	34.82	-0.66					
Orlistat 60	452	34.59	-1.46	-0.81	0.11	-1.02	-0.60	<0.001
Orlistat 120	451	34.42	-1.66	-1.02	0.11	-1.23	-0.81	<0.001
Analysis was conducted for the pooled studies (BM14149, NM14161) using the ITT population and LOCF data, all sites. Adjusted means are adjusted for study, site nested in study, lead-in period weight loss (≤ 2 kg, >2 kg), baseline BMI, and treatment by site interaction. Baseline was at the end of the lead-in period, at the start of study medication.								

Adapted from GSK Doc ID: 0900233c803c393d
NDA Document Page: 1 of 3

Table 3.5.2.B. Study NM17247: BMI Change at 4 Months - LOCF Data, ITT Population								
	Within Treatment			Difference from Placebo				
Treatment	N	Mean Baseline Value	LS Mean Change From Baseline	LS Mean	SE	95% CI Lower	95% CI Upper	P-value
Placebo	184	26.84	-0.71					
Orlistat 60 mg	194	26.82	-1.12	-0.42	0.11	-0.64	-0.20	0.000

GSK Doc ID: 0900233c8032b59e
NDA Document Page: 52 of 744

3.5.3 Anthropometry

The following tables demonstrate the change in waist and hip circumference in both obese (Table 3.5.3.A) and overweight (Table 3.5.3.B) subjects.

Table 3.5.3.A. Change in Anthropometric Measurements at 6 Months – Pooled Studies, LOCF ITT

Treatment	N	Within Treatment		Difference From Placebo				
		Mean Baseline Value	LS Mean Change From Baseline	LS Mean	SE	95% CI Lower	95% CI Upper	P-Value
Waist Circumference (cm)								
Placebo	361	103.49	-3.45					
Orlistat 60	391	103.76	-4.50	-1.08	0.40	-1.86	-0.30	0.007
Orlistat 120	398	102.60	-4.79	-1.41	0.40	-2.19	-0.64	<0.001
Hip Circumference (cm)								
Placebo	360	118.32	-2.27					
Orlistat 60	391	117.42	-3.72	-1.45	0.31	-2.06	-0.83	<0.001
Orlistat 120	398	117.23	-4.24	-1.97	0.31	-2.58	-1.36	<0.001

Analysis was conducted for the pooled studies (NM14149, BM14161) using the ITT population and observed data. Adjusted means for waist circumference are adjusted for study, site nested in study, lead-in period weight loss (<2 kg, ≥2 kg), baseline waist circumference, baseline waist circumference by site nested in study interaction, and treatment by site nested in study interaction. Adjusted means for hip circumference are adjusted for study, site nested in study, lead-in weight loss, and baseline hip circumference.

Adapted from GSK Doc ID: 0900233c803c3943
NDA Document Page: 1 of 3

Table 3.5.3.B. Change in Anthropometric Measurements at 4 Months – NM17247, LOCF ITT

Treatment	N	Within Treatment		Difference From Placebo				
		Mean Baseline Value	LS Mean Change From Baseline	LS Mean	SE	95% CI Lower	95% CI Upper	P-Value
Waist Circumference (cm)								
Placebo	184	85.61	-2.73					
Orlistat 60	194	84.90	-3.70	-0.97	0.43	-1.82	-0.11	0.026
Hip Circumference (cm)								
Placebo	184	104.33	-2.64					
Orlistat 60	194	103.89	-3.44	-0.80	0.39	-1.57	-0.04	0.040
Waist/Hip Ratio								
Placebo	184	0.82	-0.01					
Orlistat 60	194	0.82	-0.01	-0.00	0.00	-0.01	0.00	0.403

GSK Doc ID: 0900233c8032b59e
NDA Document Page: 58 of 744

Since both the waist and hip circumferences decreased to a similar extent, there was no statistically significant change in waist-to-hip ratio in pooled studies (analysis not provided) or study NM17247 (Table 3.5.3.B). The sponsor comments:

Waist circumference was used as a measure of upper body obesity and hip circumference as a measure of lower body obesity. Changes in each of these measurements are better indicators of change in overweight and obese status than change in the waist:hip ratio. The reason is that when the change in waist circumference and hip circumference are similar in magnitude and direction, the ratio of waist:hip circumference will not be sensitive to these changes.

This is true; however, if one was interested in whether there were metabolic changes attributed to the weight loss, the mean change in waist-to-hip ratio might be important as an indicator of preferential loss of central adiposity. It is well-established that weight loss causes a loss in "inches", so a decrease in waist and hip circumference would be expected to be proportional to the amount of weight lost (i.e., one would expect that subjects in the orlistat group had a greater decrease in waist and hip circumference as more weight was lost in this group).

3.5.4 Quality of Life

Quality of life measures for studies BM14149 and NM14161 were performed at baseline (the beginning of the lead-in period) and after 52 weeks of treatment (or at the time of premature withdrawal). The primary measures were changes in Satisfaction with Treatment, Overweight Distress, and Depression. The self-administered questionnaire was developed and validated specifically for Hoffman-La Roche.

Quality of life scores actually decreased (i.e., became less favorable) from baseline for both orlistat- and placebo-treated groups for the majority of questions. In study BM14149 (intensive dietary counseling), the only statistically significant change in quality of life measures for the orlistat treatment groups compared to placebo was satisfaction with medication for weight loss. In study NM14161, all quality of life measures in the orlistat-treated subjects were statistically significantly different (less negative) than those in the placebo-treated group ($p < 0.01$). In the subjects randomized to placebo, these measures appear to decrease less in the study with intensive dietary counseling (BM14149) than in the study without such counseling (NM14161).

Although technically, overweight distress and depression could be considered safety measures, they are briefly mentioned here with the rest of the quality of life measures for studies BM14149 and NM14161. There was no significant difference in the orlistat-treatment groups from placebo in the overweight distress and depression scores in these two studies. Overweight distress decreases in all treatment groups in both studies. However, it is noted that the depression scores actually *increased* from baseline in all treatment groups (after an initial decrease in the placebo lead-in) for both studies.

The 3-question treatment satisfaction questionnaire that was administered in study NM17247 appears to have been the same questionnaire used in studies BM14149 and NM14161. Most treatment satisfaction assessments were similar in the placebo and orlistat treatment groups; however, a higher percentage of placebo-treated patients reported being either 'somewhat dissatisfied' or 'very dissatisfied' with both study medication and the progress of weight loss than orlistat-treated patients. Statistical testing was not performed.

3.5.5 Supportive Studies

3.5.5.1 Study BM14150

This was a phase 2 dose-ranging protocol comparing 24 weeks of treatment with orlistat 30, 60, 120, 240 mg, and placebo, in a multicenter, double-blind, randomized, double-dummy, placebo-controlled, parallel design. Subjects included men and non-pregnant females ≥ 18 years of age with a BMI 28 to 43 kg/m^2. Subjects entered the randomized treatment phase after a 4-week placebo lead-in period. Subjects received dietary counseling throughout the study.

Table 3.5.5.1.A. Number of Subjects

	Randomized	Efficacy (ITT)
Placebo	125	123
30 mg tid	122	122
60 mg tid	124	123
120 mg tid	122	120
240 mg tid	120	117

GSK Doc ID: 0900233c803c14c4
NDA Document Page: 10 of 19

Table 3.5.5.1.B demonstrates that subjects in the orlistat 60 mg tid, 120 mg tid, and 240 mg tid groups had a statistically significantly greater decrease in body weight than the placebo treatment group at Week 24. Although it appears that a greater proportion of orlistat-treated patients lost more than 10% of initial body weight than did placebo-treated patients in a dose-related manner, statistical testing on these categorical data was not provided. Similarly, a modestly greater proportion of orlistat-treated subjects lost > 5% of body weight than placebo (51.2% placebo vs. 61.8% orlistat 60 mg); although, again, statistical testing was not provided.

Table 3.5.5.1.B. Change in Body Weight, ITT Population

Parameter	Placebo	30 mg tid	60 mg tid	120 mg tid	240 mg tid
	Change in Body Weight (ITT Population)				
Difference from placebo of least squares mean change in body weight from start of double-blind treatment to Week 24 (p-value)	-	-0.95 (0.106)	-1.86 (0.002)	-2.55 (0.000)	-2.81 (0.000)
Mean % change (SD) from initial body weight at Week 24	-6.45 (5.84)	-8.49 (6.09)	-8.79 (5.99)	-9.76 (5.40)	-9.29 (5.82)
No. (%) patients losing >10% of initial body weight at Week 24	23 (18.7)	34 (27.9)	34 (27.6)	44 (36.7)	44 (37.6)

GSK Doc ID: 0900233c8032b59e
NDA Document Page: 18 of 589

3.5.5.2 Uncontrolled Studies

In support of the nonprescription indication for orlistat, the sponsor conducted two uncontrolled studies to evaluate actual use (NM17285) and use in a naturalistic setting (RCH-ORL-002):

Table 3.5.5.2.A. Level of Dietary Intervention in Uncontrolled Studies						
Study	**Dose (mg)**	**Study Duration**	**Study Design**	**Dietary Instruction and Intervention**	**Behavioral Modification**	**Exercise**
RCH-ORL-002 N = 162	60	1 month	Open-label, uncontrolled, multi-center, mall intercept	No clinical visits during study duration	Self-instructional materials	Self-instructional
NM17285 N = 237	60-120	3 months	Open-label, uncontrolled, pharmacy-based sites	No clinical visits during study duration Self-instructional materials	Self-instructional materials	Self-instructional

These studies will be discussed in more detail in Section 4 in order to address the safety issues surrounding this product in a nonprescription setting, and by FDA reviewers from the Office of Nonprescription Products. However, efficacy findings will be briefly summarized below. These studies are clearly limited by the lack of a comparator treatment group.

3.5.5.2.1 Study NM17285

Efficacy was assessed based on self-reported weight loss, measured weight loss, satisfaction with the study drug, and perceived efficacy. Although reported weight loss appears to be similar to measured weight loss (Tables 3.5.5.2.1.A and 3.5.5.2.1.B, respectively); recall bias is highly likely for the former and loss to follow-up bias is highly likely for the latter.

Note: the amount of weight lost was asked only of subjects who indicated that they had lost weight (this is shown in the first row of Table 3.5.5.2.1.A).

Table 3.5.5.2.1.A. Self-Reported Weight Loss (Users Group N=237)								
	Day 14 Interview		**Day 30 Interview**		**Day 60 Interview**		**Day 90 Interview**	
Self-Reported Weight Loss[a]	**(N=217)**		**(N=219)**		**(N=197)**		**(N=148)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects who lost weight since starting orlistat	98	(45.2)	161	(73.5)	164	(83.2)	134	(90.5)
1 - 5 pounds	71	(72.4)	81	(50.3)	47	(28.7)	24	(17.9)
6 - 10 pounds	17	(17.3)	54	(33.5)	64	(39.0)	51	(38.1)
11 - 15 pounds	3	(3.1)	9	(5.6)	27	(16.5)	29	(21.6)
16 - 20 pounds	0		2	(1.2)	11	(6.7)	11	(8.2)
21 - 25 pounds	0		0		1	(0.6)	10	(7.5)
>25 pounds	0		1	(0.6)	4	(2.4)	6	(4.5)
Missing	7	(7.1)	14	(8.7)	10	(6.1)	3	(2.2)
Mean ± SD	4.2 +/- 3.02		5.9 +/- 3.87		9.3 +/- 6.15		11.7 +/- 7.39	
Median	3		5		8		10	
Range	1 - 15		1 - 30		2 - 45		2 - 45	
N	91		147		154		131	

[a] amount of weight lost was asked only of subjects who indicated that they had lost weight

Table 3.5.5.2.1.B. Measured Weight Loss (Users Group N=237)								
	Time of Measurement[a]							
	1 - 30 Days		31-60 Days		>60 Days		Final Return Visit[b]	
Measured Weight Loss	(N=37)		(N=77)		(N=60)		(N=106)	
	N	(%)	n	(%)	n	(%)	n	(%)
Gained weight	3	(8.1)	12	(15.6)	7	(11.7)	15	(14.2)
Lost no weight	0		2	(2.6)	2	(3.3)	4	(3.8)
≤ 5 pounds	18	(48.6)	29	(37.7)	12	(20.0)	33	(31.1)
6 - 10 pounds	8	(21.6)	21	(27.3)	10	(16.7)	28	(26.4)
11 - 15 pounds	1	(2.7)	8	(10.4)	9	(15.0)	11	(10.4)
16 - 20 pounds	2	(5.4)	3	(3.9)	5	(8.3)	5	(4.7)
21 - 25 pounds	1	(2.7)	1	(1.3)	5	(8.3)	6	(5.7)
> 25 pounds	0		0		4	(6.7)	4	(3.8)
Missing	4	(10.8)	1	(1.3)	6	(10.0)	0	
Mean +/- SD	5.5 +/- 5.70		5.1 +/- 5.72		10.1+/- 11.84		7.2 +/- 9.64	
Median	4		5		8		6	
Range	-6 - 21		-7 - 24		-8 - 52		-8 - 52	
N	33		76		54		106	

[a] days from enrollment to pharmacy visit; the last measurement in each interval was tabulated
[b] measurement taken at subject's final pharmacy visit, regardless of time from enrollment

GSK Doc ID: 0900233c8032b3ea
NDA Document Page: 50 of 78

There was a mean weight loss in those subjects who returned for a weight measurement of 7.2 lbs +/- 9.6 lbs at the final visit. Interestingly, 12-15% of subjects who returned for weight measures actually gained weight after the first month. Without a placebo group, however, it is difficult to adequately evaluate the clinical significance of these findings. Again, as stated above, follow-up bias (i.e., subjects who lost weight are more likely to follow up than those who did not) may have materially influenced the weight loss results.

In terms of satisfaction with orlistat, approximately 80% of subjects indicated they were satisfied or very satisfied; most subjects reporting 'weight loss' and 'the drug was working' as reasons. The degree of satisfaction increased with the amount of weight lost. Ten (10) – 15% of subjects were not satisfied and the main reason provided (60%) was lack of weight loss. Negative side effects were the reason provided by about 25%.

Table 3.5.5.2.1.C. Satisfaction with Orlistat (Users Group N=237)								
	Day 14 Interview		Day 30 Interview		Day 60 Interview		Day 90 Interview	
	(N=217)		(N=219)		(N=197)		(N=148)	
Satisfaction	n	(%)	n	(%)	n	(%)	n	(%)
Very satisfied	65	(30.0)	70	(32.0)	61	(31.0)	56	(37.8)
Satisfied	109	(50.2)	112	(51.1)	98	(49.7)	64	(43.2)
Unsatisfied	11	(5.1)	20	(9.1)	23	(11.7)	15	(10.1)
Not at all satisfied	6	(2.8)	9	(4.1)	9	(4.6)	8	(5.4)
No answer	25	(11.5)	6	(2.7)	4	(2.0)	2	(1.4)
Missing	1	(0.5)	2	(0.9)	2	(1.0)	3	(2.0)

GSK Doc ID: 0900233c8032b3ea
NDA Document Page: 49 of 78

3.5.5.2.2 Study RCH-ORL-002

Efficacy assessments were based on body weight data before and after treatment with orlistat in 141 subjects whose self-reported weight information was available. The mean decrease in body weight was statistically significant (mean change: -8 lbs, $p < 0.001$, two-sided paired t-test); although, again, it is difficult to make much of these findings without a placebo group and considering likely reporting bias.

Table 3.5.5.2.2.A. Summary of Body Weight before and after Study Drug Usage

VARIABLE	TOTAL
Number of Subjects	141
Beginning Weight (lbs)	
Mean	214.85
SD	41.17
Range	153.0-391.0
Ending Weight (lbs)	
Mean	206.38
SD	40.64
Range	141.0-380.0
Change[a] (lbs)	
Mean	-8.29
SD	6.39
Range	-34.0-2.0

[a] Change calculated as ending weight minus beginning weight.

4 SAFETY

4.1 Subject Enumeration and Extent of Exposure

Although subject enumeration was presented in the efficacy review, this reviewer is providing the reader with a separate section on the adequacy of the safety database to support an indication for the overweight population.

In the pooled safety studies BM14149, NM14161, and NM14302 (BMI 28-43 kg/m^2), 543 (87%) of 623 subjects on orlistat 60 mg tid and 537 (85%) of 632 subjects on orlistat 120 mg tid completed at least 24 weeks of study drug treatment. In NM17247, the 4-month trial in subjects with a BMI 25-28 kg/m^2, 154 (79%) of the 196 orlistat subjects and 139 (71%) of the 195 placebo subjects were treated within the four month window (99-140 days; orlistat, maximum: 129 days; placebo, maximum: 138 days).

As seen in Table 4.1.A, in all seven studies supporting NDA 21-887 combined, there were 671 subjects with a BMI < 30 kg/m^2 exposed to orlistat 60 or 120 mg. Of these subjects, 135 and 136 in the 60 mg and 120 mg groups, respectively, were in the study for at least 24 weeks. Although this is a relatively small number of subjects with a BMI < 30 kg/m^2 who have been exposed to orlistat for greater than six months, there is a considerable body of data regarding the safety of the 120 mg dose in those with a higher BMI. Study NM14302 has a proportionately higher number of subjects with a BMI < 30 kg/m^2 because the subjects underwent six months of dietary weight loss before being randomized to drug treatment.

Table 4.1.A. Extent of Exposure in Subjects with BMI < 30 at Randomization; Safety Population

Study	Treatment Period (weeks)	Dose	N	Time on study medication					
				>1 wk n (%)	>4 wks n (%)	>12 wks n (%)	>24 wks n (%)	>36 wks n (%)	>48 wks n (%)
BM14150	24	60 mg	23	23 (100.0)	23 (100.0)	22 (95.7)	---	---	---
		120 mg	23	23 (100.0)	23 (100.0)	21 (91.3)	---	---	---
BM14149	52[a]	60 mg	33	33 (100.0)	33 (100.0)	32 (97.0)	28 (84.8)	26 (78.8)	26 (78.8)
		120 mg	43	42 (97.7)	42 (97.7)	40 (93.0)	40 (93.0)	36 (83.7)	34 (79.1)
NM14161	52[a]	60 mg	14	14 (100.0)	14 (100.0)	14 (100.0)	12 (85.7)	11 (78.6)	11 (78.6)
		120 mg	12	11 (91.7)	11 (91.7)	11 (91.7)	9 (75.0)	9 (75.0)	8 (66.7)
NM14302	52	60 mg	105	104 (99.0)	103 (98.1)	98 (93.3)	95 (90.5)	89 (84.8)	82 (78.1)
		120 mg	110	108 (98.2)	104 (94.5)	96 (87.3)	87 (79.1)	77 (70.0)	75 (68.2)
NM17247	16	60 mg	196	189 (96.4)	178 (90.8)	158 (80.6)	---	---	---
NM17285[b]	---	60-120 mg	94	94 (100.0)	80 (85.1)	37 (39.4)	---	---	---
RCH-ORL-002	4	60 mg	33	30 (90.9)	27 (81.8)	---	---	---	---

Cell entries are number and % of subjects who entered the time interval.
[a] Data from year 1 of studies BM14149 and NM14161 are tabulated.
[b] Study NM17285 (actual use study): subjects could take 1-2 60 mg capsules for up to 90 days.

GSK NDA 21-887_Response to Info Request 29 Nov 2005 (Part 2 of 2)

4.2 Demographics

Demographics and baseline characteristics for the pooled efficacy studies BM14149 and NM14161, and pivotal study NM17247 (ITT population), were presented in Section 3.3. Table 4.2.A includes study NM14302 in the other two pooled phase 3 studies for safety.

Demographic characteristics in this pooled safety population are generally balanced between treatment groups. There were slightly more males in the orlistat 60 mg group and slightly more Blacks and Hispanics in the orlistat 120 mg group. Although the distribution of placebo subjects in the BMI groups was slightly different than that of the orlistat groups, the mean weight and BMI was similar between treatment groups.

Baseline characteristics such as blood pressure, lipids, medical history, and concomitant medications were generally well-matched between treatment groups in the individual prescription phase 3 studies.

Table 4.2.A. Demographic Characteristics; Pooled Phase III Studies (BM14149, NM14161, NM14302)						
	Placebo (N=634)		**Orlistat 60 mg tid (N=623)**		**Orlistat 120 mg tid (N=632)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Sex						
Male	106	(16.7)	138	(22.2)	107	(16.9)
Female	528	(83.3)	485	(77.8)	525	(83.1)
Race						
Caucasian	594	(93.7)	591	(94.9)	578	(91.5)
Black	25	(3.9)	21	(3.4)	29	(4.6)
Hispanic	12	(1.9)	7	(1.1)	23	(3.6)
Other Race	3	(0.5)	4	(0.6)	2	(0.3)
Age category						
< 65 years	615	(97.0)	608	(97.6)	617	(97.6)
≥ 65 years	19	(3.0)	15	(2.4)	15	(2.4)
BMI category						
≥ 25 – < 28 kg/m^2	6	(0.9)	0	(0.0)	3	(0.5)
≥ 28 – < 30 kg/m^2	58	(9.1)	52	(8.3)	51	(8.1)
≥ 30 – < 35 kg/m^2	269	(42.4)	299	(48.0)	309	(48.9)
≥ 35 kg/m^2	299	(47.2)	270	(43.3)	268	(42.4)
Missing	2	(0.3)	2	(0.3)	1	(0.2)
Age (years)						
Mean +/- SD	44.0 +/- 10.33		44.3 +/- 10.51		44.2 +/- 10.64	
(Min, Max)	(18, 72)		(20, 72)		(18, 78)	
Weight (kg)						
Mean +/- SD	97.1 +/- 14.60		97.7 +/- 14.27		96.0 +/- 14.00	
(Min, Max)	(62.3, 155.5)		(67.3, 152.0)		(63.5, 147.3)	
BMI (kg/m^2)						
Mean +/- SD	34.8 +/- 3.89		34.8 +/- 3.72		34.6 +/- 3.59	
(Min, Max)	(27.0, 45.8)		(28.0, 44.0)		(27.4, 43.4)	

Adapted from GSK Doc ID: 0900233c80357420
NDA Document Page: 1 of 2

Table 4.2.B presents the demographic data for the safety population for study NM17247. Treatment groups were well-matched for the described variables.

Both treatment groups were generally well-matched for baseline characteristics such as lipids, blood pressure, pulse, glucose, and concomitant medications. Most patients (placebo 85%; orlistat, 91%) had at least one concomitant disease during the study. The most frequently reported concomitant diseases occurred in the nervous system, the musculoskeletal system, and the respiratory system; about one-third of patients in each treatment group reported concurrent or previous diseases in these body systems. The most frequently reported specific concurrent diseases included headache, migraine, back pain, seasonal rhinitis, drug hypersensitivity, hypertension, depression, and hypercholesterolemia, each occurring in > 10% of patients in at least one of the treatment groups. There were no meaningful differences between treatment groups in the incidence of any specific concurrent diseases.

Table 4.2.B. Demographic Characteristics 4-Month Phase III Study				
	Placebo (N=195)		**Orlistat 60 mg tid (N=196)**	
	n	**(%)**	**n**	**(%)**
Sex				
Male	11	(5.6)	12	(6.1)
Female	184	(94.4)	184	(93.9)
Race				
Caucasian	174	(89.2)	174	(88.8)
Black	14	(7.2)	18	(9.2)
Other Race	7	(3.6)	4	(2.0)
Age (years)				
Mean ± SD	46.5 ± 10.97		45.8 ± 11.87	
(min, max)	(19, 72)		(20, 80)	
Weight (kg)				
Mean ± SD	72.9 ± 6.94		72.7 ± 6.95	
(min, max)	(56.2, 106.6)		(57.4, 102.5)	
BMI (kg/m^2)				
Mean ± SD	26.8 ± 0.95		26.8 ± 0.96	
(min, max)	(23.7, 28.6)		(24.5, 29.0)	

GSK Doc ID: 0900233c80357420
NDA Document Page: 35 of 88

Table 4.2.C describes the demographics and baseline characteristics for subjects from the supportive study BM14150. Slightly more subjects were male and White in the orlistat 60 mg treatment group compared to the other groups.

Table 4.2.C. Demographic Characteristics; 6-Month Phase II Study (BM14150)						
	Placebo (N=124)		**Orlistat 60 mg tid (N=123)**		**Orlistat 120 mg tid (N=120)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Sex						
Male	27	(21.8)	30	(24.4)	25	(20.8)
Female	97	(78.2)	93	(75.6)	95	(79.2)
Race						
Caucasian	117	(94.4)	120	(97.6)	108	(90.0)
Black	5	(4.0)	3	(2.4)	8	(6.7)
Other Race	2	(1.6)	0	(0.0)	4	(3.3)
Age (years)						
Mean +/- SD	42.6 ± 11.2		42.2 ± 11.3		40.4 ± 10.7	
(Min, Max)	(18, 65)		(19, 68)		(20, 66)	
Weight (kg)						
Mean +/- SD	94.8 ± 13.6		95.0 ± 13.6		94.9 ± 13.0	
(Min, Max)	(70.0, 135.6)		(71.0, 132.2)		(70.7, 128.4)	
BMI (kg/m^2)						
Mean+/- SD	34.7 ± 3.7		34.4 ± 3.8		34.7 ± 3.8	
(Min, Max)	(27.7, 43.2)		(27.3, 43.5)		(28.8, 43.5)	

GSK Doc ID: 0900233c80357420
NDA Document Page: 37 of 88

Table 4.2.D describes the demographic and baseline characteristics in the Actual Use study, NM17285. Although this study's design and results will be discussed in depth by Dr. Feibus, this table is included to highlight the following points. First, only one third of

subjects who self-selected for purchase actually met the BMI criteria for overweight, and 8% were in fact normal weight. The BMI ranged from 21 to 54 in the purchasers group. Second, although there are no subjects < 18 years old in any group, such subjects were prohibited from screening and therefore the potential for purchase in this group was not studied.

Table 4.2.D. Demographic Information; Study NM17285				
	All Screened Subjects N = 703	**Eligible Subjects N = 681**	**Purchasers Group N = 262**	**Users Group N = 237**
Sex n (%)				
Male	143 (20.3)	140 (20.6)	38 (14.5)	34 (14.3)
Female	558 (79.4)	539 (79.1)	223 (85.1)	202 (85.2)
Missing	2 (0.3)	2 (0.3)	1 (0.4)	1 (0.4)
Race n (%)				
White/Caucasian	562 (79.9)	540 (79.3)	214 (81.7)	194 (81.9)
African American	42 (6.0)	42 (6.2)	9 (3.4)	6 (2.5)
Native American	10 (1.4)	10 (1.5)	4 (1.5)	4 (1.7)
Asian	11 (1.6)	11 (1.6)	6 (2.3)	6 (2.5)
Hispanic, Spanish, Latino	55 (7.8)	55 (8.1)	17 (6.5)	15 (6.3)
Other	22 (3.10)	22 (3.2)	12 (4.6)	12 (5.1)
Missing	1 (0.1)	1 (0.1)	0	0
Age (years)				
Mean	45.8	45.4	45.0	44.9
Std Dev	14.64	14.46	13.55	13.44
Median	45.0	45.0	45.0	45.0
Range (min, max)	18, 85	18, 85	18, 80	18, 75
N	699	677	262	237
Height (in)				
Mean	65.6	65.6	65.5	65.3
Std Dev	3.45	3.47	3.30	3.29
Median	65.0	65.0	65.0	65.0
Range (min, max)	57, 80	57, 80	59, 80	59, 80
Weight (lb)				
Mean	202.8	203.1	196.2	195.3
Std Dev	47.39	47.47	43.44	43.05
Median	196.5	197.0	190.0	191.0
Range (min, max)	114, 407	114, 407	118, 353	118,353
N	696	674	262	237
BMI at beginning of study (kg/m^2)				
Mean	33.0	33.1	32.0	32.0
Std Dev	6.70	6.68	5.98	5.84
Median	32.1	32.1	31.7	31.6
Range (min, max)	20.8, 62.6	20.9, 62.5	20.9, 54.5	20.9, 53.3
N	696	674	262	237
BMI group				
< 25	54 (7.7)	49 (7.2)	20 (7.6)	18 (7.6)
25-29.9	187 (26.6)	181 (26.6)	85 (32.4)	76 (32.1)
≥ 30	455 (64.7)	444 (65.2)	157 (59.9)	143 (60.3)
Missing	7 (1.0)	7 (1.0)	0	0

In study RCH-ORL-002, the 162-subject safety population was primarily female (83.9%), with a mean age of 36.7 years (range 18 to 73 years). The safety population was primarily White (71.0%); other racial subgroups included: Hispanic (13.6%), Black (13.0%), and others (2.5%). At baseline, the mean weight was 97.4 kg (range 69.4 to 177.3 kg) and the mean BMI of the group was 34.7 kg/m^2 (range 27 to 57 kg/m^2).

4.3 Deaths and Serious Adverse Events

4.3.1 Deaths

There were four deaths reported in the studies supporting this NDA; all were in studies from the original prescription NDA. Two deaths occurred during the lead-in period: one death in a woman in study NM14302 after she was struck by an automobile, and one death in a woman in study BM14150 who had a respiratory arrest (asthma). The other two deaths were due to myocardial infarctions in subjects randomized to orlistat; one experienced by a man in study BM14149 (60 mg tid) and another man in study NM14161 (120 mg tid). This reviewer cannot reasonably attribute either of these deaths to the drug. Narratives of these deaths are listed in the Appendix. There were no deaths in studies NM17247, RCH-ORL-002, or NM17285.

4.3.2 Serious adverse events

4.3.2.1 Pooled studies

Table 4.3.2.1.A demonstrates that the incidence of serious adverse events (SAEs) in the pooled studies during the first six months of treatment was similar across the treatment groups (3.5% placebo, 3.4% orlistat 60 mg, and 3.5% orlistat 120 mg).

The incidence of gastrointestinal (GI) SAEs was similar between treatment groups; even though, as described in Section 4.5, the incidence of GI adverse events overall was greater in the orlistat-treated groups. During the first six months of treatment, there was one SAE of lower abdominal pain in the 120 mg group, and one SAE of abdominal pain in the 60 mg group. The lower abdominal pain occurred on the first day of treatment in a 34-year-old female receiving orlistat 120 mg. The pain was moderate in intensity, the duration was 264 days, and the subject recovered. The case of abdominal pain occurred in a 38-year-old female on Day 72 of treatment with orlistat 60 mg. The pain was severe in intensity, the duration was nine days, and the subject recovered. Neither of these subjects was discontinued due to these adverse events.

One case of colon adenocarcinoma in a polyp was reported in a 49-year-old female subject in the orlistat 60 mg group who had a family history of colon carcinoma. She complained of rectal bleeding on Day 89. On Day 198, a colonoscopy revealed a polyp with well-differentiated adenocarcinoma. It was successfully treated by a polypectomy. One subject (62-year-old female) in the orlistat 120 mg dose group experienced GI

bleeding due to a peptic ulcer. The subject was also taking naproxen to treat rheumatoid arthritis. Neither of these subjects was discontinued due to these adverse events.

Table 4.3.2.1.A. Serious Adverse Events in First 6 Months of Treatment, Safety Population

Body System	Placebo N = 634		60 mg tid N = 623		120 mg tid N = 632	
Preferred Term	n (%)	NAE	n (%)	NAE	n (%)	NAE
# Subjects with at Least One SAE	22 (3.5)	23	21 (3.4)	24	22 (3.5)	24
Reproductive Disorders, Female	3 (0.5)	3	2 (0.3)	3	5 (0.8)	5
Neoplasm Breast Female	0	0	1 (0.2)	1	2 (0.3)	2
Tumor Breast	0	0	0	0	1 (0.2)	1
Uterovaginal prolapse	0	0	0	0	1 (0.2)	1
Vaginal prolapse	0	0	0	0	1 (0.2)	1
Carcinoma cervix	0	0	1 (0.2)	1	0	0
Cervial dysplasia	0	0	1 (0.2)	1	0	0
Urinary System Disorders	0	0	0	0	3 (0.5)	4
Urinary Incontinence	0	0	0	0	2 (0.3)	2
Bladder prolapse	0	0	0	0	1 (0.2)	1
Ureteral calculus	0	0	0	0	1 (0.2)	1
Gastro-Intestinal System Disorders	3 (0.5)	3	5 (0.8)	5	2 (0.3)	2
Abdominal pain lower	0	0	0	0	1 (0.2)	1
GI hemorrhage	0	0	0	0	1 (0.2)	1
Hernia Inguinal	0	0	2 (0.3)	2	0	0
Abdominal pain	0	0	1 (0.2)	1	0	0
Colon carcinoma	0	0	1 (0.2)	1	0	0
Diverticulitis	0	0	1 (0.2)	1	0	0
Liver And Biliary System Disorders	4 (0.6)	4	3 (0.5)	3	2 (0.3)	2
Cholecystitis	3 (0.5)	3	2 (0.3)	2	1 (0.2)	1
Cholelithiasis	0	0	1 (0.2)	1	1 (0.2)	1
Biliary colic	1 (0.2)	1	0	0	0	0
Musculo-Skeletal System Disorders	4 (0.6)	4	2 (0.3)	2	2 (0.3)	2
Pain Knee	0	0	0	0	1 (0.2)	1
Sprains and strains	0	0	0	0	1 (0.2)	1
Intervertebral Disc Disorder	1 (0.2)	1	1 (0.2)	1	0	0
Pain nape	0	0	1 (0.2)	1	0	0
Myo-, Endo-, Pericardial & Valve Disord.	1 (0.2)	1	0	0	2 (0.3)	2
Angina Pectoris	1 (0.2)	1	0	0	1 (0.2)	1
Malf. Of prostheses and hemographs	0	0	0	0	1 (0.2)	1
Psychiatric Disorders	1 (0.2)	1	0	0	2 (0.3)	2
Depression	1 (0.2)	1	0	0	1 (0.2)	1
Suicide attempt	0	0	0	0	1 (0.2)	1
Respiratory System Disorder	0	0	2 (0.3)	2	1 (0.2)	1
Chronic obstructive lung disease	0	0	0	0	1 (0.2)	1
Dyspnea	0	0	1 (0.2)	1	0	0
Sinusitis	0	0	1 (0.2)	1	0	0
Central & Periph. Nervous Syst. Disord.	1 (0.2)	1	1 (0.2)	1	1 (0.2)	1
Headache	0	0	0	0	1 (0.2)	1
Neuralgia sciatic	0	0	1 (0.2)	1	0	0
Heart Rate And Rhythm	0	0	1 (0.2)	1	1 (0.2)	1
Fibrillation atrial	0	0	0	0	1 (0.2)	1
Paroxysmal superventricular tachycardia	0	0	1 (0.2)	1	0	0
Endocrine Disorders	0	0	0	0	1 (0.2)	1
Tumor thyroid	0	0	0	0	1 (0.2)	1

Table 4.3.2.1.A. Serious Adverse Events in First 6 Months of Treatment, Safety Population						
Body System	**Placebo N = 634**		**60 mg tid N = 623**		**120 mg tid N = 632**	
Preferred Term	**n (%)**	**NAE**	**n (%)**	**NAE**	**n (%)**	**NAE**
Vascular (Extracardiac) Disorders	0	0	0	0	1 (0.2)	1
Varicose veins	0	0	0	0	1 (0.2)	1
Body As A Whole - General Disorders	5 (0.8)	5	3 (0.5)	3	0	0
Surgical Procedure	4 (0.6)	4	3 (0.5)	3	0	0
Autonomic Nervous System Disorder	0	0	1 (0.2)	1	0	0
Syncope	0	0	1 (0.2)	1	0	0
Cardiovascular Disorders	0	0	1 (0.2)	1	0	0
Cardiac failure	0	0	1 (0.2)	1	0	0
Skin And Appendages Disorders	0	0	1 (0.2)	1	0	0
Pruritus	0	0	1 (0.2)	1	0	0
Urticaria	0	0	1 (0.2)	1	0	0
Resistance Mechanism Disorders	1 (0.2)	1	0	0	0	0

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Preferred Terms with 0 AEs in either orlistat group were omitted from the table.

Adapted from GSK Doc ID: 0900233c80357420
NDA Document Page: 1 of 4

In the evaluation of SAEs in the first year of treatment, as with the first six months, the incidence of SAEs overall was similar between groups (5.8% placebo, 5.9% orlistat 60 mg, and 5.4% orlistat 120 mg). There was a slight numerical imbalance of GI SAEs in the orlistat groups as compared to placebo (4/634, 0.6% placebo; 7/623, 1.1% orlistat 60 mg; 5/632, 0.8% orlistat 120 mg); however, there was no dose-response.

Although there has been some concern that orlistat may be lithogenic and a potential contributor to gallbladder disease (see Section 4.9), the incidence of adverse events of cholelithiasis and cholecystitis combined is similar between orlistat and placebo up to the first six months of treatment. There were three additional subjects who developed SAEs of cholecystitis in the second six months of treatment; however, two of the three subjects were in the placebo group. There were three more subjects with SAEs of cholelithiasis in the 1-year data compared to the 6-month data. One of the subjects was randomized to placebo and two were randomized to orlistat 120 mg.

4.3.2.2 Study NM17247

In study NM17247, there were two SAEs in the orlistat 60 mg group (2/196, 1.0%) and none in the placebo group (0/195): a 47-year-old White female had an umbilical hernia repair on study day 35, and a 41-year-old White female was hospitalized for a herniated disk reinjury on study day 79. Neither event appears to have been related to the drug. Please see the Appendix for narratives of these events.

4.3.2.3 Study BM14150

In the 24-week study BM14150, the number (%) of subjects who reported at least one SAE is as follows: placebo, 2 (1.6%); orlistat 30 mg, 6 (4.9%); orlistat 60 mg, 2 (1.6%); orlistat 120 mg, 1 (0.8%); and orlistat 240 mg, 3 (2.6%).

There were four reports of SAEs of abdominal pain; three events were not specified (one each in subjects randomized to orlistat 30, 60, and 240 mg) and one was attributed to diverticulitis (orlistat 30 mg). All but one of these subjects (orlistat 240 mg) prematurely discontinued from the study. The subject randomized to orlistat 60 mg tid who reported severe abdominal pain was a 28-year-old White female. The event started on study day 97 and the subject was discontinued from the study on day 108. Her symptomatology continued and she was hospitalized five days later. She underwent an extensive workup including upper and lower endoscopies and abdominal CT; however, no diagnosis could be established and she was discharged five days later. Her symptoms subsided 17 days after her last dose of orlistat.

4.3.2.4 Study NM17285

In the 3-month Actual Use study, five subjects (1.8%) experienced six SAEs (Table 4.3.2.4.A). One subject, a 46-year-old Black female with a history of iron-deficiency anemia, developed an SAE of abdominal pain one month after starting on orlistat 60 mg tid associated with severe nausea and vomiting. She was hospitalized but the cause of her abdominal pain was not established. Diagnostic tests included CT and ultrasound of the abdomen. All tests were negative except for a low blood count, for which the physician recommended a transfusion. She was discharged one day later and her abdominal pain resolved four days after discharge.

A 48-year-old White female developed severe, crushing chest and jaw pain (preferred term = chest pain) five weeks after starting treatment with orlistat. An emergency room cardiac work-up was negative, and she was discharged with a diagnosis of esophageal spasm.

Table 4.3.2.4.A. Summary of Serious Adverse Events, Safety Population		
	Orlistat 60 mg N = 284	
System Organ Class Preferred Term	**n (%)**	**NAE**
Subjects With At Least One Serious Adverse Event	5 (1.8)	6
Infections And Infestations	2 (0.7)	2
Kidney Infection NOS	1 (0.4)	1
Methicillin-Resistant Staphylococcal Aureus Infection	1 (0.4)	1
Gastrointestinal Disorders	1 (0.4)	1
Abdominal Pain NOS	1 (0.4)	1
General Disorders And Administration Site Conditions	1 (0.4)	1
Chest Pain NEC	1 (0.4)	1
Pregnancy, Puerperium And Perinatal Conditions	1 (0.4)	1
Abortion Spontaneous NOS	1 (0.4)	1
Vascular Disorders	1 (0.4)	1
Transient Ischaemic Attack	1 (0.4)	1

4.3.2.5 Study RCH-ORL-002

There were no SAEs reported in this 4-week study.

4.4 Discontinuations

4.4.1 Reasons for discontinuation

Tables 4.4.1.A and 4.4.1.B detail the causes of premature discontinuation in the pooled studies and study NM17247, respectively. The first year of the pooled studies was tabulated by the sponsor, and the first 24 weeks (second half of Table 4.4.1.A) was compiled by this reviewer and therefore should be considered exploratory. Both tables demonstrate that placebo-treated subjects were more likely to discontinue than orlistat-treated subjects, although orlistat-treated subjects were more likely to discontinue due to an adverse event (see Section 4.4.2, below), with about twice as many subjects treated with orlistat 60 mg discontinuing as those treated with placebo. Subjects treated with orlistat 120 mg had slightly more discontinuations due to adverse events than those treated with 60 mg. Rates of discontinuation are slightly higher in the 4-month study (NM17247, overweight population) than in the first 24 weeks (6 months) of the pooled studies (obese population) for both placebo and orlistat groups.

This reviewer considers that reasons for discontinuation such as, ‘refused treatment’, ‘lost to follow-up’, or ‘did not cooperate’, are likely to be related to subjects not losing weight. This may describe the imbalances between placebo and orlistat due to these reasons.

Table 4.4.1.A. Reasons for Premature Withdrawal during the First Year of Treatment; Pooled Phase III Studies						
	Placebo		**Orlistat 60 mg tid**		**Orlistat 120 mg tid**	
Reason for Withdrawal	**(N=634) n (%)**		**(N=623) n (%)**		**(N=632) n (%)**	
First Year						
Total subjects withdrawn	220	(34.7)	156	(25.0)	175	(27.7)
Adverse event	21	(3.3)	42	(6.7)	56	(8.9)
Treatment failure	14	(2.2)	10	(1.6)	8	(1.3)
Refused treatment	28	(4.4)	17	(2.7)	21	(3.3)
Died during study	0	(0.0)	0	(0.0)	1	(0.2)
Lost to follow-up	61	(9.6)	36	(5.8)	42	(6.6)
Did not cooperate	38	(6.0)	20	(3.2)	22	(3.5)
Protocol violation	14	(2.2)	10	(1.6)	11	(1.7)
Entry violation	2	(0.3)	0	(0.0)	0	(0.0)
Administrative	42	(6.6)	21	(3.4)	14	(2.2)
24 Weeks*						
Total subjects withdrawn	133	(21.0)	93	(14.9)	110	(17.4)
Adverse event	14	(2.2)	31	(5.0)	45	(7.1)
Lost to follow-up	47	(7.4)	23	(3.7)	30	(4.7)
Did not cooperate	17	(2.7)	10	(1.6)	10	(1.6)
Refused treatment	12	(1.9)	6	(1.0)	9	(1.4)
Administrative	23	(3.6)	14	(2.2)	7	(1.1)
Protocol violation	10	(1.6)	4	(0.6)	6	(0.9)
Treatment failure	8	(1.3)	5	(0.8)	3	(0.5)
Entry violation	2	(0.3)	0	(0.0)	0	(0.0)

Studies BM14149, NM14161, NM14302
*As calculated by the reviewer: up to study day 210 (end of the week 24 window); total discontinuations due to adverse events at 24 weeks is slightly different that that calculated by the sponsor (Table 4.4.2.1.A, likely due to different counting rules).

Adapted from GSK Doc ID: 0900233c80357420
NDA Document Page: 27 of 88

Table 4.4.1.B. Reasons for Premature Withdrawal; 4-Month Phase III Study				
	Placebo		**Orlistat 60 mg tid**	
Reason for Withdrawal	**(N=195) n (%)**		**(N=196) n (%)**	
Total subjects withdrawn	55	(28.2)	44	(22.4)
Adverse event[a]	6	(3.1)	14	(7.1)
Failure to return	16	(8.2)	12	(6.1)
Refused treatment[b]	30	(15.4)	11	(5.6)
Entry violation	0		2	(1.0)
Other protocol violation	2	(1.0)	2	(1.0)
Other	1	(0.5)	3	(1.5)

a includes intercurrent illness
b includes 'did not cooperate', 'withdrew consent'

Adapted from GSK Doc ID: 0900233c80357420
NDA Document Page: 28 of 88

The incidence of discontinuations overall and due to adverse events was comparable in the supportive 6-month study BM14150 to the six months of treatment in the pooled studies, and was not clearly dose-related (Table 4.4.1.C). A significantly higher proportion of subjects treated with orlistat 60 mg discontinued due to an adverse event in

the 3-month Actual Use trial NM17285 (15%). In the 4-week Consumer Use study, 3.7% prematurely discontinued due to an adverse event.

Table 4.4.1.C. Study BM14150: Summary of Reasons for Premature Withdrawal during the Double-Blind Treatment Period; All Randomized Patients

	Placebo (N = 125)		Orlistat 30 mg tid (N = 122)		Orlistat 60 mg tid (N = 124)		Orlistat 120 mg tid (N = 122)		Orlistat 240 mg tid (N = 120)	
Reasons for Withdrawal[a]	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Refused Treatment	10	(8.0)	9	(7.4)	8	(6.5)	3	(2.5)	6	(5.0)
Adverse Event	3	(2.4)	7	(5.7)	6	(4.8)	2	(1.6)	3	(2.5)
Lost to follow-up	9	(7.2)	7	(5.7)	7	(5.6)	9	(7.4)	6	(5.0)
Did not cooperate	1	(0.8)	3	(2.5)	3	(2.4)	3	(2.5)	5	(4.2)
Administrative	3	(2.4)	2	(1.6)	4	(3.2)	4	(3.3)	0	(0)
Protocol violation	1	(0.8)	1	(0.8)	1	(0.8)	1	(0.8)	0	(0)
Entry violation	0	(0)	0	(0)	0	(0)	1	(0.8)	0	(0)
Total Patients Withdrawn	27	(21.6)	29	(23.8)	29	(23.4)	23	(18.9)	20	(16.7)

a Only the primary reason is counted for each patient

4.4.2 Adverse events leading to discontinuation

4.4.2.1 Pooled studies

In the first six months of treatment, there was a dose-related incidence of discontinuation due to adverse events in the pooled studies, mostly due to gastrointestinal events.

Table 4.4.2.1.A. Adverse Events Leading to Discontinuation in the First 6 Months of Treatment, Pooled Phase III Studies						
WHO-ART Body System Preferred Term	Placebo N = 634 n (%)		60 mg tid N = 623 n (%)		120 mg tid N = 632 n (%)	
Subjects with ≥ 1 AE leading to discontinuation	13	(2.1)	30	(4.8)	46	(7.3)
Gastrointestinal system disorders	5	(0.8)	20	(3.2)	34	(5.4)
Fecal incontinence	0		7	(1.1)	10	(1.6)
Oily spotting	0		1	(0.2)	7	(1.1)
Liquid stools	0		2	(0.3)	4	(0.6)
Flatus with discharge	0		1	(0.2)	4	(0.6)
Fecal urgency	1	(0.2)	4	(0.6)	3	(0.5)
Abdominal pain	0		3	(0.5)	2	(0.3)
Flatulence	2	(0.3)	0		0	
Central & peripheral nervous system disorders	0		3	(0.5)	2	(0.3)
Vertigo	0		2	(0.3)	0	
Reproductive disorders, female	0		2	(0.3)	2	(0.3)
Neoplasm breast female	0		1	(0.2)	2	(0.3)
Myo- Endo-, Pericardial, & Valve Disorders	0		0		2	(0.3)
Psychiatric Disorders	0		2	(0.3)	1	(0.2)
Respiratory System Disorders	0		1	(0.2)	1	(0.2)
Body as a Whole – General Disorders	2	(0.3)	0		1	(0.2)
Liver and Biliary System Disorders	0		0		1	(0.2)
Endocrine Disorders	1	(0.2)	0		1	(0.2)
Urinary System Disorders	0		0		1	(0.2)
Skin and Appendages Disorders	3	(0.5)	1	(0.2)	0	
Resistance Mechanism Disorders	0		1	(0.2)	0	

Adapted from GSK Doc ID: 0900233c80357420
NDA Document Page: 66 of 88

4.4.2.2 Study NM17247

As with the pooled studies, orlistat-treated subjects in study NM17247 had a higher incidence of discontinuation due to adverse events compared to placebo (Table 4.4.2.2.A), mostly attributable to gastrointestinal events. The incidence of discontinuations in the orlistat 60 mg-treated group (when adjusting for incidence rates in the placebo group) due to adverse events overall, as well as due to gastrointestinal adverse events, is slightly higher in the 4-month study in the lower-overweight population (study NM17247) as compared to the 6-month study in the upper overweight and obese population (pooled studies).

Table 4.4.2.2.A. Adverse Events Leading to Discontinuation in 4 Months of Treatment; 4-Month Phase III Study				
MedDRA Body System Preferred Term	Placebo N = 195 n (%)		Orlistat 60 mg tid N = 196 n (%)	
Subjects with ≥ 1 AE leading to discontinuation	6	(3.1)	13	(6.6)
Gastrointestinal system disorders	2	(1.0)	10	(5.1)
Oily spotting	0		2	(1.0)
Abdominal pain lower	0		2	(1.0)
Abdominal pain upper	0		2	(1.0)
Nervous system disorders	2	(1.0)	0	
Dizziness	2	(1.0)	0	
Infections and Infestations	1	(0.5)	0	
Musculoskeletal, Connective Tissue, and Bone Disorders	0		1	(0.5)
Neoplasms Benign and Malignant	0		1	(0.5)
Renal and Urinary Disorders	1	(0.5)	0	
Vascular Disorders	0		1	(0.5)

Adapted from GSK Doc ID: 0900233c80357420
NDA Document Page: 67 of 88

4.4.2.3 Study BM14150

Most adverse events leading to discontinuation in study BM14150 occurred in only one subject each. Total adverse events leading to discontinuation were not dose-related (of note, seven subjects in the 30 mg group and three subjects in the 240 mg group discontinued due to an AE).

Table 4.4.2.3.A. Patients Prematurely Withdrawn from the Study Because of Adverse Events			
Body System Adverse Event	**Placebo N = 125**	**60 mg tid N = 124**	**120 mg tid N = 122**
Total	3 (2.4)	6 (4.8)	2 (1.6)
Gastrointestinal	1 (0.8)	2 (1.6)	2 (1.6)
Abdominal pain	1 (0.8)	1 (0.8)	0
Liquid stools	0	0	1 (0.8)
Musculoskeletal	0	0	0
Psychiatric	0	1 (0.8)	0
Depression	0	1 (0.8)	0
Reproductive, male	0	1 (0.8)	0
Skin and appendages	1 (0.8)	0	0
Liver and biliary system disorders	0	1 (0.8)	0
Laboratory abnormality	1 (0.8)	0	0
Body as a whole	0	1 (0.8)	0

Adapted from GSK Doc ID: 0900233c8032b59e
NDA Document Page: 100 of 589

4.4.2.4 Uncontrolled studies

The majority of the AEs leading to discontinuation in studies NM17285 and RCH-ORL-002 were gastrointestinal in nature.

4.5 Gastrointestinal Adverse Events

Because gastrointestinal (GI) events in subjects treated with orlistat are the most common adverse events, events most likely to lead to termination of therapy, as well as events related to the pharmacological action of orlistat, Roche (the sponsor of the original prescription NDA) devised a dictionary of descriptive preferred terms to more accurately capture potentially drug-related GI events. This dictionary (Table 4.5.A) was used in the phase 2 and 3 studies from the original prescription NDA, as well as the studies supporting the nonprescription NDA.

Table 4.5.A. Dictionary of Standard Terms for Changes in Defecation Pattern

Term	Definition
*fecal incontinence	uncontrolled, spontaneous defecation
*oily spotting	uncontrolled seepage of oil without stool
*flatus with discharge	flatus with small amounts of oil or stool
*fecal urgency	urgent, but controlled, need to produce stools
*oily evacuation	controlled discharge of oil without stool
fatty/oily stool	stools mixed with fat or with a separate oily layer
liquid stools	stools almost all liquid with very few solid parts
increased defecation	increased frequency of bowel movements
soft stools	stools mushy and deliquescent (i.e., stools not formed but of rather fluid consistency)
decreased defecation	decreased frequency of bowel movements
pellets	stools hard and in the shape of small pellets

* Events that are attributable to the pharmacological action of orlistat and were always to be considered AEs. These items appear in the list in decreasing order of clinical significance.

4.5.1 Pooled Studies

The incidence of gastrointestinal AEs was moderately higher in the orlistat treatment groups than in the placebo group, with more subjects experiencing AEs in the 120 mg dose group than those in the 60 mg group. The biggest discrepancy between placebo and orlistat groups was for the AEs of fecal urgency, oily spotting, flatus with discharge, fatty/oily stool, oily evacuation, and fecal incontinence.

Table 4.5.1.A. GI Adverse Events with Incidence ≥ 1% during 6 Months of Treatment; Pooled Phase 3 Studies						
WHO-ART Preferred Term	**Placebo (N=634)**		**Orlistat 60 mg tid (N=623)**		**Orlistat 120 mg tid (N=632)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects with ≥1 GI AE	326	(51.4)	428	(68.7)	472	(74.7)
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)
Decreased defecation	53	(8.4)	27	(4.3)	23	(3.6)
Enteritis	23	(3.6)	18	(2.9)	24	(3.8)
Toothache	12	(1.9)	14	(2.2)	15	(2.4)
Hemorrhoids	11	(1.7)	7	(1.1)	15	(2.4)
Fullness abdominal	5	(0.8)	6	(1.0)	3	(0.5)
Periodontal breakdown	4	(0.6)	5	(0.8)	9	(1.4)
Table includes events with incidence in either orlistat group ≥1% and greater than that in the placebo group. *Orlistat incidence ≥ 5% and at least twice the placebo incidence						

GSK Doc ID: 0900233c80357420
NDA Document Page: 53 of 88

Studies conducted up to four years have suggested that gastrointestinal AEs diminish over time with use of orlistat[7]. However, the extent to which this is a true "tolerance" of the effect or a function of the either the premature discontinuation of subjects who are intolerant to the GI effects or do not adhere to the reduction in dietary fat intake is somewhat unclear. This reviewer's exploratory analysis suggests that in the 6-month completers, the majority of the events were in the first few weeks. Furthermore, the sponsor notes that the first GI event in the majority of subjects occurred within the first 12 weeks, with very few subjects experiencing their first episode after six months.

The evaluation of the number of episodes experienced by the subjects during treatment, demonstrates that, as expected, the orlistat-treated subjects have a higher incidence of multiple episodes than placebo-treated subjects, although the orlistat 60 mg and 120 mg dose groups are fairly similar in rates of multiple GI episodes (Table 4.5.1.B).

7 Torgerson JS, et al. Diabetes Care; 27:155-161, 2004.

Table 4.5.1.B. Number of Gastrointestinal Adverse Events per Subject in First 6 Months of Treatment; Pooled Phase III Studies			
Number of GI AEs	**Placebo**	**Orlistat 60 mg tid**	**Orlistat 120 mg tid**
	(N=634) n (%)	**(N=623) n (%)**	**(N=632) n (%)**
0	308 (48.6)	195 (31.3)	160 (25.3)
1	142 (22.4)	100 (16.1)	107 (16.9)
2	74 (11.7)	94 (15.1)	95 (15.0)
3	46 (7.3)	71 (11.4)	82 (13.0)
4	25 (3.9)	54 (8.7)	61 (9.7)
5	14 (2.2)	34 (5.5)	22 (3.5)
6	3 (0.5)	23 (3.7)	32 (5.1)
7	7 (1.1)	10 (1.6)	32 (5.1)
8	4 (0.6)	12 (1.9)	15 (2.4)
9	5 (0.8)	8 (1.3)	8 (1.3)
10-18	6 (1.0)	22 (3.5)	18 (2.8)

GSK Doc ID: 0900233c80357420
NDA Document Page: 59 of 88

4.5.2 Study NM17247

In four months of treatment, the orlistat group experienced about twice as many gastrointestinal AEs as the placebo group; the majority of these attributable to fatty/oily stool, fecal urgency, oily spotting, flatus with discharge, and increased defecation.

Table 4.5.2.A. Gastrointestinal Adverse Events with Incidence ≥ 2% in 4 Months of Treatment; 4-Month Phase III Study				
MedDRA Preferred Term	**Placebo (N=195)**		**Orlistat 60 mg tid (N=196)**	
	n	**(%)**	**n**	**(%)**
Subjects with ≥1 GI AE	64	(32.8)	112	(57.1)
*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)
Table includes events with incidence in the orlistat group ≥ 2% and greater than that in the placebo group. *Orlistat incidence ≥ 5% and at least twice the placebo incidence.				

GSK Doc ID: 0900233c80357420
NDA Document Page: 54 of 88

Interestingly, the incidence of gastrointestinal events in the orlistat-treated group does not appear to be related to amount of weight lost in this patient population (Table 4.5.2.B), supporting the notion that orlistat can maintain efficacy in the absence of gastrointestinal side effects. Conversely, considering that the proportion of gastrointestinal AEs in subjects who did not lose weight, or even gained weight, is similar to those who lost weight, indicates that an individual should not assume the drug "is working" (i.e.,

promoting weight loss) in the absence of dietary adherence if he or she experiences drug-related effects such as oily stool or spotting.

Table 4.5.2.B. Gastrointestinal Adverse Events by Amount of Weight Lost; Safety Population								
Preferred Term	**0% loss or gain**		**> 0% to 5% loss**		**> 5% to 10% loss**		**> 10% loss**	
	Orlistat N = 27 n (%)	Placebo N = 52 n (%)	Orlistat N = 98 n (%)	Placebo N = 81 n (%)	Orlistat N = 50 n (%)	Placebo N = 42 n (%)	Orlistat N = 19 n (%)	Placebo N = 9 n (%)
Fatty/Oily Stool	5 (18.5)	1 (1.9)	25 (25.5)	1 (1.2)	11 (22.0)	3 (7.1)	3 (15.8)	0 (0.0)
Fecal Urgency	6 (22.2)	3 (5.8)	16 (16.3)	4 (4.9)	7 (14.0)	4 (9.5)	4 (21.1)	0 (0.0)
Oily Spotting	5 (18.5)	0 (0.0)	8 (8.2)	0 (0.0)	6 (12.0)	0 (0.0)	3 (15.8)	0 (0.0)
Flatus With Discharge	1 (3.7)	0 (0.0)	12 (12.2)	2 (2.5)	4 (8.0)	1 (2.4)	1 (5.3)	0 (0.0)
Increased Defecation	4 (14.8)	1 (1.9)	6 (6.1)	5 (6.2)	7 (14.0)	0 (0.0)	0 (0.0)	1 (11.1)
Stools Soft	2 (7.4)	2 (3.8)	7 (7.1)	4 (4.9)	1 (2.0)	0 (0.0)	1 (5.3)	1 (11.1)
Abdominal Pain NOS	1 (3.7)	2 (3.8)	4 (4.1)	1 (1.2)	3 (6.0)	2 (4.8)	0 (0.0)	1 (11.1)
Dyspepsia	0 (0.0)	0 (0.0)	4 (4.1)	0 (0.0)	1 (2.0)	0 (0.0)	1 (5.3)	0 (0.0)
Fecal Incontinence	3 (11.1)	0 (0.0)	3 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oily Evacuation	0 (0.0)	0 (0.0)	4 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	1 (11.1)

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4.5.3 Combined studies

This reviewer requested the sponsor to provide a table of gastrointestinal events up to four months for the three phase 3 pooled safety studies and study NM17247 combined, by BMI at randomization. For the majority of adverse events, the incidence was similar in the BMI groups up to 35 kg/m^2, with several placebo-subtracted adverse events slightly lower in the highest BMI category, such as fatty/oily stool, fecal urgency, oily spotting/evacuation, and fecal incontinence (Table 4.5.3.A). From these results, it does not appear that overweight patients are likely to experience more or fewer gastrointestinal AEs than obese patients.

Table 4.5.3.A. Adverse Events in First 4 Months of Treatment by BMI at Randomization; Safety Population									
Preferred Term	**BMI < 30 kg/m^2**			**BMI 30 - < 35 kg/m^2**			**BMI ≥ 35 kg/m^2**		
	Orlistat 60 N = 348 n (%)	**Placebo N = 372 n (%)**	**Diff**	**Orlistat 60 N = 273 n (%)**	**Placebo N = 341 n (%)**	**Diff**	**Orlistat 60 N = 198 n (%)**	**Placebo N = 216 n (%)**	**Diff**
Fatty/Oily Stool	65 (18.7)	9 (2.4)	16.3	53 (19.4)	3 (1.2)	18.2	27 (13.6)	6 (2.8)	10.8
Fecal Urgency	63 (18.1)	27 (7.3)	10.8	52 (19.0)	17 (7.1)	11.9	27 (13.6)	14 (6.5)	7.1
Oily Spotting	53 (15.2)	4 (1.1)	14.1	44 (16.1)	2 (0.8)	15.3	24 (12.1)	1 (0.5)	11.6
Flatus With Discharge	50 (14.4)	7 (1.9)	12.5	39 (14.3)	3 (1.2)	13.1	31 (15.7)	2 (0.9)	14.8
Oily Evacuation	32 (9.2)	4 (1.1)	8.1	29 (10.6)	0 (0.0)	10.6	12 (6.1)	0 (0.0)	6.1
Stools Soft	23 (6.6)	15 (4.0)	2.6	24 (8.8)	9 (3.7)	5.1	25 (12.6)	16 (7.4)	5.2
Increased Defecation	27 (7.8)	15 (4.0)	3.8	17 (6.2)	1 (0.4)	5.8	14 (7.1)	7 (3.2)	3.9
Liquid Stools	20 (5.7)	19 (5.1)	0.6	21 (7.7)	13 (5.4)	2.3	16 (8.1)	10 (4.6)	3.5
Decreased Defecation	19 (5.5)	28 (7.5)	-2.0	11 (4.0)	12 (5.0)	-1.0	3 (1.5)	19 (8.8)	-7.3
Fecal Incontinence	10 (2.9)	0 (0.0)	2.9	16 (5.9)	2 (0.8)	5.1	4 (2.0)	2 (0.9)	1.1
Pellets	0 (0.0)	3 (0.8)	-0.8	3 (1.1)	3 (1.2)	-0.1	0 (0.0)	2 (0.9)	-0.9
Diff = Orlistat 60 mg percentage - Placebo percentage									

Adapted from GSK Response to FDA Information Request of November 29, 2005

4.5.4 Study BM14150

Most gastrointestinal AEs in this 6-month dose-ranging study were dose-related (Table 4.5.4.A).

Table 4.5.4.A. N (%) Gastrointestinal Adverse Events in Study BM14150

Adverse Event	Placebo N = 124	30 mg tid N = 122	60 mg tid N = 123	120 mg tid N = 120	240 mg tid N = 117
Total	57 (46.0)	74 (60.7)	93 (75.6)	85 (70.8)	97 (82.9)
Fatty/Oily Stool	2 (2.4)	25 (20.5)	39 (31.7)	45 (37.5)	43 (36.8)
Oily Spotting	0	10 (8.2)	18 (14.6)	15 (12.5)	26 (22.2)
Stools Soft	10 (8.1)	14 (11.5)	23 (18.7)	16 (13.3)	24 (20.5)
Abdominal Pain	17 (13.7)	18 (14.8)	20 (16.3)	20 (16.7)	22 (18.8)
Increased Defecation	7 (5.6)	23 (18.9)	23 (18.7)	23 (19.2)	21 (17.9)
Fecal Urgency	2 (1.6)	7 (5.7)	10 (8.1)	8 (6.7)	16 (13.7)
Liquid Stools	15 (12.1)	14 (11.5)	24 (19.5)	20 (16.7)	15 (12.8)
Oily Evacuation	0	8 (6.6)	7 (5.7)	10 (8.3)	13 (11.1)
Flatus with Discharge	0	3 (2.5)	8 (6.5)	9 (7.5)	11 (9.4)
Fecal Incontinence	0	2 (1.6)	4 (3.3)	6 (5.0)	9 (7.7)
Flatulence	4 (3.2)	12 (9.8)	12 (9.8)	8 (6.7)	9 (7.7)
Decreased Defecation	16 (12.9)	9 (7.4)	13 (10.6)	9 (7.5)	7 (6.0)
Enteritis	6 (4.8)	4 (3.3)	4 (2.4)	3 (2.5)	5 (4.3)
Nausea	7 (5.6)	8 (6.6)	9 (7.3)	9 (7.5)	4 (3.4)
Stools Solid	3 (2.4)	4 (3.3)	3 (2.4)	3 (2.5)	4 (3.4)
Hemorrhage Rectum	0	0	0	4 (3.3)	1 (0.9)
Vomiting	4 (3.2)	1 (0.8)	3 (2.4)	3 (2.5)	3 (2.6)

Adapted from GSK Doc ID: 0900233c8032b59e
NDA Document Page: 96 of 589

4.5.5 Study NM17285

Although this study is difficult to analyze given the lack of a placebo, the wide range of BMIs, and the possibility of dose-titration, the incidence of defecation pattern AEs in this 3-month Actual Use study was comparable with the incidence of gastrointestinal AEs in the 4-month placebo-controlled trial (NM17247). Thirty-five percent of subjects had the drug interrupted or discontinued as a result of the AE.

Table 4.5.5.A. GI Adverse Events: Defecation Pattern Change Events by Action Taken									
	Safety Popn.			Action Taken[a]					
	(N=284)			None		Interrupted		Discontinued	
	n	(%)	NAE	n	(%)	n	(%)	n	(%)
Any defecation pattern change AE	136	(47.9)	322	89	(65.4)	23	(16.9)	24	(17.7)
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)

4.5.6 RCH-ORL-002

In one month of treatment in this Consumer Use study, 101 subjects (62%) experienced at least one digestive system AE. Table 4.5.6.A does not include abdominal pain, which occurred in 11 (7%) of subjects.

Table 4.5.6.A. Digestive System Adverse Events: Study RCH-ORL-002	
Adverse Event	**Orlistat 60 mg N = 162 n (%)**
Digestive System	101 (62%)
Abnormal stools	46 (28%)
Colitis	1 (1%)
Diarrhea	37 (23%)
Dry mouth	1 (1%)
Dyspepsia	6 (4%)
Fecal incontinence	9 (6%)
Flatulence	36 (22%)
Gastroenteritis	1 (1%)
Gastrointestinal disorder	62 (38%)
Loss of appetite	1 (1%)
Nausea	3 (2%)
Oily spotting	18 (11%)
Rectal disorder	1 (1%)
Thirst	1 (1%)
Vomiting	1 (1%)

Adapted from GSK Doc ID: 0900233c8032b59e
NDA Document Page: 26 of 175

4.6 Fat-Soluble Vitamins and Related Nutritional Issues

The absorption of fat-soluble vitamins (A, D, E, and K) and beta-carotene depends on efficient absorption of dietary fat in the small intestine. As orlistat interferes with the absorption of fat, the potential for fat-soluble vitamin deficiency is a concern. In the phase 3 studies conducted under the original prescription NDA, 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 (PT). Study NM14302 differed from the other phase 3 studies (prescription NDA) in that subjects were supplemented with a multivitamin daily. However, the efficacy of this supplementation during the drug treatment period is questionable as the multivitamin was given at breakfast, concomitantly with orlistat.

The sponsor provided the following table of serum concentration decreases in vitamins A, D, E, and beta-carotene from the seven original studies conducted under the prescription NDA (Table 4.6.A). During the double-blind treatment period in these studies, if the fat-soluble vitamin or beta-carotene concentrations were measured below the reference range on two consecutive measurements, the investigator provided appropriate supplementation to the subject and the concentrations continued to be monitored. This would tend to underestimate the risk of vitamin deficiency with long-term orlistat use in unsupplemented subjects.

Table 4.6.A. Frequency of Two Consecutive Plasma Levels of Vitamins Below the Lower Limit of the Reference Range in 1 Year of Treatment (Integrated Database for 7 Phase III Trials, Prescription NDA)

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

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

The lower incidence of vitamin deficiency in the orlistat 60 mg vs. 120 mg groups as shown in Table 4.6.A, is not reassuring given that the proposed label will allow patients to take up to 120 mg tid. Furthermore, these data suggest that the incidence of vitamin deficiency is greater for the orlistat groups than placebo in all cases (statistical testing not provided). Supportive of the above findings, the mean plasma concentrations of vitamins D and E and beta-carotene were significantly lower after one and two years of treatment with either orlistat 60 or 120 mg compared to placebo ($p < 0.05$) in studies done under the original prescription NDA.

There were a greater number of subjects who were supplemented with beta-carotene during the study in the orlistat 60 and 120 mg groups than placebo in studies NM14161 and NM14302. Supplementation was not reported for study NM14149 because the lab failed to identify low results for beta-carotene and subsequently inform the investigator of abnormal beta-carotene results.

Vitamin K data were not presented in the above table because vitamin K status in the prescription NDA was assessed by measurement of PT rather than serum vitamin concentration. Although the mean change in PT was not significantly different from placebo in the phase 3 studies, PT is a relatively insensitive measure for vitamin K deficiency. An individual may be considerably deficient in vitamin K before PT becomes abnormally prolonged.

Diet record analyses, including those of fat-soluble vitamins, were provided from study NM14161. All three treatment groups (placebo, orlistat 60 and 120 mg) generally showed a decrease in intake of fat-soluble vitamins, beta-carotene, and calcium from baseline in the first year of treatment, which then progressed during the second year. It is unknown whether these dietary components were statistically different between treatment groups. This reviewer acknowledges that underreporting is very common in dietary assessment; however, these findings further emphasize the importance of multivitamin use with orlistat.

In study NM17247, all subjects were provided with a multivitamin, and serum vitamin concentrations were not measured. No orlistat-treated subjects in this study were provided a vitamin, mineral, or electrolyte supplementation as a result of an AE. One placebo subject received potassium as part of treatment for a viral infection. One placebo subject received magnesium as treatment for muscle cramps.

Little is known about the long-term effect of orlistat on fat-soluble vitamin status in a lower-weight population. Although the sponsor is proposing that nonprescription orlistat will be labeled for 6-month use only (thereby minimizing the effect of orlistat on vitamin status), this reviewer considers it possible that some individuals will prolong use of this drug, potentially without appropriate vitamin supplementation.

In addition to data provided by the sponsor in the NDA submission, this reviewer searched the literature for relevant papers on orlistat and fat-soluble vitamins, as well as orlistat and other related topics, such as minerals, bone, osteocalcin, and warfarin. The published studies reviewed that examined serum fat-soluble vitamin concentrations demonstrated a significant decrease from baseline or as compared to control in at least one vitamin measured, with duration of study from nine days to four years[7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17]; this finding was notably consistent for serum 25-OH vitamin D. Little is known about orlistat use and certain populations at risk for vitamin D deficiency, such as Blacks, and older men and women.

The potential for mineral binding in the intestine to unabsorbed dietary fat was evaluated in two 21-day mineral balance studies[18, 19]. Neither study demonstrated statistically significant alterations in the balance of micro- or macrominerals in obese adolescents or obese men as compared to placebo, nor were concentrations of serum or urine electrolytes affected. However, a negative iron balance was observed in both treatment groups in both the adolescent and adult study (Table 4.6.B). In the adolescent study, 16 females were enrolled (as compared to the adult study, which was comprised of men only), and four of the females were menstruating.

Table 4.6.B. Iron Balance in Two 21-Day Studies; Mean Value over Days 15-21

	Orlistat 120 mg Mean +/- SEM	Placebo Mean +/- SEM
Adolescents[18]	N = 14	N = 13
Iron balance (µmol/24 hrs)	-64.7 +/- 20.4	-40.4 +/- 10.1
Adults[19]	N = 14	N = 14
Iron balance (µmol/24 hrs)	-18.9 +/- 10.5	-10.8 +/- 11.1
Balance = (dietary content – fecal content) – urinary content		

Data on the long-term effects of orlistat on bone are somewhat limited. One study[15] suggests that one year treatment with orlistat increases bone turnover in favor of

8 Ozcelik O, et al. Tohoku J Exp Med. 2005 Aug;206(4):313-8.
9 Czerwienska B, et al. Pol Arch Med Wewn. 2004 Dec;112(6):1415-23.
10 Derosa G, et al. Diabetes Obes Metab. 2005 Jan;7(1):47-55.
11 McDuffie JR, et al. Obes Res. 2002 Jul;10(7):642-50.
12 Hollander PA, et al. Diabetes Care. 1998 Aug;21(8):1288-94.
13 Hauptman J, et al. Arch Fam Med. 2000;9:160-167.
14 James WP, et al. Int J Obes Relat Metab Disord. 1997 Jun;21 Suppl 3:S24-30.
15 Gotfredson A, et al. Int J Obes Relat Metab Disord. 2001 Aug;25(8):1154-60.
16 Tonstad S, et al. Eur J Clin Pharmacol. 1994;46(5):405-10.
17 Melia AT, et al. J Clin Pharmacol. 1996 Jul;36(7):647-53.
18 Zhi J, et al. J Am Coll Nutr. 2003 Oct;22(5):357-62.
19 Pace DG, et al. J Nutr. 2001 Jun;131(6):1694-9.

resorption with similar decreases in bone density to placebo. However, in this trial, weight loss in the orlistat-treated group was not significantly different from placebo. In the above-mentioned 21-day mineral balance study in obese men[19], markers of bone turnover did not differ between the orlistat- and placebo-treated groups. Furthermore, although the bone marker osteocalcin is carboxylated by vitamin K, it appears to be unaltered by orlistat treatment in short-term studies[19, 20] as well as in a year-long study[15].

Orlistat's effect on warfarin is less clear. A placebo-controlled study evaluating the effect of orlistat on warfarin in healthy volunteers did not demonstrate significant alterations of the pharmacokinetics or pharmacodynamics of warfarin with concomitant orlistat therapy[20]. However, a case report described a patient receiving warfarin who had an increased international normalized ratio (INR) associated with the addition of orlistat to his drug regimen[21]. In addition, because orlistat may be associated with a decline in serum vitamin K concentrations[20], the prescription orlistat label recommends that patients on chronic stable doses of warfarin who are prescribed orlistat be monitored closely for changes in coagulation parameters.

4.7 Drug Interactions

Drug-drug interaction studies were conducted as part of the prescription orlistat NDA. The prescription label for orlistat 120 mg currently reads:

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.

The impact of orlistat on the pharmacokinetics of three highly lipophilic drugs, amiodarone, fluoxetine, and simvastatin, was recently studied[22]. Although the pharmacokinetic parameters, C_{max} and $AUC_{0-\infty}$, of fluoxetine and simvastatin were not impacted by orlistat, the absorption of amiodarone, an antiarrhythmic drug, was reduced by approximately 20-25%. The authors point out that the clinical significance of this reduction in systemic exposure is unclear. As the relationship between serum concentrations of amiodarone and its efficacy has not been well-established, at a minimum, it seems a patient's physician should be aware if both drugs are taken concomitantly.

This reviewer located one potential serious drug interaction between orlistat and amiodarone in the FDA's Adverse Event Reporting System (AERS) Database. However, the narrative provides no conclusive evidence whether a true interaction occurred. This event occurred in a 65-year-old man being treated with orlistat for overweight (BMI 27.7 kg/m^2), cyclosporine for heart transplant rejection prophylaxis, and amiodarone for arrhythmia. This patient was hospitalized for nonspecific pain and later died suddenly at

20 Zhi J. et al. J Clin Pharmacol. 1996 Jul;36(7):659-66.
21 MacWalter RS, et al. Ann Pharmacother. 2003 Apr ;37(4) :510-2.
22 Zhi J, et al. J Clin Pharmacol. 2003 Apr;43(4):428-35.

home. The reporter suspected that the patient's death might have been due to a drug interaction between orlistat and amiodarone.

The two drugs for which drug-drug interactions with orlistat have been established are warfarin and the immunosuppressive agent, cyclosporine. Literature reports of drug interactions between warfarin and orlistat were discussed in Section 4.6, above. This reviewer searched the AERS database for reports of spontaneously reported drug interactions between orlistat and warfarin. Numerous reports were found of prolonged PT with concomitant orlistat use and several other reports were found suggesting a shortening or lability in PT. This reviewer is awaiting an official tally on these drug-drug interactions reported in the AERS database from the FDA's Office of Drug Safety. Potentially important findings in the currently identified reports include serious bleeding (hemarthrosis) in one patient, and an INR reaching a level of 12.2 in another.

A reduction in the serum concentration of cyclosporine has been seen with co-administration with orlistat. Because weight gain is fairly common after organ transplantation, the concomitant use of cyclosporine and orlistat is more than a theoretical possibility, and may lead to dangerously sub-therapeutic immunosuppression[23]. Fourteen unique cases of drug interactions between the two drugs were reported in the AERS database (Table 4.7.A), and a case of a 'nonsignificant acute rejection episode' (ISHT grade 1B) in a transplanted heart was reported in the literature[24]. In that case report, the decrease from and subsequent re-establishment of an adequate trough cyclosporine level was temporally associated with the starting and stopping of orlistat, respectively.

23 Colman E, et al. N Engl J Med. 2000 Apr 13;342(15):1141-2.
24 Schnetzler B, et al. Transplantation. 2000 Nov;70(10):1540-1.

Table 4.7.A. Unique Reports of Cyclosporine-Orlistat Interaction in FDA's Adverse Event Reporting System (AERS) Database				
Age	**Sex**	**Cyclosporine Indication**	**Outcome**	**Referenced Publications**
58	M	Renal transplant	Orlistat discontinued, reestablished cyclosporine concentration	
61	M	Heart transplant	Orlistat discontinued, reestablished cyclosporine concentration	Nagele H, et al.[25]
54	M	Heart transplant	Orlistat discontinued, reestablished cyclosporine concentration	
45	M	Liver transplant	Altered cyclosporine dose	
61	M	Nephrotic syndrome	Orlistat discontinued, reestablished cyclosporine concentration	
Unknown	M	Heart transplant	Unknown	
64	M	Unknown	Unknown	
65	M	Heart transplant	Switch to Neoral improved concentrations	Le Beller C, et al.[26]
43	M	Heart transplant	Transplant rejection (ISHT-3A = moderate rejection)	
71	M	Heart transplant	Separated dosing improved concentrations	
Unknown	F	Heart transplant	Increased dose of cyclosporine	
37	F	Unknown	Unknown	
40	F	Lung transplant	Orlistat discontinued, reestablished cyclosporine concentration	Johansson M, et al.[27]
Unknown	Unknown	Heart transplant	Unknown	

We cannot necessarily assume that the labeling for nonprescription orlistat will adequately alert patients to the potential dangers of concomitant use with cyclosporine or warfarin. Indeed, data from the orlistat Actual Use study NM17285 illustrate that only one half of subjects who were on cyclosporine or warfarin at the time of screening initially recognized that orlistat was not appropriate for their use (Table 4.7.B).

25 Nagele H, et al. Eur J Clin Pharmacol. 1999 Nov;55(9):667-9.
26 Le Beller C, et al. Transplantation. 2000 Nov 27;70 (10):1541-2.
27 Johansson M, et al. Information from the Medical Products Agency. 2000; 4:80-82.

Table 4.7.B. Subjects with Unconditional Labeled Exclusions: Appropriate Initial Selection Decision; Eligible Subjects Study NM17285					
	N	**Initially said appropriate?**	**n (%)**	**Appropriate initial selection decision**	
				Total	**n (%)**
Taking cyclosporine	2	Yes	1 (50.0)	0	1 (50.0)
		No	1 (50.0)	1	
		Don't know	0	0	
Taking warfarin	14	Yes	6 (42.9)	0	7 (50.0)
		No	7 (50.0)	7	
		Don't know	1 (7.1)	0	

Adapted from GSK Doc ID: 0900233c8032b3ea
NDA Document Page: 262 of 565

4.8 Kidney Stones

Animal data suggest that the use of orlistat (particularly with diets rich in oxalate or fat) can lead to significant increases in urinary oxalate[28]. This is presumably due to the binding of unabsorbed fat and bile acids interacting with calcium in the intestinal lumen, thereby freeing oxalate to be absorbed and subsequently excreted in the urine. These animal findings are consistent with oxalate data generated in study NM14161, which demonstrated that more subjects on orlistat compared with placebo had markedly elevated levels of 24-hour urinary oxalate. In fact, as noted by Dr. Eric Colman in his original review of the nonprescription NDA[29], two individuals in the 60 mg group who had elevated levels of urinary oxalate developed nephrolithiasis during the trial. Moreover, although the absolute numbers are low, there was a slightly higher incidence of new renal stones visualized by ultrasound after two years of treatment (2 of 413 [0.5%] placebo subjects, 4 of 262 [1.5%] orlistat 60 mg subjects, and 5 of 476 [1.1%] orlistat 120 mg subjects).

This reviewer speculates that the incidence may be higher in the real world situation in which compliance with the low-fat diet will not be monitored. It is important to note, however, that the incidence of *symptomatic* renal and ureteral calculi was not increased over two years in these trials (3 of 524 placebo subjects [0.6%], 1 of 334 [0.3%] orlistat 60 mg subjects, and 2 of 613 [0.3%] orlistat 120 mg subjects).

4.9 Hepatobiliary Findings

4.9.1 Gallstones

In contrast to a possible mechanistic link to lithogenicity in the kidney with orlistat, the data supporting such a mechanism for gallstone formation is less obvious. One published study demonstrated an impairment of gallbladder motility up to one year with 60 and 120 mg of orlistat compared to placebo[30], whereas a second study demonstrated no alteration in gallbladder motility in a single dose study with orlistat and meals of differing fat

28 Ferraz RR, et al. Kidney Int 2004 Aug;66(2):676-82.
29 Medical Officer's Review of NDA 20-766; April 1997.
30 Mathus-Vliegen EM, et al. Aliment Pharmacol Ther. 2004 Mar 1;19(5):601-11.

contents[31]. A third study demonstrated that orlistat actually inhibited the adverse changes in biliary lipid composition that can lead to gallstones in subjects undergoing dietary weight loss[32], suggesting a possible *beneficial* effect. Clinical pharmacology studies conducted in obese and normal volunteers in support of the prescription orlistat NDA demonstrated that orlistat treatment did not alter gallbladder motility, the cholesterol saturation index, or gastrin or secretin concentrations. Plasma concentration of post-prandial cholecystokinin (CCK) was lowered by orlistat.

As described in Dr. Colman's review[29] of the studies supporting the prescription orlistat NDA, gallbladder ultrasounds at one year in subjects with normal baseline studies demonstrated that 3.6% of both placebo- and orlistat 120 mg-treated subjects developed gallstones and 0.2% of placebo- and 0.5% of orlistat-treated patients developed sludge. After two years, 2.8% and 3.9%, respectively, developed gallstones and 1.0% and 0%, respectively, developed sludge. However, in subjects with *abnormal* baseline ultrasounds, 3.3% of placebo and 6% of orlistat subjects developed gallstones and 0% and 0.9% developed sludge after one year.

It is well-established that weight loss can increase the risk of cholelithiasis. Symptomatic gallbladder disease was similar between groups in the pooled clinical trials supporting safety; see Section 4.3.2.1 for a discussion of the findings of SAEs of cholelithiasis and cholecystitis at six months and one year. In the 4-year XENDOS trial, the rates of patients with cholelithiasis as an adverse event were 2.9% (47/1649) for orlistat 120 mg and 1.8% (30/1655) for placebo[33]. In this trial, the increase in cholelithiasis was similar for orlistat and placebo at similar amounts of weight loss.

4.9.2 Pancreatitis

In 2002, based on spontaneous *reports* of pancreatitis in patients treated with orlistat, the European Agency for the Evaluation of Medicinal products requested that Roche add pancreatitis to the Undesirable Effects section of the European Union (EU) orlistat package insert.

Based on review of data from controlled clinical trials, the Company's Global Drug Safety Database (used to calculate the proportional reporting ratio for pancreatitis), a general epidemiological database from the UK, preclinical studies, and relevant published literature, Roche concluded that there was no evidence for a causal relationship between orlistat and pancreatitis. The current EU label does not include pancreatitis in the Undesirable Effects section.

Based on an initial review of the orlistat-pancreatitis question, the Division of Metabolism and Endocrinology Products requested that Roche include in the prescription orlistat labeling information the increased incidence of cholelithiasis in orlistat vs. placebo-treated subjects from a large, 4-year controlled trial (results discussed above in

31 Froehlich F, et al. Dig Dis Sci. 1996 Dec;41(12):2404-8.
32 Trouillot TE, et al. Am J Gastroenterol. 2001 Jun;96(6):1888-94.
33 Internal data.

Section 4.9.1, gallstones).

Because nonprescription drugs carry a greater burden of safety than prescription agents, GlaxoSmithKline's proposal to take orlistat over-the-counter led the Division of Metabolism and Endocrinology Products to revisit the orlistat-pancreatitis issue.

In addition to an update on the number of *reports* of pancreatitis in subjects exposed to orlistat, a count of *reports* of pancreatitis associated with sibutramine, the only other drug FDA-approved for long-term weight loss, was requested from FDA's Office of Drug Safety. Sibutramine serves as a crude control for the potential confounding effect of weight loss on the incidence of gallstones.

Sibutramine was approved by FDA in November 1997 and orlistat in April 1999. Since 1999, the number of prescriptions for orlistat in the US is estimated to be approximately 1.5 times that of sibutramine[33]. As of November 2005, there were a total of 94 unique *reports* of acute pancreatitis (29 from the US) for orlistat and 8 for sibutramine (1 from the US) in FDA's Adverse Event Reporting System.

Based on a number of different analyses, Roche concluded in 2003 that there was no evidence to support a causal association between orlistat and pancreatitis. An up-to-date accounting from FDA's Adverse Event Reporting System identifies a sizable imbalance in the number of *reports* of pancreatitis for orlistat in comparison with sibutramine.

The Division's investigation of the orlistat-pancreatitis data continues as of this writing. We anticipate a more detailed discussion of this issue at the 23 January 2006 Advisory Committee Meeting.

4.9.3 Liver findings

The effect of orlistat on the liver was reviewed in the literature and in the clinical trial database. As of this writing, there are four published case reports of hepatotoxicity temporally associated with the use of orlistat[34, 35, 36, 37]. In two of these reported cases, the patient developed subacute hepatic failure requiring liver transplantation[34, 37]. A causal relationship cannot be definitively established from these reports; however, in the case of the two cases of liver failure requiring transplant, neither of the patients was on any other drug therapy and there was a clear temporal relationship to orlistat administration.

This reviewer, in an exploratory search of AERS, found nine unique cases of orlistat associated with acute or subacute hepatic failure or cholestatic hepatitis. Two of these cases were reported in the literature as discussed above[34, 35]. Two other cases resulted in death, and one case resulted in liver transplantation. Several of the patients were on concomitant medications and one consumed excessive alcohol. None of these case

34 Montero JL, et al. J Hepatol. 2001 Jan;34(1):173.
35 Lau G, et al. Med Sci Law. 2002 Oct;42(4):309-12.
36 Kim DH, et al. Taehan Kan Hakhoe Chi. 2002 Sep;8(3):317-20.
37 Thurairajah PH, et al. Eur J Gastroenterol Hepatol. 2005 Dec;17(12):1437-8.

reports demonstrate a definitive association between orlistat and hepatic failure or hepatitis.

As seen in Section 4.10 on laboratory findings, the incidence of markedly abnormal ALT, AST, and total bilirubin in the clinical studies supporting safety was similar between treatment groups. One subject in the clinical studies (orlistat 30 mg, study NM14302) had an ALT value 46x the upper limit of normal on study day 78. She was diagnosed with hepatitis A (IgM antibody positive). She discontinued the study, and follow-up laboratory values demonstrated improvement.

Finally, several authors have in fact reported an improvement in steatohepatitis associated with orlistat-induced weight loss[38, 39, 40].

4.10 Laboratory Findings

4.10.1 Safety laboratory values

Mean changes in hematology and chemistry safety parameters in the pooled safety studies and study NM17247 were for the most part similar between treatment groups. In particular, there were no clinically significant mean differences over time or between treatment groups in serum values of sodium, potassium, or phosphorus, or in hemoglobin values.

It is noted that mean alkaline phosphatase values were higher in the orlistat groups as compared with placebo in the pooled studies at six months of treatment (Table 4.10.1.A), and the mean difference in alkaline phosphatase between treatment groups was statistically significant in the 4-month pivotal study (mean difference in change: 1.41, 95% CI: 0.06, 2.76; orlistat versus placebo). Although alkaline phosphatase is unfractionated, making it difficult to conclusively determine its source, this finding is consistent with a study[15] evaluating the effect of orlistat on other markers of bone turnover (see Section 4.6, above), and has been reported elsewhere[40]. Although the clinical significance is debatable, such increases may reflect an indolent vitamin D insufficiency.

38 Hatzitolios A, et al. Indian J Gastroenterol. 2004 Jul-Aug;23(4):131-4.
39 Harrison SA, et al. Aliment Pharmacol Ther. 2004 Sep 15;20(6):623-8.
40 Sabuncu T, et al. Rom J Gastroenterol. 2003 Sep;12(3):189-92.

Table 4.10.1.A. Serum Alkaline Phosphatase; Pooled Studies Safety Population (normal range: 40-150 U/L)			
	N	**Mean Value at Visit +/- SD**	**Mean Change from Baseline +/- SD**
Placebo			
Day 1	632	88.5 +/- 26.14	
Week 12	584	89.9 +/- 24.81	1.1 +/- 11.62
Week 24	537	90.5 +/- 25.94	1.5 +/- 12.32
Week 52	398	91.2 +/- 27.28	1.5 +/- 16.82
Orlistat 60 mg			
Day 1	622	87.1 +/- 25.09	
Week 12	602	91.6 +/- 26.62	4.7 +/- 11.81
Week 24	549	91.8 +/- 26.85	4.5 +/- 12.54
Week 52	431	91.1 +/- 25.34	3.1 +/- 13.74
Orlistat 120 mg			
Day 1	629	87.0 +/- 24.69	
Week 12	597	91.8 +/- 25.12	4.8 +/- 12.03
Week 24	551	91.2 +/- 25.18	4.7 +/- 13.25
Week 52	425	89.1 +/- 25.96	2.5 +/- 16.00

Adapted from GSK Doc ID: 0900233c80357420
NDA Document Page: 21 of 26

The sponsor summarized the incidence of marked laboratory abnormalities in the pooled studies as well as study NM17247 (Tables 4.10.1.B and 4.10.1.C, respectively). Please see the Appendix for a table of cut-offs for marked laboratory abnormalities. The incidence of marked laboratory abnormalities in one year of treatment in the pooled studies was generally similar between treatment groups. Although there was a greater percentage of subjects in the orlistat 60 mg group in study NM17247 (Table 4.10.1.C) with overall marked abnormalities than the placebo group, the incidence of individual laboratory tests with these abnormalities was generally similar between groups, with the exception of markedly low serum phosphorus (0.5% placebo, 2.6%, orlistat). This finding was not noted in the pooled studies.

Table 4.10.1.B. Frequency of Marked Laboratory Abnormalities in Year 1 of Treatment; Safety Population; Pooled Studies						
	Placebo N = 634		**60 mg tid N = 623**		**120 mg tid N = 632**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects with 1 or more marked abnormalities	37	(5.8)	33	(5.3)	42	(6.6)
Marked High Abnormalities						
Creatine Phosphokinase	14	(2.2)	15	(2.4)	13	(2.1)
GGT	3	(0.5)	1	(0.2)	5	(0.8)
Potassium	4	(0.6)	3	(0.5)	3	(0.5)
Phosphorus	0		1	(0.2)	3	(0.5)
ALT (SGPT)	2	(0.3)	0		3	(0.5)
Hematocrit	1	(0.2)	0		2	(0.3)
Hemoglobin	0		0		2	(0.3)
Thyroid Stimulating Hormone	2	(0.3)	1	(0.2)	1	(0.2)
Neutrophils	0		0		1	(0.2)
Platelet Count	1	(0.2)	0		1	(0.2)
AST (SGOT)	1	(0.2)	1	(0.2)	0	
Total Bilirubin	1	(0.2)	1	(0.2)	0	
Eosinophils	1	(0.2)	1	(0.2)	0	
Basophils	0		1	(0.2)	0	
Alkaline Phosphatase	1	(0.2)	0		0	
Sodium	1	(0.2)	0		0	
Marked Low Abnormalities						
WBC	2	(0.3)	5	(0.8)	6	(0.9)
Neutrophils	3	(0.5)	4	(0.6)	3	(0.5)
Platelet Count	4	(0.6)	4	(0.6)	2	(0.3)
Lymphocytes	0		0		2	(0.3)
Sodium	0		0		1	(0.2)
Hematocrit	2	(0.3)	1	(0.2)	0	
RBC	1	(0.2)	1	(0.2)	0	
Hemoglobin	2	(0.3)	0		0	

Adapted from GSK Doc ID: 0900233c80357420
NDA Document Page: 1 of 2

Table 4.10.1.C. Frequency of Marked Laboratory Abnormalities in Four Months of Treatment; Safety Population; Study NM17247				
	Placebo N = 195		**60 mg tid N = 196**	
	n	**(%)**	**n**	**(%)**
Subjects with 1 or more marked abnormalities	15	(7.7)	22	(11.2)
Marked High Abnormalities				
ALT (SGPT)	5	(2.6)	4	(2.0)
AST (SGOT)	4	(2.1)	3	(1.5)
GGT	2	(1.0)	3	(1.5)
Potassium	1	(0.5)	1	(0.5)
Phosphorus	0		1	(0.5)
Total Bilirubin	0		1	(0.5)
Marked Low Abnormalities				
Phosphorus	1	(0.5)	5	(2.6)
Neutrophils	2	(1.0)	4	(2.0)
Lymphocytes	2	(1.0)	2	(1.0)
WBC	2	(1.0)	2	(1.0)
Platelet Count	1	(0.5)	1	(0.5)
Monocytes	0		1	(0.5)
Chloride	1	(0.5)	0	

GSK Doc ID: 0900233c80357420
NDA Document Page: 2 of 2

4.10.2 Glucose and insulin

Table 4.10.2.A illustrates changes in fasting glucose over one year in the pooled safety studies BM14149, NM14161, and NM14302, combined. Data for changes in insulin were not pooled similarly to other safety measures in the Integrated Summary of Safety in the nonprescription NDA; however, it is clear that orlistat-related weight loss is associated with predictable improvements in measures of glucose homeostasis and insulin sensitivity. It is noted that subjects receiving orlistat 120 mg in studies from the original prescription NDA had statistically significant decreases in glucose, insulin, and insulin resistance (assessed by HOMA) compared to subjects receiving placebo over a one- and two-year period.

Moreover, a 4-year study demonstrated that 120 mg of orlistat tid plus lifestyle intervention reduced the incidence of the development of type 2 diabetes in obese patients with impaired glucose tolerance compared to those receiving placebo plus lifestyle intervention[7].

Overweight subjects treated with orlistat 60 mg in study NM17247 achieved modest improvements in serum glucose over placebo, but the difference between groups was statistically significant in the ITT LOCF analysis population only (Table 4.10.2.B).

Table 4.10.2.A. Fasting Glucose (mmol/L): Safety Population; Pooled Studies BM14149, NM14161, NM14302						
Study Day	**Value at Scheduled Visit**			**Change from Start of Study Medication**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
Placebo						
Day 1	632	5.58	0.763	632	0.00	0.000
Week 12	580	5.59	0.736	578	0.00	0.556
Week 24	537	5.61	0.794	537	0.02	0.593
Week 52	398	5.69	0.715	398	0.13	0.508
Orlistat 60 mg tid						
Day 1	622	5.58	0.720	622	0.00	0.000
Week 12	600	5.54	0.657	599	-0.05	0.442
Week 24	547	5.54	0.650	546	-0.05	0.447
Week 52	429	5.62	0.689	428	0.02	0.531
Orlistat 120 mg tid						
Day 1	629	5.55	0.584	629	0.00	0.000
Week 12	594	5.51	0.609	591	-0.05	0.462
Week 24	552	5.51	0.655	549	-0.06	0.481
Week 52	424	5.60	0.801	422	0.03	0.585

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NDA Document Page: 1 of 6

Table 4.10.2.B. Change in Fasting Glucose (mmol/L) Measurements at 4 Months – Study NM17247								
Treatment	N	Within Treatment		Difference From Placebo				
		Mean Baseline Value	LS Mean Change From Baseline	LS Mean	SE	95% CI Lower	95% CI Upper	P-Value
ITT LOCF								
Placebo	175	4.90	0.04					
Orlistat 60	188	4.93	-0.07	-0.11	0.05	-0.21	-0.02	0.023
Completer								
Placebo	140	4.88	0.05					
Orlistat 60	152	4.92	-0.02	-0.07	0.06	-0.18	0.04	0.207
ITT Observed								
Placebo	138	4.87	0.06					
Orlistat 60	154	4.92	-0.03	-0.09	0.06	-0.19	0.02	0.126

Adapted from GSK Clinical Update

An additional consideration in the discussion of glucose and insulin changes, particularly as it relates to the nonprescription use of orlistat, is the safety of orlistat in patients with diabetes on antihyperglycemic therapy. Certainly, improvements in hemoglobin A1c (HbA1c) and decreases in antihyperglycemic medication dose are significant benefits of weight loss in patients with diabetes.

However, because of the risk of hypoglycemia in patients on antihyperglycemic therapy who are losing weight, and the fact that modification in diabetes therapy should be done in concert with the health care provider, this reviewer believes that orlistat would be used most safely by these patients in the prescription drug setting. This concern is amplified by the results provided in Table 4.10.2.C below. Although the label as written for the Actual Use study included the exclusion 'taking medicine for diabetes', only 35% of such subjects in study NM17285 made an appropriate initial selection decision.

Table 4.10.2.C. Subjects with Unconditional Labeled Exclusions: Appropriate Initial Selection Decision; Eligible Subjects, Study NM17285					
	N	**Initially said appropriate?**	**n (%)**	**Appropriate initial selection decision**	
				Total	**n (%)**
Taking medicine for diabetes	46	Yes	24 (52.2)	0	16 (34.8)
		No	16 (34.8)	16	
		Don't know	6 (13.0)	0	

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NDA Document Page: 262 of 565

4.10.3 Lipids

Orlistat has been touted as having a beneficial impact on lipid parameters. Short-term studies demonstrate that orlistat treatment is associated with reduced delivery of dietary lipid and fatty acids to the liver[41]; and long-term evidence of lowered total and LDL-cholesterol may be a byproduct of weight loss or adherence to a low-fat diet.

The orlistat 60 mg and 120 mg treatment groups exhibited approximate decreases in total cholesterol of 3.1% and 4.9%, respectively, as compared to an increase of 2.1% in the placebo group at six months. At one year, the total cholesterol in the placebo group increased to 2.3% of baseline, whereas the improvements (decreases) in the orlistat 60 and 120 mg were attenuated somewhat, to 1.2% and 3.1%, respectively. 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 six months. Given the weight loss in the placebo group, the mean increases in total and LDL cholesterol is somewhat puzzling, especially as these subjects reportedly followed a low-fat diet. An increase in HDL cholesterol was seen in all treatment groups at six months, with the highest increase seen in the placebo group (6.6%) versus orlistat 60 mg (3.3%) and 120 mg (0.8%).

Table 4.10.3.A illustrates the lipid changes observed in the 4-month nonprescription trial in overweight subjects. Total and LDL cholesterol decreased in both groups, with a significantly greater decrease in the orlistat group. As for HDL cholesterol, whereas the placebo group had a mean increase, the orlistat group had a mean decrease; the difference between groups was not statistically significant, however. Both groups had a decrease in LDL/HDL ratio, with the orlistat group demonstrating a slightly greater decrease; the difference between groups was not statistically significant. Both groups had an approximately 15% increase in triglycerides, possibly as a result of a greater contribution of carbohydrate to the diet.

41 Reitsma JB, et al. Metabolism. 1994 Mar;43(3):293-8.

Table 4.10.3.A. Percent Change of Least Square Means in Lipids — LOCF Data, ITT Population; Study NM17247								
Treatment	**Within Treatment**			**Difference From Placebo**				
	N	**Mean Baseline Value**	**LS Mean % Change From Baseline**	**LS Mean**	**SE**	**95% CI Lower**	**95% CI Upper**	**P-Value**
Total Cholesterol								
Placebo	175	5.35	-0.09					
Orlistat 60mg	188	5.27	-3.77	-3.69	1.32	-6.28	-1.09	0.006
LDL Cholesterol								
Placebo	175	3.24	-0.48					
Orlistat 60mg	187	3.12	-5.93	-5.44	2.10	-9.57	-1.32	0.010
HDL Cholesterol								
Placebo	175	1.49	0.42					
Orlistat 60mg	188	1.51	-1.90	-2.32	1.46	-5.20	0.55	0.113
LDL/HDL Ratio*								
Placebo	175	2.32	-0.05					
Orlistat 60mg	187	2.19	-0.12	-0.07	0.05	-0.17	0.02	0.122
Triglycerides								
Placebo	175	1.37	15.06					
Orlistat 60mg	188	1.41	14.80	-0.26	5.92	-11.90	11.39	0.966
* Not a percentage change.								

4.11 Vital Signs and Electrocardiograms (ECGs)

4.11.1 Blood Pressure

In the pooled studies BM14149, NM14161, and NM14302, the mean change in systolic blood pressure was small for all treatment groups. At 6 months, both 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. At one year, the mean change in systolic blood pressure for both the 60 mg and 120 mg orlistat groups was 0.5 mmHg compared to a mean change of 1.0 mmHg for the placebo group. Mean changes in diastolic blood pressure were small as well. At 6 months, the orlistat 60 mg group demonstrated a mean change of -0.3 mmHg, the orlistat 120 mg group had a mean change of -0.6 mmHg, and placebo showed a mean change of 0.4 mmHg.

In the LOCF ITT population in study NM17247, the least squares mean change from baseline to the end of treatment at 4 months for systolic blood pressure was -4.51 mmHg for orlistat-treated subjects and -2.34 mmHg for placebo-treated subjects (adjusted for center and baseline value); this difference was statistically significant (p=0.035). The least squares mean change from baseline to the end of treatment at 4 months for diastolic blood pressure was -2.77 mmHg for the orlistat-treated subjects and -0.30 mmHg for the placebo-treated patients; this difference was statistically significant (p=0.001). It is notable that these measurements were not adjusted for amount of weight lost; therefore, this reviewer assumes that the significant differences are due to acute weight loss rather than an independent drug effect. Furthermore, as demonstrated by the pooled studies

discussed above, any effect in blood pressure is likely transient because differences between orlistat groups and placebo appear to decrease with time.

In study NM14150 (phase 2 dose-ranging), decreases in systolic and diastolic blood pressure after six months were less in the orlistat treatment groups (60 mg: -0.97 and -0.54 mmHg, respectively; 120 mg: +3.51 and -2.01 mmHg, respectively) as compared to the placebo group (-1.23 and -2.08 mmHg, respectively); none of the adjusted differences between groups were statistically significant.

4.11.2 Pulse

Mean heart rate changes were small and similar between orlistat and placebo treatment groups in all studies.

4.11.3 ECGs

Twelve-lead ECGs were performed at screening, baseline, and after each year of treatment in the pooled safety studies, and at screening only in study NM17247. There were no clinically significant differences in ECG findings or changes between orlistat and placebo groups in these studies.

5 SPECIAL POPULATIONS

5.1 Children and Adolescents

To support the labeled indication for Xenical use in adolescents (patients aged 12-16), Roche submitted two studies under NDA 20-766 for review by the Agency under a written request for pediatric exclusivity: 1) a 21-day placebo-controlled mineral balance study in 32 subjects (results published October 2003[18]), and 2) a 54-week placebo-controlled study, including a 2-week placebo lead-in, of 539 obese (BMI > 97th percentile) subjects (results published June 2005[42]). The indication for use in this age group was approved December 12, 2003.

The mineral balance study was discussed in Section 4.6. There were no deaths or serious adverse events in this 21-day study, with the majority of adverse events from the gastrointestinal system (81% orlistat, 56% placebo). One Black female subject had an increase of ALT from 23 U/L at baseline to 79 U/L on day 22, AST from 15 U/L to 33 U/L, and GGT from 52 U/L to 76 U/L. There were no follow-up values in this subject.

The primary objectives of the 54-week study were to characterize the efficacy and safety of orlistat 120 mg tid as an adjunct to diet in the treatment of obese pediatric patients. Safety was defined by gastrointestinal tolerability; linear growth and Tanner pubertal stage assessment; bone mineral content and body composition; fat-soluble vitamin, beta-carotene; and gallbladder and renal ultrasound. All subjects received a multivitamin. After one year, orlistat use resulted in a statistically significant decrease in BMI as compared to placebo (-0.55 kg/m^2 versus +0.31 kg/m^2, p = 0.001). In the subgroup of subjects who underwent dual-energy x-ray absorptiometry (DEXA) evaluation, subjects in the orlistat group gained a similar amount of fat-free body mass and lost significantly more fat mass than those in the placebo group. Gastrointestinal adverse events were more common in the orlistat-treated group. Two female subjects underwent cholecystectomy; one was for cholelithiasis and one was for functional disorder of the gallbladder. No subject developed cholecystitis during the study. Of the subjects with normal gallbladder ultrasounds at baseline, six orlistat-treated subjects and one placebo-treated subject had gallstones at the end of the study. There was no evidence that orlistat treatment impacted growth, sex hormone concentrations, or sexual maturation. In the subgroup of subjects who underwent DEXA, bone mineral content and bone mineral density increased similarly in the two treatment groups independently of sex. The mean concentrations of measured fat soluble vitamins and beta-carotene increased in both groups, as a result of multivitamin supplementation. The adjusted mean difference from placebo in beta-carotene was significantly different (-2.4 µg/dL, p < 0.001), and there was a trend toward a difference between orlistat and placebo in vitamin E (adjusted mean difference: -40.26 µmol/L, p = 0.089). In subjects with normal renal ultrasound at baseline, there were two abnormalities seen in the orlistat group (mild left hydronephrosis and 6 mm echogenic focus) and none in the placebo group.

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42 Chanoine JP, et al. JAMA. 2005 Jun 15;293(23):2873-83.

There are limited studies in the literature that examine the effects of treatment with orlistat in obese adolescents or children; all studies have been open-label and do not appear to have uncovered any additional concerns.

As discussed in Section 6.1, although misuse is a possibility in this population, there are no published reports of adolescents with eating disorders misusing orlistat. One case report discusses the case of a 16-year-old female who developed significant gastrointestinal side effects from combining orlistat with olestra[43]. In this patient, discontinuing olestra use improved the adverse side effects.

Finally, and most importantly, it is clear that the diagnosis and treatment of obesity in children and adolescents requires the involvement of a learned intermediary, both to exclude organic causes of obesity and to provide the requisite interdisciplinary services to these children. Therefore, although the safety profile of orlistat in the pediatric population is similar to that of adults, nonprescription drug treatment of obesity in this population is considered inappropriate.

5.2 Elderly

Older people derive significant benefit from weight loss. It can ameliorate disease complications, improve mobility, and enhance quality of life. However, aging is associated with a loss of lean body mass and bone, and therefore, weight loss in older individuals should be undertaken with care to avoid further losses of these tissues. As discussed in Section 3.1, ruling out concomitant illness and addressing nutritional issues are two important roles for the health care provider in the management of weight loss in the elderly population. In addition, the potential for multiple drug-drug interactions is increased as older people are maintained on more medications. This section will briefly discuss the limited data on orlistat-mediated weight loss in the elderly population.

Current guidelines for the management of obesity in older adults[6] assert that the available data from drug trials are insufficient to determine the efficacy and safety of pharmacotherapy for obesity in older persons because these trials tend to exclude older subjects. In the clinical trials primarily supporting efficacy and safety in this application (BM14149, NM14161, NM14302, and NM17247), mean age was approximately 45 years, with a range up to 80 years. However, because only approximately 2.4% of orlistat-treated subjects were aged 65 years or older (about 15 per group in the pooled safety studies), it is difficult to make any conclusions about safety or efficacy of orlistat in this population based on these studies.

The distribution of subjects in the following age groups: 60-69 years, 70-79 years, and ≥ 80 years from the Actual Use study NM17285, is presented in Table 5.2.A. Approximately 15% of subjects in the purchasers and users groups were 60 years of age or older, and 4.2-4.6% of subjects were 70 years of age or older. The mean age of

43 Heck AM, et al. Ann Pharmacother. 2002 Jun;36(6):1003-5.

subjects in the Consumer Use study, RCH-ORL-002 was 36 years with a range of 18-73 years.

Table 5.2.A. Number and Percent of Subjects ≥ 60 Years by Group, Study NM17285								
Age Group	**All Screened Subjects N = 703**		**Eligible Subjects N = 681**		**Purchasers Group N = 252**		**Users Group N = 237**	
	n	%	n	%	n	%	n	%
60-69 Years	100	(14.2)	96	(14.1)	29	(11.1)	24	(10.1)
70-79 Years	36	(5.1)	29	(4.3)	11	(4.2)	11	(4.6)
≥ 80 Years	4	(0.6)	4	(0.6)	1	(0.4)	0	

Adapted from GSK Doc ID: 0900233c8032b3ea
NDA Document Page 247 of 565

To the knowledge of this reviewer, there have been no studies conducted with orlistat designed specifically to address the safety and efficacy of this drug in the elderly population. Specific safety concerns beyond that of general weight loss include: nutritional deficiencies such as that of vitamin D, drug-drug interactions, and gastrointestinal intolerability, which may result in social or hygiene problems.

Therefore, given the limited data and multiple complexities with weight management in this population, further consideration should be given to the nonprescription availability of orlistat to the elderly.

6 NONPRESCRIPTION ISSUES

6.1 Misuse/Abuse

Because orlistat is systemically absorbed to a very limited extent and is not believed to affect the central nervous system, the sponsor considers the risk of abuse potential, that is, physical dependence, to be low. The gastrointestinal side effects of orlistat are typically a deterrent to its misuse or of dietary indiscretion. Nevertheless, the use of orlistat as a purgative after binge episodes has been reported in four patients with bulimia nervosa[44, 45, 46]. In such cases, orlistat has actually been shown to have the opposite of the desired effect on eating behavior, where it is used during a high-fat binge, in some sense, enabling the maladaptive eating behavior. A misconception soon after orlistat arrived on the market was that one could eat whatever he or she wanted while taking the drug and still lose weight[47]. The concern certainly remains that the misconception will prevail, particularly with the greatly broadened availability and marketing that occurs with switching a drug to nonprescription status. Furthermore, given the prevalence of weight concern experienced by adolescents and even younger children[48], this reviewer believes there is likely going to be some degree of inappropriate use of nonprescription orlistat in this population, despite limiting its labeling to ≥ 18 years.

6.2 Historical Perspective

Phenylpropanolamine (PPA), a decongestant and anorectant, was withdrawn voluntarily from the market in 2000 due to its association with hemorrhagic stroke. Prior to its withdrawal, the extended release formulation was marketed as a nonprescription weight loss drug for short-term use (up to 12 weeks). Its demonstration of efficacy was based on four studies, 6-12 weeks in duration, which demonstrated statistically significant weight loss from placebo in overweight and obese subjects on a hypocaloric diet[49]. Unlike the

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44 Fernandez-Aranda F, et al. Int J Eat Disord. 2001 Dec;30(4):458-61.
45 Malhotra S, et al. Am J Psychiatry. 2002 Mar;159(3):492-3.
46 Cochrane C, et al. Eat Behav. 2002 Summer;3(2):167-9.
47 Garrow J. BMJ. 1998 Sep 26;317(7162):830-1.
48 Field AE, et al. Pediatrics. 2001 Jan;107(1):54-60.
49 The following studies were described in a letter from FDA to Nonprescription Drug Manufacturers Association, May 1994:
(1)Weintraub M, et al. "Phenylpropanolamine OROS (Acutrim) vs. placebo in combination with caloric restriction and physician-managed behavior modification," Clinical Pharmacology and Therapeutics, 1986 May;39(5):501-9.
(2)Schteingart D. "A Double Blind Clinical Evaluation of the Anorectic Activity Of Phenylpropanolamine (75mg) Compared with Placebo in the Treatment of Exogenous Obesity," unpublished study in Comment No. CP11, Docket No. 81N-0022, Dockets Management Branch.
(3)Greenway F. "A Double Blind Clinical Evaluation of the Anorectic Activity Of Phenylpropanolamine (75mg) Compared with Placebo in the Treatment of Exogenous Obesity," unpublished study in Comment No. CP11, Docket No. 81N-0022, Dockets Management Branch.
(4)Atkinson R. "A Double Blind Clinical Evaluation of the Anorectic Activity of Phenylpropanolamine (75 mg) Compared with Placebo In the Treatment of Exogenous Obesity," unpublished study in Comment No. CP14, Docket No. 81N-0022, Dockets Management Branch.

current regulatory requirements for approval of prescription drugs for weight loss, at that time the Agency's criterion for a weight control ingredient to be considered effective was that it had to demonstrate statistically significant weight reduction in double-blind, placebo-controlled studies lasting six to 12 weeks. In the referenced studies, 75 mg daily of extended-release PPA was shown to affect a placebo-subtracted weight loss of 0.14 to 0.25 kg/week. It should be noted that the adjusted mean placebo-subtracted weight loss in overweight subjects taking orlistat 60 mg (-1.2 kg over 16 weeks in study NM17247) is equivalent to a weight loss of only 0.075 kg/week. Even in the obese population, the adjusted mean placebo-subtracted weight loss of -2.3 kg over 24 weeks (pooled studies) is equivalent to 0.096 kg/week.

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

7 CONCLUSIONS

The National Institutes of Health's 2000 *Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*[1] recommends weight loss through a combination of diet modification, increased physical activity, and behavior therapy for obese patients, and for patients who are overweight or have a high-risk waist circumference, when accompanied by two or more risk factors. In the event that lifestyle changes do not promote weight loss after 6 months, drugs should be considered as adjunctive therapy for select patients who have a BMI $\geq$ 30 kg/m^2, or a BMI $\geq$ 27 kg/m^2 if concomitant obesity-related risk factors or disease exist. This mirrors FDA's current approach to the approval of prescription weight-loss drugs.

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

FDA currently uses two criteria to judge the efficacy of prescription weight-loss drugs: 1) The mean drug-associated weight loss exceeds the mean placebo-associated weight loss by at least 5% or 2) The proportion of subjects who reach and maintain a loss of at least 5% of their initial body weight is greater in subjects on drug than in those on placebo.

The efficacy benchmark of 5% is based on evidence that, in obese individuals, clinically meaningful improvements in blood pressure, cholesterol, glycemic control, and other metabolic and cardiovascular risk factors can be achieved with as little as a 5% reduction in body weight[2].

Obesity and overweight tend to be chronic conditions[3]. Successful drug treatment is therefore expected to be chronic. To assess the long-term efficacy and safety of prescription weight-loss drugs, FDA currently recommends that pre-approval trials be at least one year in duration.

In support of their proposal to take orlistat over-the-counter for short-term weight loss in overweight and obese individuals, the sponsor provided efficacy data from the 6-month time point of two 1-year studies of individuals with BMIs $\geq$ 28 kg/m^2 from the original prescription NDA, and the data from one 4-month study of individuals with BMIs of 25 - 28 kg/m^2, which was designed for the nonprescription NDA.

In the pooled studies from the prescription NDA, 42% of subjects treated with orlistat 60 mg, 45% of subjects treated with orlistat 120 mg, and 23% of those treated with placebo achieved a weight loss of $\geq$ 5% at six months ($p < 0.001$, orlistat vs. placebo).

By contrast, in the nonprescription NDA clinical study, 36% of orlistat 60 mg-treated subjects vs. 28% of placebo-treated subjects lost at least 5% of their baseline body weight

at four months (p = 0.104). In an analysis proposed by the sponsor, the percent of orlistat-treated subjects achieving a 3% weight loss was statistically significantly greater compared to placebo after four months of treatment (57% versus 42%, p = 0.004).

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

These findings raise the possibility that orlistat may be less effective in mildly overweight individuals (i.e., BMIs 25 - 28 kg/m^2) than in obese subjects. The sponsor has not studied the effects of 6 months of orlistat therapy in this population, however.

Treatment with orlistat was associated with small favorable changes in blood pressure, lipids, and fasting glucose. Although not studied by the sponsor, it is well-known that once weight-loss treatment is stopped, lost weight is quickly regained and improvements in co-morbidities undone[1].

Since very small amounts of orlistat are absorbed from the GI tract into the blood stream, the potential for systemic toxicity with this drug is presumably low. In addition to the risk for fat-soluble vitamin deficiencies, the greatest documented harms associated with orlistat's use are drug-drug interactions.

Since its approval as a prescription weight-loss drug in 1999, FDA has received numerous reports of adverse interactions between orlistat with cyclosporine and warfarin. Patients on cyclosporine who started orlistat have rapidly developed subtherapeutic levels of cyclosporine, increasing their risk for organ rejection. Patients on warfarin who initiated treatment with orlistat have developed markedly elevated prothrombin times, increasing their risk for hemorrhage. This effect is presumably due in whole or part to orlistat-associated vitamin K deficiency or insufficiency.

The prescription orlistat labeling includes warnings about the potential for adverse drug-drug interactions with cyclosporine and warfarin. It is somewhat concerning that in a pilot nonprescription actual use study, 50% of patients who were on cyclosporine or warfarin failed to heed the labeled precautions regarding the concomitant use of orlistat.

In summary, the sponsor is proposing to market nonprescription orlistat for short-term weight loss in overweight and obese individuals. The efficacy criterion of a significantly greater proportion of subjects on drug attaining 5% weight loss than placebo was achieved in the pooled studies from the prescription NDA (subjects with BMIs ≥ 28 kg/m^2) at 6 months, but not in the 4-month nonprescription study (subjects with BMIs 25 - 28 kg/m^2). Treatment of overweight and obese subjects with orlistat for 4 to 6 months has been shown to decrease weight by an average of 1.2 kg to 2.9 kg (1.6% to 3.1% of baseline weight) relative to placebo. Once treatment is stopped after 6 months, it is assumed that lost weight will be regained. The principal documented risks associated

with orlistat are reduced levels of fat-soluble vitamins and drug-drug interactions with warfarin and lipid-soluble drugs such as cyclosporine and perhaps amiodarone. Other potential safety concerns include nephrolithiasis, cholelithiasis, hepatitis, and possibly pancreatitis, although the causative role of orlistat in these conditions remains inconclusive, and in the case of pancreatitis, currently under investigation.

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8 APPENDIX

8.1 Narratives of Deaths

NM14302

Subject 13144/0083 (Diet Lead-in): A 40-year-old obese white female weighing 81.0 kg at screening (BMI = 34.6) died on day 107 of the weight loss lead-in period due to a closed head trauma resulting from being struck by an automobile. On day 105 of the weight loss lead-in period, the subject was struck by an automobile while crossing the road. She experienced blunt trauma to her head, neck, thorax, abdomen, and upper and lower extremities. She was hospitalized and experienced complications due to increased brain swelling which necessitated surgery. On day 106, a partial frontal lobectomy and placement of an intracranial pressure catheter was performed. The subject died the next day, on day 107, due to a cerebral hemorrhage.

BM14149

Subject 12823/M019 (60 mg tid): A 61-year-old obese white male weighing 96.8 kg (BMI = 32.7) at screening died after 449 days of treatment due to a myocardial infarction. The subject presented at screening with a significant past medical history of ischemic cerebral insult and a myocardial infarction (MI) seven years before the study. The subject was known to have a history of coronary heart disease for eight years. Ongoing coronary heart disease was treated with acetylsalicylic acid (250 mg/day), pravastatin (20 mg/day), and magnesium (121.6 mg/day). The subject was a non-smoker and had a waist circumference > 100 cm. The ECG done 28 days before randomization was abnormal, indicating left axis deviation, supraventricular premature contractions, ST segment elevation (leads Vl to V5), and evidence of an old MI; it was considered clinically significant by the investigator. Serum lipid values assessed at screening were normal. Fasting insulin was elevated at screening (39 mU/L; normal range 0-14) and remained abnormal during the study. Creatine phosphokinase (CPK) values were elevated at screening (387 U/L; normal range 0-250) and also at baseline (316 U/L) and remained abnormal throughout the study. The subject refused an ECG scheduled at the baseline visit. An ECG performed on day 367 showed no new changes from the screening ECG. The lipid profile was normal, except for an elevated lipoprotein [a] (1000 U/L; normal range 0-800). CPK was also elevated at 403 U/L. On study day 449 the subject experienced heartburn and took Kompensan® (1 tablet). He was subsequently found unconscious. Cardiac resuscitation was attempted but was not successful. The cause of death as stated by the investigator was sudden cardiac death from severe coronary artery disease complicated by angina. An autopsy was not performed and no additional information is available.

NM14161

Subject 12329/408 (120 mg tid): A 55-year-old obese white male weighing 122.8 kg (BMI=38.8) at screening, died of an acute myocardial infarction on study day 317. At screening, the subject indicated that he had never smoked and had no history of hypertension, hypercholesterolemia, or diabetes mellitus. Also, he had no other significant medical history and required no concomitant medications. There was no known family history of cardiac disease. His screening and baseline ECGs were within normal limits, as was his baseline chest x-ray. The subject's waist circumference at baseline was > l00 cm. Baseline lipid results were within normal limits. Fasting glucose measured before randomization was abnormal (310 mg/dL; normal range 60-125), with a 3+ glucose in urine (normal range 0-0). Both were abnormal sporadically during the study. An oral glucose tolerance test performed at baseline indicated impaired glucose tolerance. After 122 days of double-blind treatment, the subject was diagnosed with hypertension. On day 205 of treatment, antihypertensive therapy with lisinopril 10 mg/day was begun. On day 301, the subject developed an upper respiratory infection, which was treated with erythromycin 1 g/day until day 311. Late in the evening of day 316, the subject experienced chest pain for two hours and later vomited. He went to the emergency department early on day 317 and he suddenly died from an acute myocardial infarction. The subject's weight was last recorded at 128.2 kg. The subject had no other adverse events and did not take medications other than those described during the study.

BM14150

Subject BR13966/0373 (placebo lead-in period) died due to respiratory failure (asthma) on day 24 of the lead-in period. The subject, a 45 year-old obese white female, had a history of chronic obstructive pulmonary disease. There was no autopsy performed.

8.2 Narratives of Serious Adverse Events; Study NM17247

Patient 37460/2401 (orlistat 60 mg), a 47 year-old white female weighing 67.6 kg (BMI = 25.8 kg/m^2) at baseline, was hospitalized on study day 35 for repair of an umbilical hernia. The patient had secondary diagnoses of chronic sinusitis, fibromyalgia, migraines, headache, heartburn, dysmenorrhea/symptomatic fibroid uterus, Epstein-Barr virus, biliary dyskinesia, lower-back pain, hypertension, decreased defecation, osteoarthritis and mononucleosis. At the time of the event she weighed 68.5 kg (BMI = 26.14 kg/m^2) and was taking guafenesin, venlafaxine, dyazide, sumatriptan, rofecoxib, ibuprofen, Metamucil, Centrum multivitamins, and calcium carbonate. On study day 22 the patient was diagnosed with an umbilical hernia, repair of which was performed on study day 35. In addition to the hernia repair, the patient elected to undergo total abdominal hysterectomy with bilateral salpingo-oopherectomy for a pre-existing condition of symptomatic fibroid uterus that was not worsening. She received pitressin, bisacodyl, vasotec, morphine sulfate, propoxyphere with acetaminophen and ibuprofen. Study medication was interrupted from study day 34 to study day 36. The investigator considered this event to be moderate in intensity. The event resolved on study day 35

and patient was discharged on study day 37. The patient completed study drug administration and took the last dose of study medication on study day 111.

Patient 37466/2701 (orlistat 60 mg), a 41 year-old white female weighing 80.1 kg (BMI = 27.15 kg/m^2) at baseline, was hospitalized on study day 79 for lower back pain due to herniated disk reinjury. The patient had a history of herniated disk and secondary diagnosis of allergy to codeine and furodantin. At the time of the event she weighed 78 kg (BMI = 26.4 kg/m^2) and was taking co-enzyme Q10 and Centrum multivitamin as supplements. On study day 49 the patient reported the onset of lower-back pain, for which she started taking Vioxx on study day 51. She stopped taking Vioxx on study day 78 and commenced taking percocet. On study day 75 a MRI revealed large disc extrusion at L4-L5 compressing the right L5 nerve root and disc degeneration at L1-L2 and L3-L4. A lumbar disectomy and lumbar laminectomy were performed on study day 79. The event was considered moderate to severe in intensity and resolved on study day 81. Study medication was interrupted due to this event. The patient did not complete the study and the last dose of study medication was taken on study day 98.

8.3 Cut-offs for Marked Laboratory Abnormalities

Table 8.3.A. Cut-offs for Marked Laboratory Abnormalities

Laboratory Test	Units	Pooled Studies		NM17247	
		Low	High	Low	High
Hemoglobin	g/L	100	199	110	200
Hematocrit	fraction	0.30	0.60	0.36	0.60
RBC	10^{12}/L	3.0	8.0	3.50	5.60
WBC	10^9/L	3.0	20.0	3.0	18.0
Neutrophils	10^6/L	1000	15000	1500	---
Eosinophils	10^9/L	0	1.4	0	1.5
Basophils	10^9/L	0	0.40	0	0.30
Monocytes	10^9/L	0	2.00	0.08	2.0
Lymphocytes	10^9/L	0.5	10.0	1.0	6.3
Platelets	10^9/L	100	700	100	700
AST (SGOT)	U/L	0	150	0	50
ALT (SGPT)	U/L	0	150	0	60
GGT	U/L	0	152	0	120
Alkaline phosphatase	U/L	0	375	0	190
Total bilirubin	µmol/L	0	61.6	0	34.2
Creatinine	µmol/L	0	221	0	154
BUN	mmol/L	0	17.9	0	14.3
Creatine phosphokinase	U/L	0	500	---	---
Sodium	mmol/L	130	150	130	150
Potassium	mmol/L	3.0	6.2	3.0	6.0
Chloride	mmol/L	80	120	95	115
Calcium	mmol/L	1.75	2.99	2.00	2.90
Phosphorus	mmol/L	0.61	2.26	0.75	1.60
Albumin	g/L	20	80	27	---
Total protein	g/L	45	100	55	87
TSH	µU/mL	0	10	0	10.0