

May 11, 1998

Memorandum

To: NDA 20-766 orlistat (Xenical Capsules)

From: Solomon Sobel M.D., Director, Division of Metabolic and
Endocrine Drug Products

Subject: Approvable status for Orlistat

IS/ 5-11-98

The Division has concluded that the efficacy of orlistat has been demonstrated to be adequate. Although, the mean difference between placebo and drug at orlistat is only about 3% and this fails our criterion of a 5% difference as suggested in our guidance, the categorical analysis shows significantly more subjects lost 5% and 10% of their baseline body weights than placebo subjects. This demonstration of moderate effectiveness is considered satisfactory for approval from an efficacy standpoint.

However, there is a major outstanding safety issue.

The occurrence of 10 cases of breast cancer in the treatment group versus 1 case in the placebo group during the study period and a cumulative incidence found in a follow-up survey through October of 1997 of 12 cases in the treatment group and 2 patients in the placebo group raises the question of a carcinogenic potential, probably promotional in nature.

There is also some evidence that there is a dose response.

During the clinical trial period, the incidence of cases was 9 in the 120 mg group, one case in the 30/60 group and one case in the placebo group.

When the cases discovered during the telephone survey were added there were 11 in the 120 group, 1 in the 30/60 group, and 2 in the placebo group.

When the analysis was performed by person years on trial the incidence of cases in the placebo group was 1.4 per 1000 patient years; the patients who had a consistent exposure to 120mg had an incidence of 8.47 per 1000 patient years; those with consistent exposure to 60 mg had an incidence of 3.18 per 1000 patient years. Data from the crossover studies (placebo year 2 after 120 year 1 and 60 year 2 after 120 year one had very few patient years for analysis (104 and 49 patient years respectively and yielded unstable estimates of 0 to 20.4 cases per 1000 patient years).

This finding was discussed extensively. Although there is reason to believe that a number of breast cancers were present before the study started and that the finding may represent a failure in randomization, one cannot dismiss the finding. Even eliminating the more problematic cases in regard to causality (e.g. evidence for preexistence, and early occurrence during the trial there still remains a finding, albeit at a p value of 0.12, of imbalance of occurrence in the treatment vs. placebo group. Also, it should be noted that the postulated failure in randomization would have occurred over 4 independent randomizations in the 4 different studies which had cases of breast cancer.

Another source of concern is the nature of the histology of the cancers.

Various surveys in the medical literature report the frequencies of diagnoses of lobular versus ductal carcinomas in the general population.

The incidence of ductal carcinoma is greater than lobular carcinoma with ranges up to ratios of 5:1.

It was noted that there seemed to be an unusual occurrence of the diagnosis of lobular carcinoma in the cases associated with orlistat (the cases were evenly split between ductal and lobular carcinomas.) The sponsor has performed statistical analyses and has concluded that there is no statistical difference between histological types found in the orlistat vs. the placebo group; neither, the sponsor concluded, was there statistical difference in the histological types occurring in the 1st and 2nd years.

The small number of cases make the analyses in respect to histologic type problematic.

The number of cases in the cells are very small with only 2 cases in the placebo group. Rather, it is more useful to observe the rather unusual numerical occurrence of lobular histology in the orlistat group.

Conclusion:

The Division believes that the findings in respect to breast carcinoma cannot be dismissed.

We acknowledge that there is a good possibility that this is a chance finding perhaps related to a faulty randomization of pre-existing cases.

The efficacy of orlistat is modest but acceptable for approval. We believe it would be prudent to issue an approvable letter with final approval granted only after additional data of a reassuring nature in respect to the occurrence of breast carcinoma becomes available.

We have contacted the sponsor in respect to the ongoing phase 3 studies which may be sufficient to provide reassurance in respect to breast carcinoma.

Recommendation: An approvable letter may be issued.

/s/

Solomon Sobel

CC: NDA 20-766

HFD-510 | Div File

HFD-510 | E Colman | G Troendle | B Stadel

Obese94

NDA 20766
Hoffmann-La Roche
Orlistat (Xenical)

Team Leader's note on approval of orlistat (Xenical) for obesity control

See my Comments of 4/28/97. That memorandum addressed the safety and efficacy of orlistat as it was known at that time. The efficacy was based on seven adequate and well-controlled trials. Mean weight loss or gain in one year was 1.1 to 3.7 kg (1.3 to 3.5% of initial body weight) when placebo was given, 4.8 and 5.7kg (5-5.6% body weight) when 60 mg Xenical was given, and 3.8-6.7kg (4.2-7%) when 120 mg was given. 2-year results in placebo patients were 1.3 kg loss to 5.7kg gain, and losses retained on 60 mg drug were 2-4.2kg, and on 120 mg were 1.3-5.7kg. Associated risks included failure to absorb adequate amounts of fat-soluble vitamins.

An additional safety problem surfaced at the subsequent Advisory Committee meeting, where the excess of breast cancer seen in the subjects treated with 120 mg Xenical was noted. Follow-up indicated that this finding was not replicated in similar patients. Interim results in a population of approximate size from on-going studies showed an excess of breast cancer in placebo patients. It did not appear that risk of breast cancer was significant, and it can now be approved. These on-going studies will be completed and breast cancer occurrences will be reported to the Agency.

Recommendation: Approval

AP

/s/

Gloria Troendle

4/12/99

Distribution: Original NDA, Division File HFD-510, HFD-510/GTroendle, EColman, BStadel, MHess

Orlistat (Xenical) for weight control April 28, 1997

Team Leader Comments on NDA

Orlistat is a lipase inhibitor (tetrahydrolipostatin) which produces a defect in digestion and absorption of fats, steatorrhea, and loss in the stool of fats and fat-soluble materials such as bile acids and vitamins. Only negligible amounts of orlistat are absorbed, and systemic toxicity derives from the intestinal malabsorption, not from direct systemic drug effects. It is intended for weight loss and maintenance of the loss.

Seven studies are submitted for safety and efficacy. In all of them, the primary efficacy variable is weight. Study numbers all start with BM14 or NM14 and then have 3-digit distinguishing numbers. For simplicity and to save space I use the first letter and the last three digits. The study numbers beginning with B are non US and those with N are US studies.

All of the seven studies cited for efficacy are multicenter, randomized, double-blind and placebo controlled. The objectives were to determine effects on weight-loss relative to placebo and the effects on weight regain and on correlated risk factors (waist to hip ratio, serum lipids, fasting serum glucose, insulin, and blood pressure). Study populations were obese (generally BMI >30 or with comorbidities BMI >27), male and female (about 80% female), mostly caucasian, ≥ 18 years of age and in good health. Exceptions are noted below. Quality of life was measured in some studies. During the first year of study, diet was calculated to be hypocaloric by 600 kcal/d, and, during the second year, eucaloric. Each group generally lost a mean of about 3k in 4 week diet run-in periods. Fat soluble vitamins, retinol, vitamin D, alpha-tocopherol, beta carotene and prothrombin time were measured in several studies.

The following chart shows study # (8.1 to 8.7 study numbers in Dr. Colman's review are included in the chart below, because B119 refers to two studies, C and B), doses, N/% completing, wt loss in kg/% of initial body wt lost, percent of patients who had at least 5 or 10% loss. ↑ means increased; ↓ means decreased; - indicates resulted in or yields; thus in the weight loss column, - is used to indicate the weight loss at the end of the second year, after combining year one losses with year two gains. In study N302 no drug was given during the 6 months weight loss run-in before randomization of those who lost at least 8% of initial body weight. During the subsequent one-year double-blind drug period, the endpoint is weight regain in percent of initial loss.

Stdy #	Duration & Dose	N/% compl	Wt loss/ % loss	5%	10%	Comments
B119	yr1 0	343 /76	2.5k /3	33	7	LDLC↓, VitD, Vita, β- carotene↓
C	120	345 /82	6.7k /7	66	29	
8.1	yr2 0/0	126 /81	+5.7 --1.5	25		
	0/120	127 /80				
	120/0	138 /85				
	120/120	135 /85	+3 - -4.7	47		
B149	yr1 0	243 /56	3.7k /3.5	33	16	LDLC↓, Lp(a)↓, insulin & C- peptide↓, VitD, Vita, β- carotene↓
8.2	60	242 /58	5.2k /5.6	52	26	
	120	244 /65	6.2k /6.9	60	31	
	yr2 0/0		1.3k	30		
	60/60		4.2k	41		
	120/120		5.2k	46		
N161	yr1, 0	214 /57	1.1k /1.3	25	7	LDLC↓, returned to baseline, urinary oxalate↑, possible increased risk of nephrolithiasis
8.3	60	214 /72	4.8k /5.0	36	17	
	120	214 /71	5.1k /5.7	47	25	
	yr2 0	/43	1.3k	11	1	
	60	/56	2.0k	23	10	
	120	/55	2.2k	25	18	
B119	1yr 0	114	1.8k /2.5	28	8	LDLC↓, β- carotene↓
8.4	120	114	4.3k /5.8	44	27	
N185	1yr 0	224 /62	3.5k /3	33	15	Rerandomized 443 orlistat pts @ 1y. 133 continue on P. 70% completed. LDLC ↓
8.5	120	668 /69	6.5k /7	55	25	
	2yr 0	138	+3.0	30	14	
	60	152	+3			
	120	153	+5.5	43	25	

Stdy #	Duration & Dose	N/% complet	Wt loss/ % loss	5%	10%	Comments
N302	6 mo diet	1313	11%			Hypocaloric diet 6 mo, randomized if 8% wt loss
8.6	1y 0	188 /73	+54%regain			
		30	187 /75	+50% "		
		60	173 /77	+49% "		
		120	181 /70	+31% "		
N336	1y 0	159 /72	1.8 /2.1	16	5	Pts with NIDDM Basel Loss = 2k hypoglycem drug reduced 9 vs 23% LDLC ↓
8.7		120	163 /85	3.8 /4.2	34	

The following table includes the mean weight losses and percent of patients who lost 5 or 10 percent of initial body weight for most of the studies. It differs from the above table in that results are given as difference from placebo.

Stdy#	Dose	1y - Mean loss- 2y	1y - 5% - 2y	1y - 10% - 2y
B119C	120	-4.2k	-3.2k	33% 22% 22%
B149	60	-1.5k	-2.9k	19% 11% 10%
	120	-2.5k	-3.9k	27% 16% 15%
N161	60	-3.7k	-0.7k	11% 12% 10% 9%
	120	-4.0k	-0.9k	22% 14% 18% 17%
B119B	120	-2.5k		16% 19%
N185	120	-3.0k	-2.6k	22% 13% 18% 11%
N336	120	-2.0k		18% 5%
Summary		-1.5-4.2k	.7-3.9k	11-33% 11-22% 5-22% 9-17%

After 1 year, subjects on drug had mean weight losses of 1.5 to 4.2 kg more than placebo patients; 11 to 33% more drug-treated than placebo-treated subjects had lost at least 5% of initial body weight; and 5-22% more drug than placebo patients had lost at least 10%.

After 2 years, compared to placebo patients, drug-treated subjects still had losses of 0.7 to 3.9 kg, and 11 to 22% retained 5% losses, 9-17% retained 10% losses. During the second year (Studies B119C, B149, N161, and N185) subjects were on a eucaloric diet, and in every case regained weight in spite of drug. In Study B149, the differential between drug and placebo

was a little greater at the end of 2 years than at 1 year, but in Study N161, the differential was virtually gone by the end of year 2. These are very modest results.

Not absorbing fats might be expected to help control LDLC, and indeed it appears that most of the time there is a small reduction. Other risk factors do not show consistent, significant effect, but generally move slightly in the right direction. Certain fat-soluble vitamins show a disturbing tendency to decrease during treatment, and supplementation may be necessary. Vitamins D, E and K and beta-carotene are of concern. Vitamins D and K both may affect calcium/bone metabolism, a problem in post-menopausal women. Vitamin K was assessed by prothrombin time which is relatively insensitive to levels of the vitamin. I do not know whether it is adequate for detection of problems with bone metabolism. Perhaps under-carboxylated osteocalcin would have been more useful. Vitamin E may still prove of benefit in reducing coronary heart disease, and has recently been reported to reduce progression of Alzheimer's disease. Perhaps it will prove of value in delaying onset of this condition. Although Vitamin A was not reduced, liver stores might be depleted over a long period of treatment, especially since absorption of beta carotene was reduced.

However, orlistat does not seem to have the disturbing adverse effects seen with dexfenfluramine and sibutramine, and its efficacy is similar to the efficacy of those drugs. It seems very likely that orlistat will be used in conjunction with these drugs, and the interaction has not been studied, but I know of no reason to think toxicity will be increased by the interaction. Also, orlistat has not been known to interfere with the effects of other drugs, so it may be unlikely to reduce the effectiveness of the appetite suppressants.

Recommendations:

Xenical should be discussed by the E & M Advisory Committee as scheduled.

Sponsor should do a study of the effects of orlistat on fat soluble vitamins, calcium and magnesium.

Drug should be approved with commitment to do phase 4 trial.

The fat-soluble vitamins should be monitored and/or vitamin supplements should probably be recommended.

Gloria Troendle

cc: NDA/HFD-510/HFD-510/GTroendle/EColman/MHess

**U.S. FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND ENDOCRINE
DRUG PRODUCTS**

MEMORANDUM TO THE FILE

SUBJECT: Roche's response to Approvable Letter issued 05/12/1998 and safety update

DATE of DOCUMENT SUBMISSIONS: 01/18/1999 and 03/12/1999

DATE of REVIEW: 03/22/1999

NDA#: 20-766

DRUG: Orlistat (Xenical)

SPONSOR: Roche

RELATED FDA DOCUMENTS: see memorandums dated 03/09/1999 from Dr. Bruce Stadel (HFD-510) and 03/18/1999 from Dr. H.W. Ju (HFD-344).

Background

This document is a review of Roche's response to the Agency's Approvable Letter for orlistat and the sponsor's most recent safety update for this drug.

APPROVABLE LETTER

The original NDA submission for orlistat received an Approvable Letter on 05/12/1998. The drug was not approved at that time because of concern regarding the excess number of breast cancer cases in the orlistat (10) vs. the placebo-treated (1) women, 45 years of age and older.

The Agency's May 12, 1998 Approvable Letter stated, in part:

"...final approval is contingent upon submission and review of additional data that support a conclusion orlistat does not increase the risk of breast cancer. These data should come from randomized, double-blind, placebo-controlled, parallel-group clinical studies. In the aggregate, these data should provide information on approximately as many women 45 years of age or older, and approximately as many women-years of treatment with orlistat 120 mg t.i.d. and with placebo, as did the (3a) clinical studies that showed an increase in the occurrence of breast cancer in women 45 years of age or older who were treated with orlistat 120 mg t.i.d. compared to the occurrence in otherwise similar women who were treated with placebo."

Phase 3b and XENDOS Studies

On January 18, 1999, Roche submitted their response to the Approvable Letter. The aggregate database (cut-off date of 12/31/1998) submitted was comprised of 23 randomized, double-blind, placebo-controlled trials, 6 open-label trials (5 are extensions from double-blind trials), and the XENDOS trial, which is a double-blind, placebo-controlled trial being conducted in Sweden. These studies are referred to as the phase 3b and XENDOS studies, respectively. Unlike the phase 3b studies, the XENDOS trial required all women to have a pretreatment mammogram. Those women with Class 3, 4, or 5 abnormalities were excluded from the study. This trial also differed from the phase 3b studies in that all women received a one-year follow-up mammogram.

Extent of Exposure in 3b and XENDOS Studies

The table below provides the number and patient-years of exposure to placebo and orlistat 120 mg t.i.d. for women aged 45 years and older.

Study	Placebo		Orlistat 120 mg	
	N	Patient-Years	N	Patient-Years
3b Studies	1813	635	2143	814
XENDOS	353	381	353	381

Number and Description of Breast Cancer Cases

There was one case of breast cancer reported from the 3b studies. This case was in a patient receiving placebo. There were two cases of breast cancer reported from the XENDOS trial. Both of these patients were also receiving placebo.

The one case from the 3b studies was a 53-year old female who was diagnosed with breast cancer on study day 65 after having a routine mammogram. The pathology report indicated a well to moderately differentiated infiltrating ductal carcinoma of the left breast. There was evidence of axillary node metastasis and the tumor was ER+ and PR-.

One of the cases from the XENDOS trial was a 43-year old female who was diagnosed with breast cancer 3 months after withdrawing from the study due to inadequate response. She had

received 288 days of drug (placebo) treatment. The diagnosis of bilateral breast cancer was initiated following abnormal findings on a routine mammogram. Needle biopsy confirmed the presence of bilateral infiltrating ductal carcinoma. The tumors were ER+ and PR+.

The second case from the XENDOS trial was a 52-year old female who was diagnosed with a left-sided breast cancer after receiving 288 days of double blind treatment with placebo. On study day 287 the patient felt a suspicious mass in her left breast. Cytological examination of the material aspirated from the left breast tumor showed malignant cell with low-level differentiation. Partial resection of the breast confirmed the diagnosis of atypical medullary cancer of Elston grade III. No there was no evidence of nodal involvement and the tumor was found to be negative for estrogen and progesterone receptors.

Summary of Roche's Response to Approvable Letter

Roche has submitted data from ongoing and completed placebo-controlled orlistat studies from various countries around the world. These data are comparable in scope to the data reported from the phase 3a studies. Three cases of breast cancer have been reported, all from patients taking placebo.

SAFETY UPDATE

In response to the Division's request, Roche has submitted a safety update including serious adverse events reported in the phase 3b studies, the XENDOS trial, and from post-approval experience in the countries where orlistat is currently approved. The clinical cut-off date for these data is 01/31/1999 (03/01/1999 for breast cancer).

The phase 3b and XENDOS databases were described above. As of 01/31/1999, orlistat has been available by prescription in 11 countries with over [REDACTED] prescriptions having been dispensed.

The majority of the phase 3b studies and the XENDOS trial are still blinded and therefore assignment to treatment groups is unknown in most cases. This obviously limits (or eliminates) the ability to assess the true adverse event profile of orlistat. Nonetheless, the tally of serious adverse events by COSTART terms from the phase 3b and XENDOS studies and the post-approval surveillance database indicates few cases for any particular term. There have been no spontaneous post-approval breast cancer cases reported from the countries in which orlistat is currently marketed.

Summary of Safety Update

No new safety issues are identifiable in the recently submitted safety update.

OVERALL SUMMARY AND CONCLUSIONS

The original orlistat application (phase 3a database) was not approved because of concern regarding the imbalance in the number of breast cancer cases in the orlistat vs. placebo-treated women. In response to the conditions outlined in the Approvable Letter issued 05/12/1998, the company has submitted data from their phase 3b program and the XENDOS trial. These data, comparable in scope to the phase 3a data, do not indicate that there is an increased risk for the diagnosis of breast cancer in women treated with orlistat compared with placebo.

The absence of replication of the phase 3a breast cancer findings in the phase 3b and XENDOS studies, coupled with the biological implausibility for an association between drug use and breast cancer risk, lead this reviewer to conclude that the original imbalance in breast cancer cases was a chance finding. As such, orlistat can be deemed appropriate for marketing for the indications outlined in the final approved labeling.

[redacted] /SI
3/31/99 [redacted] [redacted]
Eric Colman, MD /SI [redacted]
/ 3/31/99 [redacted]
cc: NDA Arch /SI [redacted]
HFD-510: Hess/Troendle/Stadel [redacted]

APPEARS THIS WAY ON ORIGINAL

ORIGINAL
MEMORANDUM

20-766

DATE: 9 March 1999

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology

/s/

SUBJECT: NDA 20-766, Xenical (orlistat) Capsules, 120 mg/Hoffman-La Roche, Inc.
Review of response to 12 May 1998 Approvable Letter, dated 18 January 1999
and called "Integrated Summary of Breast Cancer Information"

TO: Solomon Sobel, MD
Director, Division of Metabolism & Endocrine Drug Products

This is a follow-up to my Memo of 10 March 1998 on "Orlistat and Breast Cancer," which pertains to the 7 phase 3 randomized, double-blind, placebo-controlled, parallel-group clinical trials of orlistat that were available for review when that Memo was written. I will refer to those 7 clinical trials as the "3a studies."

In the 3a studies:

- A total of 579 women 45 years of age or older were exposed to placebo, for a total of 713 person-years (P-Y). The mean length of this exposure to placebo was 1.2 years. One case of breast cancer was diagnosed during this exposure to placebo.
- A total of 798 women 45 years of age or older were exposed to orlistat 120 mg tid, for a total of 944 P-Y. The mean length of this exposure to orlistat 120 mg tid was 1.2 years. Eight cases of breast cancer were diagnosed during this exposure to orlistat 120 mg tid.

The Approvable Letter for orlistat, dated 18 January 1999, states that:

"...final approval is contingent upon submission and review of additional data that support a conclusion orlistat does not increase the risk of breast cancer. These data should come from randomized, double-blind, placebo-controlled, parallel-group clinical studies. In the aggregate, these data should provide information on approximately as many women 45 years of age or older, and approximately as many women-years of treatment with orlistat 120 mg t.i.d. and with placebo, as did the [3a] clinical studies that showed an increase in the occurrence of breast cancer in women 45 years of age or older who were treated with orlistat 120 mg t.i.d. compared to the occurrence in otherwise similar women who were treated with placebo."

In a teleconference between the Division and the Sponsor, on 22 July 1998, agreement was reached that:

- The contingency in the Approvable Letter about breast cancer could be met by new data from additional phase 3 randomized, double-blind, placebo-controlled, parallel-group clinical trials and related open-label studies or orlistat 120 mg tid.

- The new data would come from trials/studies that did not have mammographic screening at baseline in the protocols, since this was not in the protocols of the 3a studies.
- The new data from these trials/studies would refer to more women 45 years of age or older, with more than 80% as many P-Y of exposure to orlistat 120 mg tid and placebo, as in the 3a studies.

In a submission dated 18 January 1999, the Sponsor provided new data, collected through 31 December 1998, from the following studies:

- (1) 23 randomized, double-blind, placebo-controlled, parallel-group clinical trials that have been completed (3 trials) or are in progress (20) trials and that did not have mammographic screening at baseline as part of the protocols. These provide data on 5512 women, including 3939 women who were 45 years of age or older at the time of randomization and who had a total of 1340 P-Y of exposure to orlistat 120 mg tid or placebo. From the data provided, it can be calculated that 2126 women 45 years of age or older had 705 P-Y of exposure to orlistat 120 mg tid and that 1813 women 45 years of age or older had 635 P-Y of exposure to placebo. (For trials in progress, the exposure to orlistat 120 mg tid and placebo is calculable from the total number of women and the P-Y of exposure in each trial, and the treatment allocation ratio for that trial.)
- (2) 6 open-label studies of orlistat 120 mg tid that did not have mammographic screening at baseline as part of the protocols, including: 5 open-label extensions of trials described in (1) above that provide data on 388 women including 269 women who were 45 years of age or older at the time of randomization in the trials, and 1 open-label study that is not a trial extension and that provides data on an additional 43 women including 17 women who were 45 years of age or older. In these 6 studies, the total of 286 women who were 45 years of age or older had a total of 109 P-Y of exposure to orlistat 120 mg tid.
- (3) 1 randomized, double-blind, placebo-controlled, parallel-group clinical trial that is in progress and that did have mammographic screening at baseline as part of the protocol. This study provides data on 1862 women including 706 women who were 45 years of age or older at the time of randomization and who had a total of 761 P-Y of exposure to orlistat 120 mg tid or placebo. From the data provided, it can be calculated that 353 women 45 years of age or older had 381 P-Y of exposure to orlistat 120 mg tid and that 353 women 45 years of age or older had 381 P-Y of exposure to placebo.

I will refer to the studies described under (1) and (2) above as the "3b studies," and to the study described under (3) above as the "Xendos study." ("Xendos" is the term that is currently used by Hoffman-La Roche for a study in Sweden that is formally entitled "Weight reducing and NIDDM preventing effects of Xenical in obese patients.")

In the new data from the 3b studies:

- A total of 1813 women 45 years of age or older had been exposed to placebo, for a total of 635 P-Y. The mean length of this exposure to placebo is 0.4 years. One case of breast cancer had been diagnosed during this exposure to placebo.
- A total of 2143 women 45 years of age or older had been exposed to orlistat 120 mg tid, for a total of 814 P-Y. The mean length of this exposure to orlistat 120 mg tid is 0.4 years. No cases of breast cancer had been diagnosed during this exposure to orlistat 120 mg tid.

In the new data the Xendos study: A total of 353 women 45 years of age or older had been exposed to placebo, for a total of 381 P-Y. The mean length of this exposure to placebo is 1.1 years. One case of breast cancer had been diagnosed during this exposure to placebo. A total of 353 women 45 years of age or older had been exposed to orlistat 120 mg tid, for a total of 381 P-Y. The mean length of this exposure to orlistat 120 mg tid is 1.1 years. No cases of breast cancer had been diagnosed during this exposure to orlistat 120 mg tid.

CONCLUSIONS

The new data from the 3b studies are responsive to the contingency in the Approvable letter about breast cancer, although the mean length of exposure to orlistat 120 mg tid in the 3b studies, as of 31 December 1998, was only about one-third of the mean length of exposure in the 3a studies.

The new data from the Xendos study are supportive of the 3b studies, and the mean length of exposure to orlistat 120 mg tid, as of 31 December 1998, was comparable to the mean length of exposure in the 3a studies, but the number of women exposed to orlistat 120 mg tid is not large.

The total and mean length of exposure to orlistat 120 mg tid in the 3b studies should increase rapidly over the months following 31 December 1998, since most of these are ongoing studies.

cc:

Archive NDA 20-766

HFD-510: Bstadel

Gtroendle

EColman

LLutwak

Bschneider

GTroendle

MHess

HFD-715: ENevius

LPian

APPEARS THIS WAY ON ORIGINAL