Meeting Date: May 11, 1998 Time: 3:30 p.m. – 4:30 p.m. Location: Dr. Sobel's office

NDA 20-766 Xenical (orlistat)

Type of Meeting: General (teleconference)

Meeting Chair: Dr. Solomon Sobel

Meeting Recorder: Ms. Maureen Hess

External participant lead: Dr. Daniel Zabrowski

FDA attendees and titles:

Dr. Solomon Sobel	Director, DMEDP
Dr. Gloria Troendle	Deputy Director, DMEDP
Dr. Bruce Stadel	Medical Officer, DMEDP
Dr. Eric Colman	Medical Officer, DMEDP
Ms. Maureen Hess	CSO, DMEDP
Dr. Bruce Schneider	Medical Officer, DMEDP

External participant and titles:

Dr. Dan Zabrowski	Hoffmann La-Roche, Regulatory
Dr. Jonathon Hauptman	Hoffmann La-Roche, Clinical Research
Dr. John Mathieson	Hoffmann La-Roche, Statistician
Mr. Don Cooper	Hoffmann La-Roche, Project Management
Dr. Marty Huber	Hoffmann La-Roche, Clinical
Dr. Russell Ellison	Hoffmann La-Roche, Medical Affairs

Meeting Objectives:

Requested by Hoffmann La-Roche to discuss the Agency's intended action letter and preliminary planning of follow-up data that will be required.

Discussion Points:

- Roche requested confirmation that the Agency plans to issue an Approvable letter on May 12, 1998. The Division confirmed. The firm stated that they will issue a press release regarding the Approvable status of Xenical, but would like the Agency to review it before issuance. The Division agreed.

- Roche stated that it is their understanding that they will need to provide follow-up data from a randomized, double-blind, placebo-controlled database to gain approval for Xenical. These studies should come from the Phase 3b program. The Division agreed. The sponsor added that the Xendos trial should be included in the database,

as it is a large, randomized, controlled study. The Division disagreed stating that the inclusion of entry mammography screenings in this study would decrease the sensitivity of the study. A complete absence of cancers would make the study results difficult to interpret. The Division added that if the study does not uncover cancers it would not be helpful. The Division suggested that Xendos could run until there are a certain number of cancers in the placebo group, but then that would have to be addressed in labeling. However, it strongly believes that data from Xendos should be considered as supportive evidence. The sponsor noted the Division's position regarding the Xendos data.

- The Division asked the sponsor to elaborate on the other studies (excluding Xendos) in the Phase 3b program. The sponsor stated that they estimate the other studies will have 600 patient years for women >45 years of age. If Xendos were to be included, that would provide about 400-500 patient years. The sponsor added that they would expect five to six cases of breast cancer on treatment, if the same phenomenon that occurred in 3a also occurred in 3b. The Division inquired about the start date of the Phase 3b studies. The sponsor did not have the date readily at-hand, but referred the Division to the April 9, 1998 submission which included the start date.

- The sponsor inquired about the definition of "approximately" that is stated in the pending Approvable letter. The Division responded that "approximately" means similar to that of the trial base. The Division added that it would like to see an outline in terms of how close the sponsor can come to producing a dataset similar to that of 3a, keeping in mind that Xendos would be considered supportive. The sponsor inquired if the Division is looking for a proposal regarding the number of patient years of exposure in women >45 years of age. The Division replied that the goal is to see if there is a replication of overt cancer and would like to see an expansion of the May 9, 1998 submission as far as a proposal. The sponsor agreed.

- The Division inquired about the timeline for resubmission. The sponsor replied that currently, it plans to have a full response to the Approvable letter in December 1998. The Division replied that if it were calculating things correctly, if the resubmission comes in at that time, there would not be enough exposure. The Division expressed reservations about the data coming in at that time, adding that it wants to see a dataset similar to that which gave rise to the breast cancer finding from the Phase 3a database. The sponsor replied that it understands the Division's position but disagrees with its reservations.

- The sponsor inquired if it would be acceptable to submit the follow-up data in summary format in that there will be no write-ups on clinical studies or efficacy or other adverse events included. The submission would be similar to that of the tables in the May 9, 1998 submission as well as include reports of breast cancer and information on each breast cancer case. The Division agreed that this would be acceptable.

- The sponsor inquired if no difference is found in breast cancers between the treatment and placebo group, would it be acceptable to label the original finding as is done for Pravastatin, in the Adverse Reaction section? The Division agreed that this would be acceptable. The sponsor requested the Division to define "no difference." The Division responded that "no difference" couldn't be answered with exact precision before the data are submitted. The findings will have to be reviewed and judged when the data are officially submitted, therefore the Division cannot define the term for the sponsor at this time. The sponsor acknowledged the Division's position.

- The sponsor inquired if another Advisory Committee will need to be convened to review the data from the Phase 3b program. The Division stated that it does not foresee that another Advisory Committee will be needed.

- The sponsor requested the Division to commit to a two to three month review to completely review the resubmission/follow-up data. The Division could not make that commitment because the inspections for this NDA will be expired when the NDA is resubmitted. According to PDUFA 2 any resubmission that requires inspections is coded as a Class II (6 month review time). However, the Division agreed to work with the sponsor on this issue. The sponsor stated that they have other products that use the same facilities as Xenical will use and have passed inspection. The sponsor offered to submit this information to the Division so that they could collaborate with Compliance. The Division agreed.

- The sponsor inquired if it would be possible to negotiate the label before resubmission. The Division stated that it couldn't guarantee that as they will not be on the PDUFA clock and those NDAs on the clock have priority. The Division advised the sponsor to wait on the labeling until resubmission.

[redacted]

Action Items:

- FDA will issue an Approvable letter for NDA 20-766 on May 12, 1998.

- Roche will submit its press release for NDA 20-766 to the Agency for review before issuance.

- The sponsor will submit a proposal for a database that is an expansion of their May 9, 1998 submission and that is similar in size to Phase 3a.
- Upon resubmission, the sponsor will submit its data in summary format.
- Sponsor will submit information on products and facilities that have recently passed inspection.
- The Division will confer with DSI regarding auditing foreign studies that will not be submitted to an IND.

Signature, minutes preparer: /S/ [redacted]

Concurrence chair: /S/ [redacted]

Concurrences: Bstadel/8.4.98/EColman/8.4.98/SSobel/8.5.98/

Cc: NDA 20-766
HFD-510/Div. File
HFD-510/MHess/BStadel/EColman/GTroendle/

Meeting Date: March 31, 1998 Time:2:00 p.m. - 3:00 p.m. Location: PKLN 1456

NDA 20-766 Xenical (orlistat)

Type of Meeting: General

Meeting Chair: Dr. Solomon Sobel

Meeting Recorder: Ms. Maureen Hess

External participant lead: Dr. Dan Zabrowski

FDA attendees and titles:

Dr. Solomon Sobel	Director, DMEDP
Dr. Gloria Troendle	Deputy Director, DMEDP
Dr. Bruce Stadel	Medical Officer, DMEDP
Dr. Eric Colman	Medical Officer, DMEDP
Ms. Maureen Hess	CSO, DMEDP
Dr. Leo Lutwak	Medical Officer, DMEDP
Dr. David Orloff	Medical Officer, DMEDP

External participant and titles:

Dr. Dan Zabrowski	Hoffmann La-Roche, Project Leader, Regulatory
Dr. Jonathon Hauptman	Hoffmann La-Roche, Clinical Research
Dr. Tim Anderson	Hoffmann La-Roche, Toxicology and Pathology
Dr. Martin Huber	Hoffmann La-Roche, Clinical Research, Oncology
Ms. Peggy Jack	Hoffmann La-Roche, Regulatory
Dr. Russell Ellison	Hoffmann La-Roche, Clinical Marketing, Epidemiology
Mr. Don Cooper	Hoffmann La-Roche, Project Management

Meeting Objectives:

Meeting requested by Hoffmann-La Roche to exchange views and obtain the Agency's feedback on the March 13, 1998 Advisory Committee (AC) Meeting. The sponsor also requests a discussion on next steps concerning the application.

Discussion Points:

- The firm began the meeting by requesting the Division's feedback on the outcome of the AC meeting. The Division responded that it feels that the committee conveyed that there is concern regarding orlistat and its effect on breast cancer and would like to see further studies before approval, either from current or new studies. The firm replied that this is the same committee that felt it didn't have the expertise last year to address this issue and this year they felt capable to vote, including no votes. The Division responded that the March AC addressed the breast cancer findings more

thoroughly and completely, whereby the Committee felt more knowledgeable and comfortable voting on this specific issue. The Division added that it doesn't want to analyze the votes and that the strongest message that the Committee sent was that more studies need to be done. Based on the current information, the Division is not enthusiastic about approving Xenical and feels that the additional studies need to be completed before approval. Roche responded that they feel they have thoroughly addressed the findings and that they aren't related to the drug and inquired what more the Agency wants them to do? The Division replied that a relative risk of two or more carries a variety of connotations and that a large simple trial, with a large N, for approximately one year, might bring closure to this problem. Roche replied that they have run the numbers for this scenario and assuming the same age distribution, approximately 50,000 patients would be needed in order to get enough placebo events to detect a relative risk of two with 90% power and; 8,000-9,000 patients to detect a relative risk of three. The bottom line is that it involves very large numbers and Roche believes that this would have to be done post-marketing. The Division remarked that it appreciates hearing the numbers and clarified that its comment made at the AC on replicating the NDA means if the overall pattern/rate is seen.

- Roche stated that they believe the breast cancer findings can be answered in a post-approval environment. The Division disagreed, stating that women will get breast cancer and we will have no way of determining whether it is drug related. The Division added that randomized trial data is needed to properly answer the question. Roche responded that they propose labeling that would state that women > 45 years of age should not take the drug. The Division replied that labeling restriction is not logical nor reassuring. Roche replied that is only part of their post-marketing surveillance plan proposal and would like to outline the rest of it to the Division. Roche proceeded to outline their proposal as follows:

    1. Approval of the NDA
    2. Labeling that includes disclosure of the breast cancer imbalance as well as restriction for age and disease and monitoring of women before and during drug treatment. The firm added that they would then work toward removing the age and disease restrictions, relying on the data that will be available in 1999, 2000 and 2001 from the 3B studies.
    3. Establishment of an obesity registry program- not limited to Xenical patients.
    4. External data monitoring safety board- purpose is to advise the company and monitor the breast cancer situation without compromising the integrity of the trials.

- The Division requested Roche to submit their proposal in writing and stated that there will be a Center level meeting to discuss this application and the post-marketing proposal can be presented at this meeting. The Division added that it is still not enthusiastic about approving the drug and recommended to Roche that they withdraw their application again for further study. Roche rejected the Division's request to withdraw stating that if they took such an action, it would "kill their drug."

- The Division stated that they will review the written post-marketing surveillance plan and provide it to Center management.

Signature, minutes preparer: /S/ [redacted]

Concurrence Chair: /S/ [redacted]

Concurrences:Bstadel/5.5.98/Llutwak/5.5.98/GTroendle/5.5.98/EColman/5.5.98/Ssobel/5.6.98

cc: NDA 20-766
HFD-510/Div. File
Attendees

Meeting Date: February 11, 1998 Time:2:30 p.m. - 4:00 p.m. Location: PKLN 13B45

NDA 20-766 Xenical (orlistat)

Type of Meeting: General

Meeting Chair: Dr. Solomon Sobel

Meeting Recorder: Ms. Maureen Hess

External participant lead: Dr. Dan Zabrowski

FDA attendees and titles:

Dr. James Bilstad	Director, ODE II
Dr. Solomon Sobel	Director, DMEDP
Dr. Gloria Troendle	Deputy Director, DMEDP
Dr. Bruce Stadel	Medical Officer, DMEDP
Dr. Eric Colman	Medical Officer, DMEDP
Ms. Maureen Hess	CSO, DMEDP
Dr. Leo Lutwak	Medical Officer, DMEDP
Dr. Bruce Schneider	Medical Officer, DMEDP
Dr. Karen Johnson	Medical Officer, DODP
Dr. Julie Beitz	Medical Team Leader, DODP
Dr. Lee Pian	Statistician, DMEDP
Ms. Kathleen Reedy	Advisory Committee Staff, CDER

External participant and titles:

Dr. Dan Zabrowski	Hoffmann La-Roche, Project Leader, Regulatory
Dr. Jonathon Hauptman	Hoffmann La-Roche, Clinical Research
Dr. Susan Sacks	Hoffmann La-Roche, Epidemiology
Dr. Tim Anderson	Hoffmann La-Roche, Toxicology and Pathology
[redacted]	[redacted]
Dr. Martin Huber	Hoffmann La-Roche, Clinical Research
Mr. Rudy Lucek	Hoffmann La-Roche, Regulatory

Meeting Objectives:

Requested by Hoffmann-La Roche to discuss the presentation of Xenical at the March 13, 1998 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee.

Discussion Points:

- Hoffmann-La Roche began by stating that the key points of this meeting for them include; FDA thoughts on resubmission, update on safety report, logistics of the Advisory Committee (AC) meeting. They asked the Agency to explain how they foresee the AC meeting.

- Dr. Colman stated that he will begin the FDA presentation with an overview of efficacy and other safety issues, but will not discuss the breast cancer issue in his segment. Dr. Stadel will follow with a presentation on the breast cancer issue and Dr. Colman will close the FDA presentation with summary/conclusions and possibly a risk/benefit slide.

- Ms. Reedy provided an update on the status of the AC members. She stated that Dr. Roger Illingsworth (E & M member) will not be present. Dr. Richard Simon (biostatistician) and Dr. Derek Raghavan (oncologist), both members of the FDA oncology drugs AC, will serve on the 3/13/98 AC meeting and will have voting privileges. Dr. Sobel added that the Agency is attempting to engage breast cancer epidemiology experts to serve as consultants.

- The sponsor stated that they plan on presenting a brief overview of the efficacy, but that the majority of their time will be devoted to the breast cancer issue. The breast cancer issue will include discussion on how the problem was discovered, how the patients were identified, expert reviews, a summary of patient data, possible mechanisms and their conclusions. They are planning to have representatives from several disciplines available to answer questions as well as to make formal presentations. [redacted]

  The sponsor stated that they plan to provide an update on the second follow-up survey, including risk factors, and ongoing Phase 3B clinical trials. The sponsor stated that it will provide all information to the Division for review before it is presented to the AC and that there will be no other information on analyzed data that will be presented other than that the Division already has. The Division requested that no other material be submitted after 2/17/98. The sponsor agreed.

- Dr. Stadel distributed a background packet on orlistat and breast cancer. This backgrounder is the basis for his presentation and requested that the sponsor review the packet to ensure accuracy of the data. Dr. Stadel also requested the sponsor to provide the missing information in sections 3.2.1 and 3.4. The sponsor agreed.

- The sponsor requested the Agency's feedback on the November 1997 resubmission. Dr. Johnson stated that she reviewed volumes 1, 2 and 3. She acknowledged and agreed that some cases of the breast cancer cases are pre-existing, but that there should have been pre-existing cases on placebo as well, so the submission does not alleviate the safety concerns. Dr. Beitz added that many cases weren't suitable for analysis, therefore it was difficult to assess what is occurring. The sponsor stated that their consultants say there is no evidence of abnormal tissue growth (stimulation) or tumor growth. Dr. Johnson inquired if this conclusion is based on proliferative markers? The firm stated that this conclusion is based on pure histology only. Dr. Colman inquired if this is subjective opinion? The firm replied affirmatively. In reference to the table in the resubmission that noted estrogen receptor status, Dr. Johnson inquired if this will be updated. The firm replied that it will not. Dr. Beitz inquired if other cancers were found and if there were any in men. The firm responded that there are 15 other cancer cases and it has not been broken down by gender. The firm added that they will be providing this information shortly, in a table of all cancers by body system that Dr. Colman previously requested.

- The sponsor inquired about the basis for the Division's request for more information on the Swedish (Xendos) Study. The Division replied that if there is a causal relationship, this trial may be able to provide more useful information. The sponsor disagreed, stating that the study will not be long or large enough to see a meaningful difference. In addition, they stated it is not ethical to conduct a trial to determine whether or not the drug causes breast cancer. The Division replied that should not be the purpose of the trial. The null hypothesis should be the absence of an increase in risk and the trial could proceed until there is breast cancer occurrence in placebo. The sponsor stated that would have to be discussed and want to keep the focus of this meeting on the upcoming AC.

- Roche requested that another meeting occur shortly before the AC to discuss the presentations in depth. The Division agreed to another meeting.

Decisions (agreements) reached:

- The Division will meet with the sponsor again prior to the AC meeting.

Signature, minutes preparer: /S/ [redacted]

Concurrence Chair: /S/ [redacted] 3/31/98

Concurrences:
JBeitz/3.23.98/Bstadel/3.23.98/Lpian/3.23.98/Llutwak/3.23.98/GTroendle/3.24.98/Ecolman/3.24.98/Ssobel/3.25.98/Bschneider/3.23.98/

cc: NDA 20-766
HFD-510/Div.File
Attendees

FEB 3 1998

Meeting Date: January 14, 1998 Time: 10:30 a.m.- 11:15 p.m. Location: PKLN 1456

NDA 20-766 Xenical (orlistat)

Type of Meeting: General (internal)

Meeting Chair: Dr. Eric Colman

Meeting Recorder: Ms. Maureen Hess

FDA Attendees

Dr. Solomon Sobel, Director, DMEDP
Dr. Eric Colman, Medical Officer, DMEDP
Dr. Gloria Troendle, Deputy Director, DMEDP
Dr. Lee Pian, Statistician, DOB
Dr. Rob Shore, Biopharmaceutist, DPE-2
Dr. Leo Lutwak, Medical Officer, DMEDP
Ms. Maureen Hess, CSO, DMEDP
Dr. Bruce Schneider, Medical Officer, DMEDP
Dr. Mike Fossler, Biopharmaceutist, DPE-2
Dr. Bob DeLap, Director, DODP, (HFD-150)
Dr. Karen Johnson, Medical Officer, DODP, (HFD-150)
Dr. Julie Beitz, Medical Team Leader, DODP, (HFD-150)
Dr. Lynn van Ummersen, Fellow, Georgetown University (HFD-150)

Meeting Objectives:

Meeting requested by DMEDP to discuss the breast cancer data and possible association with Xenical use.

Discussion Points:

- Dr. Johnson stated that after reviewing Roche's resubmission, she concludes that there is inconclusive clinical data to link a possible association between orlistat use and the risk of developing breast cancer. Dr. Johnson added that she feels that their resubmission cannot fully address the issue and has concerns regarding incomplete data. She stated that they didn't fully describe hormone receptor status and the mammographer was not blinded. In addition, missing from the expert reviews, is consideration of a potential hypothesis beyond noting the absence of effect in pre-clinical carcinogenicity studies.

- Dr. Colman inquired about the possibility of orlistat having a promotional effect. Dr. Johnson replied that it is possible that orlistat may be acting as a promoter, at

least indirectly, but that the current data does not address this issue. She added that additional studies would be needed to look for a possible promotional effect, if there were concern that a real association existed (i.e., not due to chance or bias).

- Dr. Schneider stated that it appears some orlistat is absorbed, (a few mg/day) and that promotional effects on endocrine responsive tumors can be rapid, affecting cell size and cell number.

- Dr. DeLap indicated that there is an overwhelming likelihood that the cancer occurrences are a false signal. He added that if the drug is approved, it might be helpful to put into place some type of monitoring system. DMEDP questioned the need for mammograms should the drug get approved. DODP replied that special guidelines would not be needed and stated that the current mammography recommendations for American women would suffice.

- DMEDP inquired whether DODP would like to make a presentation at the 3/13/98 Advisory Committee meeting. DODP felt that it was not necessary, stating that they would help DMEDP by reviewing the slides and participating in meetings with the company if necessary.

Decisions (agreements) reached:

- Presentations at the March 13, 1998 Advisory Committee meeting will be the sole responsibility of DMEDP.

- DODP will provide DMEDP with their written review by the end of the month.

Signature, minutes preparer: /S/ [redacted]

Concurrence Chair: /S/ [redacted]

Concurrences:
LPian/1.26.98/RShore/1.26.98/MFossler/1.27.98/LLutwak/1.27.98/EColman/1.27.98/GTroendle/1.28.98/BSchneider/1.28.98/SSobel/1.28.98/KJohnson/2.2.98/JBeitz/2.2.98/RDeLap/2.2.98

cc: NDA 20-766
HFD-510/Div.File
HFD-510/Stadel
Attendees
HFD-150

Meeting Date: August 26, 1997 Time: 1:30 p.m. - 2:30 p.m. Location: Dr. Bilstad's office

NDA 20-766 Xenical (orlistat)

Meeting Type: Advice

Meeting Chair: Dr. Sobel and Dr. Bilstad

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External participant lead: Dr. Dan Zabrowski

Meeting recorder: Ms. Maureen Hess

FDA attendees and titles:

Dr. Jim Bilstad, Director, ODEII
Dr. Solomon Sobel, Director, DMEDP
Ms. Maureen Hess, CSO, DMEDP

External participants and titles:

Dr. Dan Zabrowski Hoffmann-La Roche, Vice President
[redacted] [redacted]

Meeting Objectives:

Meeting requested by Hoffmann-La Roche to discuss their option of withdrawing their new drug application for Xenical (orlistat).

Discussion Points:

- Hoffmann-La Roche (HLR) stated it is considering withdrawing the NDA for orlistat but would like more information about the process of withdrawal and of resubmission. HLR asked whether the drug could be approved for use in a patient population not at risk for breast cancer, viz., in men. FDA stated it would not consider that to be a viable option. If the drug is a breast cancer promoter in women, it is possible the drug may have the same effect in men. Furthermore, even if the drug were to be approved only for use in men, it likely would be used by a large number of women.

- HLR stated that if the NDA is withdrawn, it would aim to resubmit the application in September 1997, by which time the overall response rate for the survey should be about 80% (85% in the U.S. and 75% in Europe). Any further information on the survey obtained after that time would be submitted in a safety update. HLR expressed concern, however, about the amount of time the FDA might take to make a filing decision and

- The firm inquired as to whether the mineral balance study needs to be presented. The Division recommended that since the final study report is not available, to present the whole mineral balance study. The firm replied that the data would be no different than what was submitted to the Agency. The Division replied that the firm should present whatever data is available at the time of the AC meeting.

- The Division stated that it plans to present the following:

    1. Overview of Phase 3 studies
    2. Efficacy-pooled data sets
    3. Safety- (study 302), vitamin supplementation, percentage with two consecutive low values
    4. Renal ultrasound
    5. Bone metabolism-DEXA and PTH

- The Division inquired about the firm's plans regarding presentation of the vitamin supplementation issue. The firm replied that they will present that the more obese a patient, the more depleted the vitamin levels.

- The firm requested the Division's advice on whether or not to present the breast cancer cases. The Division recommended that the firm present the breast cancer findings as well as their conclusions. The firm agreed.

Decisions (agreements) reached:

- What will be presented to the Advisory Committee on May 14, 1997 by the firm and the Division.

Unresolved issues or issues requiring further discussion:

- None

Action Items: [redacted] APPEARS THIS WAY ON ORIGINAL

- None

Signature, minutes preparer: [redacted] /S/

Concurrence Chair: [redacted] /S/

cc: NDA 20-766
HFD-510/Div. File
Attendees
HFD-510/DLawson