Meeting Date: August 25, 1997 Time 10:00 a.m. - 11:40 a.m. Location: PKLN 1456

NDA 20-766 Xenical (orlistat)

Meeting Type: Advice

Meeting Chair: Dr. Sobel and Dr. Bilstad

NOV 5 1997

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
Mr. Wayne Pines	APCO Associates, President, Health Care Practice
Dr. Steve Hill	Hoffmann-La Roche, Head of Global Development (on speaker phone)

Meeting Background and Objectives:

As reported in the NDA (received on 11/27/96), among women age 45 or older involved in the phase 3 studies, there were 9 cases of breast cancer among the 747 (1.47%) women taking orlistat, 120 mg tid, compared to only 1 case among the 579 women in the placebo group. Because of this significant imbalance of breast cancer cases among women treated with orlistat and because breast cancer was not specifically looked for in the clinical studies, the FDA requested the sponsor to attempt to contact all women age 45 or older who had taken part in the phase 3 clinical studies to determine their breast cancer status. In an NDA amendment dated 8/21/97, Hoffmann-La Roche reported that the survey was 72% complete (1188/1642) and that 2 additional breast cancer cases had been detected among women taking orlistat, 120 mg tid, and 1 additional case among women in the placebo group.

This meeting was requested by Hoffmann-La Roche to obtain a preliminary assessment of the 8/21/97 submission and to discuss what action the Agency will take on 8/27/97 (PDUFA goal date).

Discussion Points:

- FDA staff noted the findings of the survey to date are not reassuring with 2 additional cases of breast cancer in the 120mg orlistat group and 1 in the placebo group. FDA stated it now believes a new prospective clinical study will be needed to address this issue, which could possibly be done in the study Hoffmann-La Roche (HLR) is planning to conduct in Sweden.

- HLR representatives stated it was their understanding that FDA is concerned if there is a statistically significant difference in the number of breast cancer cases between the orlistat and placebo groups. FDA noted that the .05 level of statistical significance is more applicable to efficacy than to safety concerns and that it also takes into consideration, e.g., the relative risk. HLR asked how low the relative risk would need to be for the application to be approved. FDA responded that it was unwilling to cite a specific level, but that it is a matter of judgment taking into consideration all the information known about the drug.

- HLR stated it does not believe orlistat causes breast cancer because the drug is not systemically absorbed and the genotoxicity studies are negative. HLR believes the findings are either due to chance or detection bias. FDA responded by noting that the amount of drug absorbed in humans is not known. Although it is likely to be less than 1 to 2 % based on the animal studies, FDA noted it cannot thereby infer that the drug could not have a role, e.g., as a cancer promoter. Furthermore, the breast cancer cases were spread out over multiple investigators and studies and were not clustered in one or two locations. In addition, there is no evidence to support a detection bias, even though that had been explored, e.g., whether weight loss leads to increased detection of breast cancer.

- FDA action options were discussed. HLR suggested FDA could take an approvable action. FDA explained it was unwilling to do so in this situation because such an action implies that the Agency believes the drug ultimately will be approved after certain items are completed or information is submitted. In this case the FDA does not have sufficient reassurance that the drug does not cause breast cancer to take an approvable action.

  FDA said the only option available at present is to issue a non-approval letter unless HLR withdraws the application. HLR said it would be unwilling to withdraw the NDA, but suggested FDA simply allow the application to go overdue, which would then allow the survey to be completed. HLR also suggested this issue be taken back to the Advisory Committee before any action is taken. FDA stated it is unwilling to let the application go overdue either to complete the survey or to allow further discussion at an Advisory Committee meeting. FDA noted the survey is nearing completion and the likelihood is

too small that the results in the remaining patients would favor the drug sufficiently to allay the concerns with the current imbalance. FDA noted that it had discussed this issue at numerous internal meetings including a CDER Policy meeting and that the consensus from these meetings was that a non-approval letter should be issued. However, FDA also said it would be willing to present the breast cancer issue again to the Advisory Committee after the survey is completed and the data have been submitted and reviewed by FDA.

- HLR said that if the FDA issues a non-approval letter, it would have to make a public statement to the financial community and would like the Agency to look at it before it issued. FDA agreed to do so.

Decisions (agreements) reached:

- None

Unresolved issues or issues requiring further discussion:

- None

Signature, minutes preparer: /S/ [redacted]

Concurrence, chair: /S/ [redacted] /S/ [redacted]

Meeting Date: August 19, 1997 Time 1:30 p.m. - 2:30 p.m. Location: PKLN 1456

NDA 20-766 Xenical

Meeting Type: General (Teleconference)

Meeting Chair: Dr. Sobel

External participant lead: Dr. Dan Zabrowski

FDA attendees and titles:

Dr. Solomon Sobel, Division Director, DMEDP
Dr. Bruce Stadel, Medical Officer, DMEDP
Dr. Lee Pian, Statistician, DOBII
Dr. Eric Colman, Medical Officer, DMEDP
Dr. Ed Nevius, Supervisory Statistician, DOBII
Ms. Maureen Hess, CSO, DMEDP

External participants:

Mr. Harry Bohigian	Hoffmann-La Roche, Business
Mr. Don Cooper	Hoffmann-La Roche, Project Management
Dr. Russell Ellison	Hoffmann-La Roche, Clinical Marketing
Ms. Peggy Jack	Hoffmann-La Roche, Regulatory
Dr. John Mathieson	Hoffmann-La Roche, Statistics
Dr. Tony Rhymer	Hoffmann-La Roche, Clinical Research
Mr. Tom Silberg	Hoffmann-La Roche, Business
Dr. Dan Zabrowski	Hoffmann-La Roche, Regulatory

Meeting Objectives:

Meeting requested by Hoffmann-La Roche to discuss their on-going data collection of the breast cancer survey as well as the discovery of three new breast cancer cases.

Discussion Points:

- Dr. Sobel began the teleconference by stating that the Division would like to explain to the firm the new calculations that have been performed with the inclusion of three new cases of breast cancer, bearing in mind that all the data has not yet been received. Dr. Stadel stated that focusing on those women in the studies who are greater than 45 years of age, adding the three new cases puts the Fishers exact test at .08; the odds ratio is 4.3. He added that there is still a serious margin of concern, and there is a tremendous vulnerability associated with the

drug.

- The firm responded that the breast cancer submission will be hand delivered on August 21, 1997.

- The Division would like more time to thoroughly explore and address the breast cancer findings and asked the firm if they had any suggestions for a proposed time frame. The firm responded by stating that they feel they have been very diligent in their efforts and will have obtained >80% of the results. The final update will be provided to the Division on 9/1/97. The firm added that it does not expect the number of new cases to change very much and will also be providing reports by several consultants that address pre-existing conditions. The Division replied that confounding at baseline is improbable and it is invalid to look at pre-existing conditions only in the breast cancer cases, need to also look at the pre-existing conditions in those who did not have a breast cancer diagnosis.

- The firm stated that their statistical analysis consists of person years of exposure as the denominator and then compare treatment with relative risk. The firm added that it believes this denominator is the most appropriate, relevant and valid. The Division replied that the most rigorous analysis is an intent to treat analysis and is the most appropriate.

- The Division reiterated its desire to review the breast cancer findings thoroughly and correctly and expressed the need for more time. The firm replied that if they withdrew the application, they would be admitting there is a problem with the drug and therefore, are not willing to withdraw. The firm requested the Division to extend the PDUFA clock. The Division replied that the clock has already been extended once and cannot be extended a second time. The firm asked that if they don't withdraw the application, the Agency will take issue some type of action letter on 8/27/97. The Division responded affirmatively. The firm replied that they received a unanimous vote for approval by the Advisory Committee and something should be able to be done within CDER management. The Division referred the firm to the Advisory Committee transcripts and stated that the Advisory Committee still had questions regarding the breast cancer findings associated with the drug.

- The firm stated that they feel the different calculation method the Division uses is a major issue. The issue of using person years in the denominator vs using the number of people randomized makes it difficult to evaluate the data. The Division asked for clarification that, if exposure time was used, the firm is

implying that the exposure to drug exceeds the 2:1 randomization. The firm replied affirmatively. The Division asked for further explanation. The firm stated that using an exposure time, an event is counted as long as the firm knew about the patient. The Division asked if a completer denominator is being used. The firm replied negatively. The Division stated that it comes down on whose risk one is willing to err on.

- The Division inquired as to what will be included in the submission. The firm stated that their hypothesis is that there is no association of Xenical with breast cancer and feel the submission will support that. The submission will contain the following:

  1. Number of observed cases
     Person Years at Risk

     120 mg vs placebo
     60 and 30 mg vs placebo
     All Xenical vs placebo

  2. Analysis of the above calculations and comparison to the SEER database with age standardization.

  3. Analysis by Dr. Ken Rothman looking at cumulative exposure of drug over time.

- The Division stated that they have a clear impression that dose is related (120 mg) to the findings and inquired as to what Dr. Rothman has found. The firm replied that his analysis shows that the breast cancer findings are more due to chance.

- The firm stated that they will hand deliver the submission the afternoon of August 21, 1997. The Division stated that it would contact the firm after it has had a preliminary look at the findings.

Decisions (agreements) reached:

- The firm will hand deliver breast cancer submission on August 21, 1997.

- The Division will teleconference with the firm after it has had a preliminary look at the submission

Action Items:

- None

Signature, minutes preparer: /S/ [redacted]

Concurrence Chair: /S/ [redacted]

Concurrences: LPian/9.11.97/BStadel/9.11.97/EColman/9.12.97/SSobel/9.15.97

cc: NDA 20-766
HFD-510/Div. Files
Attendees
HFD-715/ENevius/LPian
HFD-510/DLawson

APPEARS THIS WAY ON ORIGINAL

JUL 18 1997

Meeting Date: July 1, 1997 Time: 10:30 a.m. - 11:30 a.m. Location: PKLN 14B56

NDA 20-766 Xenical

Type of Meeting General (teleconference)

Meeting Chair: Dr. Sobel

External participant lead: Ms. Peggy Jack

Meeting Recorder: Maureen Hess

FDA attendees and titles:

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

External participants:

Ms. Peggy Jack	Hoffmann-La Roche, Director, Regulatory Affairs
Dr. Anthony Rhymer	Hoffmann-La Roche, Clinical
Dr. John Mathieson	Hoffman-La Roche, Statistician

Meeting Objectives:

Requested by FDA to discuss the additional information that was submitted by Hoffmann-La Roche on May 23, 1997 on patients with breast cancer.

Discussion Points:

- The Division reviewed the incidence of breast cancer with the firm. The Division feels that there is not enough evidence at this time to support detection bias. The Division stated that weight loss was not substantial enough to facilitate detection. In addition, the Division stated that it is concerned that Xenical could in theory be a breast cancer promoter. The Division requested the firm to execute a follow-up survey to determine who has received a diagnosis of breast cancer among all women who were 45 years or older when randomized. Dr. Sobel reiterated that he stated at the Advisory Committee meeting that a rapid ascertainment of the database should be performed. Dr. Sobel further stated that the following should be part of the survey: when was last mammogram and has there been a diagnosis of breast cancer.

- The Division asked if this information could be obtained in approximately a month on all women greater than 45 years of age when randomized. The firm replied that it may not be feasible and inquired if it is acceptable to survey a few centers. The Division replied that a complete ascertainment is preferred. The firm stated that this will be a very difficult undertaking and in no way will be complete, except for Scandinavia's data. The Division agreed with the firm that it is a difficult task to undertake, but added that women > 45 years have a breast cancer incidence of one in eight or nine and with Xenical, currently there is an odds ratio of seven. The Division added that breast cancer is an extremely volatile issue and this issue needs to be thoroughly investigated before the drug goes on the market.

- The Division summarized that it advised the firm, in February 1997, to get consultants to look at this issue. However, the firm's presentation at the Advisory Committee was superficial and there is currently no clear evidence that the association between orlistat and breast cancer was due to detection bias. The firm replied that it will look at the feasibility of surveying the women and will get back to the Division within two weeks regarding what they feel is possible to do.

Decisions (agreements) reached:

- The firm will contact the Division within two weeks.

Unresolved issues or issues requiring further discussion

- None

Action Items

- None

Signature, minute's preparer: /S/ [redacted]

Concurrence Chair: /S/ [redacted]

cc: NDA Arch
HFD-510
Attendees
HFD-510/DLawson

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MAY 28 1997

Meeting Date: May 19, 1997 Time: 10:30 a.m.- - 11:30 a.m. Location: Dr. Sobel's office

NDA 20-766 Xenical (orlistat)

Type of Meeting: General (Teleconference)

Meeting Chair: Dr. Sobel

Meeting Recorder: Maureen Hess

FDA attendees and titles:

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

External Participant attendees and titles:

Dr. Tony Rhymer	Hoffmann-La Roche, Medical
Dr. John Mathison	Hoffmann-La Roche, Statistician
Dr. Jerry Kamm	Hoffmann-La Roche, Toxicologist
Ms. Peggy Jack	Hoffman-La Roche, Regulatory Affairs

Meeting Objectives:

Requested by FDA to obtain more information on breast neoplasms cited in the NDA.

Discussion Points:

- The Division began the teleconference by reviewing the fax that was sent to the firm on May 16, 1997.

- The Division inquired as to how many patients were in the controlled studies. The firm replied approximately 4,200. The Division inquired about the other 2,800 patients. The firm replied there were no known cases of breast cancer. The Division asked how long were the exposures. The firm replied two weeks, they were clinical pharmacology studies.

- The Division requested that the firm also provide information on the number of post menopausal women (by treatment group) stratified by hormone replacement therapy who developed vaginal bleeding on drug.

- The Division inquired as to how many patients were in the crossover studies. The

firm replied, approximately 150. The Division inquired as to how many patients received pure placebo. The firm replied approximately 1400. The Division asked the firm if it is correct to conclude that all breast cancers were in the non-crossover studies. The firm replied that is correct.

- The Division inquired as to whether the firm had any studies that examined examined changes in the estrogen catechol pathway. The firm replied that they will have to check, but it is doubtful.

- The Division stated that the breast cancers were in four different studies and asked the firm's opinion on whether there is a common denominator. The firm replied that they have not been able to find one.

- The Division asked whether the age distribution was similar in study 119C. The firm replied affirmatively and added that BMI was also similar.

- The firm stated that the 149 study was a concern to them.

Decisions (agreements) reached:

- The firm will fax the requested information May 20, 1997.

Unresolved issues or issues requiring further discussion:

- None at this time.

[redacted] BEST POSSIBLE

Action Items:

- Firm will fax the requested information and the Division will review the data.

Signature, minutes preparer: /S/ [redacted]

Concurrence Chair: /S/ [redacted]

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

HESS

MAY - 9 1997

Meeting Date: May 6, 1997 Time: 2:00 p.m. - 2:40 p.m. Location: PKLN 1456

NDA 20-766 Xenical (orlistat) Capsules

Type of Meeting: Advice (Teleconference)

Meeting Chair: Dr. Colman

External participant lead: Ms. Peggy Jack

Meeting Recorder: Maureen Hess

FDA participants:

Dr. Eric Colman, Medical Officer DMEDP
Ms. Maureen Hess, CSO, DMEDP

External participants:

Dr. John Hauptamn	Hoffmann-La Roche,
Dr. Bill Canovatchel	Hoffmann-La Roche,
Dr. Dan Pace	Hoffmann-La Roche,
Dr. Tony Rhymer	Hoffmann-La Roche,
Ms. Peggy Jack	Hoffmann-La Roche, Director, Regulatory Affairs

Meeting Objectives:

Requested by Hoffmann-La Roche for guidance on preparation for May 14, 1997 Advisory Committee Meeting.

Discussion Points:

- Hoffmann-La Roche began the teleconference by stating that they would like:

  1. Overview with the Division what they plan to present to the Advisory Committee.
  2. Overview of the Division's presentation.
  3. Issues the Division would like the firm to present.

- The firm stated that for clinical efficacy, they will present study 119C and 185 both one and two year data. They will also present two year data for study 149 as well as lipid data, OGTT. In addition, diabetes study 336 will also be included. Safety will include overall exposure, withdrawals, serious adverse events (including neoplasms), GI effects, gallbladder ultrasound, renal ultrasound, lab findings, fat soluble vitamins A, D, E, K and calcium and mineral balance study.

Meeting Date: July 22,1998 Time: 1:30 p.m. – 3:00 p.m. Location: PKLN 1456

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. Bruce Stadel	Medical Officer, DMEDP
Dr. Eric Colman	Medical Officer, DMEDP
Ms. Maureen Hess	CSO, DMEDP
Dr. Todd Sahlroot	Statistician Team Leader, DOBII

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
Ms. Peggy Jack	Hoffmann La-Roche, Regulatory Affairs
Dr. Marty Huber	Hoffmann La-Roche, Clinical
Dr. Russell Ellison	Hoffmann La-Roche, Medical Affairs
Mr. Chris Hellman	Hoffmann La-Roche, Clinical Investigations
Dr. Charles Lucas	Hoffmann La-Roche, Clinical Marketing
[redacted]	

Meeting Objectives:

Requested by Hoffmann-La Roche to discuss the proposed aggregate database that was submitted by the firm on May 27, 1998. The firm intends to use this aggregate database to support the conclusion that treatment with orlistat 120 mg does not increase the risk of breast cancer in females ≥45 years of age.

Discussion Points:

- The Division began by reviewing the 5/12/98 approvable letter, specifically, that 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 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. The Division added that after reviewing the firm's 5/27/98 aggregate database proposal, only point #1, "Randomized, placebo-controlled, double-blind studies" would satisfy that which is stated in the AE letter. The Division added that it will be necessary to have a body of data that is strong and indisputable in order to adequately evaluate the breast cancer finding seen in Phase 3a. The Division further commented on the remaining proposal stating that it does not recommend using data from open-label extension of the European placebo-controlled, double blind studies. The Xendos data may not reveal if there is promotional activity. Data from the Phase 3a studies in which no breast cancer cases were reported is inappropriate to use; new data is needed to resolve the breast cancer issue. The firm acknowledged the Division's position.

- In reference to page two of the firm's proposal, the Division commented that the number of proposed patients for placebo and orlistat 120 mg (949 per arm) exceeds 3a by 19%, but the years of exposure (518 per arm) falls short of 3a by 45%. The Division requested that the firm increase the patient years of exposure. The firm replied that orlistat will be launched in Europe in approximately 30 days and with the availability of the drug, it will then be difficult to manage the trials. The Division commented that open-label extension data would not provide placebo data for comparison. The Division stated that the sponsor is free to submit whatever data they want but advised them that the current plan is that the reviews and recommendations will be based on the double-blind data that is submitted. The sponsor replied that it was decided during the May 11, 1998 teleconference that the size of the database would be defined as the four phase 3 studies submitted in the original NDA in which breast cancer was reported. The Division responded that they do not recall that agreement. The sponsor added that it was included in their record of the 5/11/98 minutes that was faxed to the Division. The Division replied that it will have to go back and look at those meeting minutes again, but currently, it does not support the size of the database defined in that manner and it would not have supported it then. The sponsor inquired that if the Division believes the size is off by 45%, what range would be acceptable? The Division replied, $\pm$ 20%. The sponsor acknowledged the Division's position.

- The Division referred to the sponsor's July 17, 1998 submission, specifically to the report of two patients with known breast masses. The Division requested that the sponsor submit detailed follow-up information on each patient. The follow-up information should include, but not limited to mammogram reports and pathology reports. The sponsor agreed.

- The sponsor inquired if they can resubmit the NDA early, although it will not be a complete response. The Division advised the firm that they could submit whatever they like, however, the PDUFA clock will not start until a complete response to the AE letter is submitted. The Division also added that NDAs on the clock have review priority and the majority of resources will be devoted to those applications.

- The sponsor inquired about the Division's current position on auditing of the European study sites. The Division replied that it has consulted with the Office of Compliance and even though the European studies are not under an IND, the data that they will generate is for the NDA, therefore, FDA has the authority to audit those studies. The sponsor replied that they have their own compliance group and offered to submit the results of their audit to the Division as an option to a FDA audit. The Division acknowledged the sponsor's offer but stated that a self-audit most likely would not suffice. The Division explained that the data are critical, it is an NDA issue and it is being treated like any other NDA. The Division inquired why the sponsor objects to a FDA audit. The sponsor replied that it is a resource issue. It will be a burden on the local affiliates and investigators and these studies were never intended to be registered for an NDA. The Division replied that the audit will most likely be focused on the breast cancer findings, but will consult with Compliance again on this issue.

Decisions (agreements) reached:

- Firm acknowledged the Division's position that randomized, placebo-controlled, double-blind studies should be used in the aggregate database.

- Division will review the sponsor's minutes of the May 11, 1998 meeting.

- Sponsor will submit information on the two patients with breast masses.

[redacted]

- Division will continue to work with the Office of Compliance on auditing of the European Studies.

Post-Meeting Action Items:

[redacted]

- The Division reviewed the sponsor's minutes of the 5/11/98 meeting. The following was communicated to the sponsor on 7/24/98:

  Item 5, sentence 2 states that "The database from the phase 3a program was defined as the four studies from which breast cancer cases were reported." The Division missed the implication of this in the first review of the minutes and the database from the phase 3a program consists of data from the seven trials that made up that program.

  Item 7, sentence 1 states "If there is no difference between breast cancer reports.." It would be more precise stated as, "If there is no difference in breast cancer rates.."

  Item 7, last sentence, "If the results from the aggregate database are confounding..." It is noted that the term "confounding" is used in a general way and not according to the technical use in epidemiology, where the term is specific to an entanglement in data of outcomes arising from different exposures.

Signature, minutes preparer: /S/ [redacted]

Concurrence, Chair: /S/ [redacted]

Concurrence: BStadel/9.2.98/EColman/9.2.98/TSahlroot/9.3.98/SSobel/9.3.98

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