Original NDA Database

During the teleconference on May 11, 1998, the original NDA database was defined as the Phase 3a studies in which breast cancer was reported in the orlistat 120 mg treatment group. Of the 9 cases observed in the orlistat 120 mg treatment groups, three cases were diagnosed within the first six months of treatment and two additional cases were diagnosed within the first year of treatment. These cases occurred in the following 4 studies in the Phase 3a program.

	Placebo		orlistat 120 mg	
Protocol	Patients*	Years Exposure	Patients*	Years Exposure
NM14302	90	80	93	79
BM14149	108	173	98	162
NM14161	57	81	66	111
NM14185**	86[1]	117	78[2]	120
			81[3]	72
			68[4]	58
Total	341	451	484	602

* Patients are defined as women age 45 or over.

** Two-year study with four treatment arms:

[1] 2 years placebo (86 patients),

[2] 2 years orlistat 120 mg (78 patients),

[3] year 1 on orlistat 120 mg and year 2 on orlistat 60 mg (81 patients),

[4] year 1 on orlistat 120 mg and year 2 on placebo (68 patients).

Therefore, these total figures for the placebo and orlistat 120 mg treatment groups will be used to develop an aggregate database as requested by the Agency in the approvable letter, dated May 12, 1998.

Proposed Aggregate Database from Ongoing Clinical Program and Completed Studies

The aggregate database that will be submitted to FDA in response to the approvable letter is derived from five different sources:

1. Randomized, placebo-controlled, double-blind studies - Phase 3b
2. Open-label extension of the European placebo-controlled, double-blind studies — No
3. XENDOS study - if 4 mg through
4. Phase 3a studies in which no breast cancer cases were reported - No
5. Phase 2 studies 2-6 months

Actual and estimated accrual rates and projected dropout rates were used to estimate the size of the database at a given time period. The sponsor believes that there will be sufficient data available in December 1998 to address the Agency's request for follow-up data on breast cancer from the ongoing clinical program to support a conclusion that orlistat does not increase the risk of breast cancer. The data summarized in this section are projected to be available by the end of the year.

1. Randomized, Placebo-Controlled, Double-Blind Studies

The primary information for this database will be provided from the randomized, double-blind, placebo-controlled, Phase 3b studies being conducted in Europe, Australia, Mexico and South America. These studies will provide an internal control for comparison to the orlistat 120 mg treatment group. Each study has equal randomization of patients in the placebo and orlistat 120 mg treatment groups. The number of patients in each treatment group and patient years of exposure are summarized in the following table.

Placebo		orlistat 120 mg	
Patients*	Years Exposure	Patients*	Years Exposure
949	518	949	518

* Patients are defined as women age 45 or over.

The number of patient years exposure in the placebo group exceeds the amount in the original NDA database.

2. Open-Label Extension of the European Placebo-Controlled, Double-Blind Studies

A number of European patients were entered into an open-label extension of the randomized, placebo-controlled, double-blind studies. This cohort includes patients who have completed a double-blind study in the Phase 3b program during which approximately one half of these patients were treated with orlistat 120 mg. This patient population is pertinent in addressing the breast cancer question because:

1. These patients have longer duration of exposure to orlistat 120 mg
2. The likelihood of detection and reporting of breast cancer in this patient population is the same as the original study to which they were randomized

The number of patients and years exposure in the extension phase are summarized in the following table:

Orlistat 120 mg	
Patients*	Years Exposure
444	154

* Patients are defined as women age 45 or over.

Among the 444 patients, 226 will have been on orlistat during the double-blind phase, and more than 75% of this group will be exposed to orlistat 120 mg for a period of time greater than 9 months.

3. XENDOS Study

This study is a double-blind, placebo-controlled study of 3,300 patients conducted in Sweden to determine if orlistat 120 mg can prevent or delay the development of type 2 diabetes in obese men and women. As part of the entry criteria for that study, all women received a mammogram at the time of screening. Patients with a screening mammogram exhibiting class 3, 4 or 5 findings (possible, probable and definite malignancy, respectively) were not allowed to enter the study. Out of a total of 2,400 women who entered the screening process, 20 were found to have class 3 findings, 2 had class 4 findings and 2 were observed with class 5 findings. All women who entered into the study will have a follow-up mammogram after 1 and 2 years after randomization into the study, regardless if they discontinue the study prematurely. A total of 1,800 women were eventually randomized into the study.

This study supplements the experience from the Phase 3b program and is well-designed to address the question of whether or not orlistat stimulates the growth of breast cancer. At any given time in a population of women, especially peri- and post-menopausal women, pre-existing cancers are at various stages of growth and development. Excluding women with class 3, 4 or 5 findings from study entry only removes those women with tumors that are clinically obvious. However, it does not detect tumors in the range of 1 cm or less. Therefore, if one were to believe that orlistat could stimulate the growth of breast tumors, these smaller tumors would increase in size during the period of a year which would allow for them to be clinically detected through mammogram or physical examination. The follow-up mammogram after 1 year in the XENDOS study could serve as a sensitive analysis with an internal control regarding the potential for growth stimulation because it follows a well-defined population of patients in a systematic matter and avoids several confounding factors that may be present with spontaneous reports of breast cancer.

The number of patients in each treatment group and patient years of exposure are summarized in the following table.

Placebo		Orlistat 120 mg	
Patients*	Years Exposure	Patients*	Years Exposure
352	351	352	351

* Patients are defined as women age 45 or over.

4. The Phase 3a Studies in Which No Breast Cancer Cases Were Reported

The three Phase 3a studies in which no breast cancer was observed provide additional supportive information regarding the lack of association between breast cancer and treatment with Xenical. These studies were conducted in a similar manner and in the same countries as the 3a studies where the breast cancer cases were reported. The number of patients in each treatment group and patient years of exposure are summarized in the following table.

	Placebo		Orlistat	
Protocol	Patients*	Years Exposure	Patients*	Years Exposure
NM14336	58	48	73	68
BM14119B	38	30	37	30
NM14119C**	62[1]	119	60[2]	117
	51[3]	51	51[3]	46
	29[4]	13	25[4]	12
			68[5]	69
Total	238	261	314	342

* Patients are defined as women age 45 or over.

** Two-year study with two treatment arms (drug and placebo) in year 1; at end of year 1 both groups were re-randomized to drug and placebo resulting in four treatment arms for those patients who continued in the 2nd year of the study:

[1] 2 years placebo

[2] 2 years orlistat 120 mg

[3] year 1 on placebo and year 2 on orlistat

[4] year 1 on placebo or orlistat 120 mg only

[5] year 1 on 120 mg orlistat and year 2 on placebo (This placebo group of patients are not included in the table as they were exposed to orlistat during year 1 of treatment; however, there were 68 patients with 62 years of placebo exposure in this group.)

5. Phase 2 Studies

The Phase 2 program included 421 placebo patients and 980 orlistat patients in 11 double-blind, placebo-controlled studies. The majority of studies ranged from 2 - 6 months of treatment. Four of these studies evaluated patients with hyperlipidemia and 7 studies evaluated patients with obesity. The number of patients and patient years of exposure in the Phase 2 program are summarized in the following table.

Placebo		Orlistat 120 mg	
Patients*	Years Exposure	Patients*	Years Exposure
129	38	163	55

* Patients are defined as women age 45 or over.

Although the duration of exposure in this patient population is lower than the other components of the aggregate database, it provides secondary evidence in another cohort of patients treated with orlistat.

Conclusion

In December 1998, the years of patient exposure from the proposed aggregate database exceeds the amount of exposure in the studies from the original NDA where breast cancer was observed. For the Phase 3b program (double-blind studies and corresponding extensions), approximately 450 patients will have received orlistat 120 mg for more than 6 months with 250 patients on orlistat 120 mg for 9 months or more. The XENDOS study and the three trials from the original Phase 3a program, in which no breast cancer was observed, provide additional patients with long-term exposure to orlistat 120 mg.

In the original NDA database, the majority of breast cancer cases were reported in the first year of treatment with a difference in the number of cases reported in the orlistat 120 mg treatment group compared to placebo. Therefore, in the proposed aggregate database, there are both sufficient patient years exposure and patients exposed to orlistat 120 mg to mimic the original NDA database and to determine whether or not the original breast cancer observation is replicated.

If data from this aggregate database support the overall conclusion that orlistat does not increase the risk of breast cancer and that the original breast cancer observation was a chance finding, the product labeling should include the original breast cancer observation only in the ADVERSE REACTIONS section. This approach is consistent with the pravastatin labeling.

Roche

May 15, 1998

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 - Xenical® (orlistat) Capsules, 120mg
Response to Approvable Letter

Reference is made to the Agency's letter dated May 12, 1998 indicating that the above-mentioned application is approvable and further states that final approval of this application is contingent upon the submission and review of additional data that support a conclusion that orlistat does not increase the risk of breast cancer. The approvable letter further states that changes to the labeling will be required after the additional data have been received.

In accordance with 21 CFR 314.110, we are herewith notifying the Agency of our intent to file an amendment to this application at such time when the requested additional data becomes available.

If you have any questions concerning this application, please contact the undersigned or Dr. D. Zabrowski at 973-562-3710.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs
(973) 235-4463
(973) 562-3554/3700 (Fax)

MJJ/JMD
HLR No. 1998-1272

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

To: **Dr. Bruce Stadel**

May 9, 1998

From: **Peggy Jack**

Re: **NDA 20-766 Xenical (orlistat)**
Exposure data requested

Dr. Stadel,

Enclosed please find three tables of the data requested. Table 1 includes the Phase IIIB patient exposure as of May 8, 1998 for the studies which are randomized, double-blind, placebo controlled. Table 2 includes similar data for the Phase IIIB studies which are not placebo controlled. The data for the Xendos trial is also provided in Table 3.

We will provide the information of recommended frequency of breast examinations on a country by country basis early next week. I will be out of the office on Monday, May 11 only so if additional information is needed please call Dr. Dan Zabrowski's office on May 11 at 973-562-3710. I will return to the office on Tuesday, May 12. My office number is 973-235-4463 and my home number is 973-983-9050.

Peggy Jack

Table 1. Phase IIIB studies which are randomized, double-blind, placebo controlled trials of orlistat, 120 mg.
May 8, 1998

Region Country	Protocol No.	Planned Duration of Treatment	No. of Patients Randomized	Total No. of Females	No. of Females ≥ 45 yrs	Ratio Drug:Placebo	Total Exposure all Patients (days)	Total Exposure all Females (days)	Total Exposure Females ≥45 yrs (days)
Australia									
Australia	M37018	12 months	54	28	26	1:1	3,657	1,816	1,744
Europe									
Austria	M37007	6 months	252	195	99	1:1	41,564	31,665	16,064
Belgium	M37020	6 months	56	47	33	1:1	2,403	1,997	1,407
Germany	M37002	12 months	178	72	65	1:1	37,873	16,067	14,907
Spain	M37005	6 months	121	86	82	1:1	17,743	13,429	12,956
Spain	M37006	6 months	139	115	89	1:1	16,008	13,749	11,306
Sweden	M37004	12 months	376	240	198	1:1	92,007	59,529	49,796
UK	M37001	6 months	142	86	70	1:1	21,727	13,289	11,044
UK	M37009	12 months	105	82	49	1:1	6,801	5,264	3,172
Yugoslavia	M37019	6 months	47	35	17	1:1	5,089	3,819	1,852
Mexico									
Mexico	M37014	3 months	81	75	26	1:1	7,768	7,252	2,402
Mexico	M37015	3 months	47	41	21	1:1	5,750	4,944	2,556
S. America									
Argentina	M37012	6 months	109	64	52	1:1	11,418	6,402	4,903
Brazil	M37013	6 months	44	28	24	1:1	3,303	1,965	1,705

851

135,814 = 372 years

Table 2. Phase IIIB studies which are not placebo-controlled and all patients are receiving 120 mg orlistat.
May 8, 1998

Region Country	Protocol No.	Planned Duration of Treatment	No. of Patients Randomized	Total No. of Females	No. of Females ≥ 45 yrs	Total Exposure all Patients (days)	Total Exposure all Females (days)	Total Exposure Females ≥45 yrs (days)
Australia								
Australia	M37601	18 months	1	1	1	237	237	237
Europe								
Austria	M37507	6 months	188	145	76	36,421	27,819	14,579
UK	M37003	6 months	97	61	53	17,349	11,179	9,761

130

24,577 = 67 years

Table 3. Xendos Trial
May 8, 1998

Average Exposure - 5 to 8 months		
No. of Patients Randomized	Total No. of Females	No. of Females ≥ 45 years
3305	1825	705

5 to 8 / 12 · 705 = 293 to 470 years

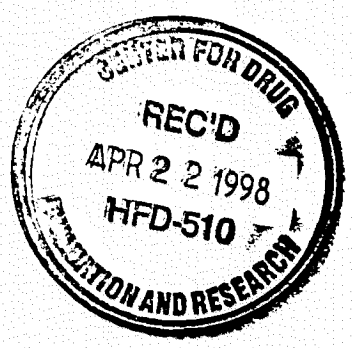
T47758

Roche

NEW CORRESP

April 21, 1998

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706



Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120mg
Submission of Estrogen Data Previously Provided via Fax
and Additional Estrogen Data Not Previously Submitted

Reference is made to a telefax sent to Ms. Maureen Hess, CSO, dated March 11, 1998 in which an assessment of estrogen levels was provided for a population of women 45 years and older at the time of their enrollment in studies NM14185 and NM14161. The women included in this estrogen assessment were all postmenopausal based on a FSH level of >30 mIU/ml at the time of randomization, were not receiving hormonal replacement therapy, and had retained plasma samples available for such analyses from day 1 (randomization), and after 6 months of treatment with either orlistat or placebo. The purpose of this submission is to provide the data previously faxed to the Agency in a formal submission to the above-mentioned application and to provide additional relevant information on the estrogen assessments.

The data provided in this submission that was previously faxed to the Agency includes the mean serum concentrations for follicle stimulating hormone (FSH) and sex hormone binding globin (SHBG), and the mean plasma concentrations of estradiol (E_2) and estrone (E_1) for day 1 and following 6 months of treatment for the previously described population, see Attachment 1.

This submission also includes information not previously provided to the Agency such as the individual patient data listings for the above-mentioned parameters and the analytical methodology for E_2, E_1, FSH and SHBG, see Attachments 2 and 3 respectively. Attachment 3 is the methodologies referred to as Appendix A in the information faxed to the Agency March 11, 1998.

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

Please contact the undersigned if you have any questions concerning this submission.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs
(973) 235-4463 (Telephone)
(973) 562-3554/3700 (Fax)

MJJ:LS/mi
HLR No. 1998-1042

Roche

Pharmaceuticals

April 16, 1998

James Bilstad, M.D.
Food and Drug Administration
Office of Drug Evaluation II (HFD-102)
Room 13-B28
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-766, Xenical® (orlistat) Capsules, 120 mg
Follow up to Teleconference on April 13, 1998

Dear Dr. Bilstad:

We appreciate the need for the FDA to responsibly address the breast cancer observation in the phase 3 clinical studies, although no plausible biological mechanism has been identified to explain the imbalance. In addition, we share the objective with the Agency to ensure the responsible marketing and use of orlistat.

Within this letter, we hope to provide you and other senior managers at FDA additional assurance that Roche has proposed a comprehensive program that continues to address the breast cancer observation in a meaningful manner and to manage the use of this product in the marketplace. We believe that the program accomplishes the objectives described in the first paragraph and can provide the Agency with sufficient justification to proceed directly to NDA approval by the user fee action date in May.

In our submission, dated April 9, 1998, Roche proposed labeling that advises the physician to restrict the use of the drug and encourage screening and monitoring of patients before and during treatment. Roche also described in that submission an extensive post-marketing surveillance program, including placebo-controlled, double-blind studies and an extensive registry program. The components of our submission allow for Roche to:

1. collect sufficient patient exposure from a variety of sources to meaningfully address the breast cancer finding,
2. obtain an early signal of a problem in the market,
3. reduce potential "risk" through the significant labeling changes proposed in the package.

As I mentioned to you during our teleconference, Roche understands that, due to the prevalance of breast cancer in women and the indication for which we seek approval, there will be spontaneous reports. It is our goal to limit the number of women with confounding factors who take this drug and encourage the continued use of the drug only for patients who are most likely to benefit from therapy. Our proposed labeling provides key elements to achieve this objective:

Hoffmann-La Roche Inc. Nutley, New Jersey 07110 U.S.A. PDR
Tel. 973 562 3710
Fax 973 235 2834
daniel.zabrowski@roche.com

1. discloses information regarding the breast cancer observation in the NDA program,
2. restricts the use of orlistat in women with existing or suspected breast cancer,
3. advises that a thorough breast exam be conducted before and during treatment,
4. encourages monitoring of women treated with orlistat,
5. provides a guidance to assess response to treatment and recommends discontinuation of treatment for patients who do not respond.

This labeling is modeled after the Premarin labeling, as suggested by the FDA Oncology Division. It is our understanding that health professionals will follow recommendations as those described for screening and monitoring for breast cancer.

Although we agree that the indication does allow for large numbers of patients to take weight loss drugs, recent market data (IMS on Meridia) suggest that physicians and patients are more cautious before they take drugs in this therapeutic area. Our market research indicates that the new statements in our proposed labeling will discourage widespread use of orlistat in women over the age of 45. Therefore, when assessing the benefit/risk of approving orlistat now, it is reasonable to consider that the patients who are taking this drug for periods of 3 months or greater are most likely going to be the subset of clinically obese patients who are truly benefiting from the drug. As Dr. Hauptman showed during the recent Advisory Committee meeting, patients who lost 5% of their body weight were able to maintain that loss for the full 2-year period of the study.

It is our strong belief, which is shared by Dr. Simon from the National Cancer Institute, that the only way to obtain sufficient patient exposure to meaningfully address the breast cancer observation is through a post-marketing program. Other information, short of this type of program, is supportive at best and is not adequate to make definitive conclusions about the breast cancer finding. Additional strengths of our proposed post-marketing surveillance program are:

1. all detected cases, from any source, will be subject to intensive data collection using an enhanced data collection instrument specific to breast cancer;
2. the program will generate several cohorts of obese patients from a variety of clinical settings that will provide data in a timely and ongoing fashion;
3. an independent Data and Safety Review Committee will be established from a multitude of disciplines (e.g., oncology, pathology, epidemiology, women's health policy) and will review all breast cancer cases on a regular basis and perform safety analyses on aggregate data.

The reports from this Committee will be provided to FDA on a semi-annual basis as part of the periodic safety report or immediately, if the Committee identifies an early signal of a problem.

Finally, per your request, we have obtained additional supportive evidence on the breast cancer finding. As you are aware, we are following patients in our ongoing phase 3b program. After 1400 patient-years of exposure in women, of which approximately 50% is collected from the Swedish study, there has not been a single report of breast cancer. Of note, within the same patient-years of exposure in the phase 3 NDA studies, we had received 4 reports of breast cancer in women taking orlistat.

In conclusion, the breast cancer imbalance observed in the phase 3 clinical trials was reported and analyzed in the original NDA, submitted in November 1996, and has been the subject of significant discussion between Roche, the Agency, Advisory Committee members and outside experts. We agreed to accept a delay of NDA approval while we continued to study this matter for the past several months. During that time period, we collected all available clinical, histopathologic and mammographic information on the women who reported breast cancer. This information was then reviewed by a large number of outside, independent experts. In addition, we investigated, both clinically and preclinically, possible biological mechanisms (e.g., hormonal, stimulation) that may have explained the imbalance of breast cancer reports in the phase 3 trials. We also have followed patients who completed studies in the phase 3 trials or who are currently enrolled in our phase 3b program.

After this extensive work, the concordance of the results was remarkable. There is no single piece of evidence that substantiates the breast cancer observation in the phase 3 clinical trials. Moreover, there is general agreement between Roche, the Agency and the outside experts that the majority of these cases were pre-existing. Therefore, it is reasonable to conclude that the imbalance was due to chance based on a larger number of pre-existing cases of breast cancer being randomized onto the orlistat treatment group in the phase 3 clinical trials.

Roche believes that it has worked diligently to study the breast cancer finding prior to approval and has completed all tasks requested by the Agency. This effort has already resulted in a 1-year delay of NDA approval. The program outlined in the submission of April 9 is responsible and comprehensive. It allows for Roche to collect sufficient patient exposure to meaningfully address the breast cancer observation, obtain an early signal of a problem in the market and reduce potential "risk" through the significant labeling changes proposed in the package. Given the lack of strength of evidence supporting a biological association of orlistat with breast cancer, the proposed program offers the most expeditious manner by which to continue to address the breast cancer finding. Therefore, Roche believes that there is sufficient justification for the Agency to approve the NDA by the user fee action date in May.

We respectfully request that you forward this letter to the other members of the NDA decision-making team prior to your meeting.

I look forward to our continued discussion on this matter. Please feel free to contact me directly if you have any questions or require further information.

Sincerely,

Hoffmann-La Roche Inc.

Daniel L. Zabrowski, Ph.D.
Vice President and Global Head of Drug Regulatory Affairs

HLR #1998-1011
DZ:di

CC: NDA 20-766

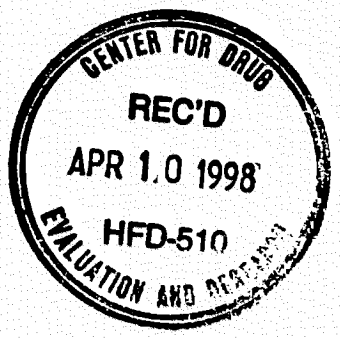
Roche

T 48629

NEW CORRESP

April 9, 1998

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706



Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120mg
Proposed Post-Marketing Commitments

Reference is made to the March 31, 1998 teleconference between the Division and Roche to exchange views regarding the recommendations/outcomes of the March 13, 1998 Endocrinologic and Metabolic Drugs Advisory Committee meeting. During the teleconference, Roche briefly outlined for the Agency their proposal for post-marketing surveillance commitments to be implemented following the approval of this application. The purpose of this submission is to provide a more detailed presentation of this proposal.

his proposal consists of two major components:

1. Draft labeling for Xenical
2. Post-Marketing Surveillance Program

As per our March 31 teleconference, this submission also includes responses to questions raised at the Advisory Committee on March 13, 1998.

The proposed Xenical labeling included in this submission is modeled after the Premarin labeling as recommended by the Oncology Review Division. This label restricts the use of the drug to patients most likely to receive a clinical benefit and recommends screening and monitoring for breast cancer both prior to and after initiation of therapy.

The primary goal of the post-marketing surveillance program is to detect any meaningful increased risk for breast cancer in women treated with Xenical. A secondary goal is to accumulate substantial evidence to demonstrate that no association exists between orlistat exposure and breast cancer in women.

Both the proposed draft labeling and the post-market surveillance program are in accordance with the recommendations of the Advisory Committee and the safety review of this application by the Oncology Division.

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

If you have any questions concerning this submission, please contact the undersigned or Dr. Daniel Zabrowski at (973) 562-3710.

If you have any questions concerning this submission, please contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs
(973) 235-4463 (Telephone)
(973) 562-3554/3700 (Fax)

MJJ:LS/mi
Attachment
HLR No. 1998-943

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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